Lifestyle Interventions and Independence for Elders

The LIFE Study Pilot

Protocol

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1. **Summary**

As the life expectancy of older Americans increases, prevention of age-associated physical function decline and disabilities has emerged as a major clinical and public health priority. A critical factor in an older person's ability to function independently is mobility, the ability to move without assistance. Older people who lose mobility are less likely to remain in the community, have higher rates of morbidity, mortality, and hospitalizations and experience a poorer quality of life. While several studies suggest that physical activity may prevent physical disability, including mobility disability in both healthy and frail older adults, definitive evidence is lacking. A Phase 3 randomized, controlled trial is needed to fill this evidence gap. Currently data to estimate sample size needs for such a trial are insufficient and further feasibility data should be gathered before such a trial can be effectively designed and implemented.

To refine key trial design benchmarks (including sample size calculations to demonstrate the feasibility of a full-scale trial and refining/developing recruitment, procedures, materials and organizational infrastructure), the LIFE (Lifestyle Interventions for Independence in Elders) study conducts a pilot, single-blind randomized, controlled trial involving comparison of a physical activity program of moderate intensity to a successful aging program. A total of 400 sedentary persons aged 70-<90 years who are at risk of disability are followed for at least one year at four intervention sites: Wake Forest University School of Medicine in Winston Salem, NC, the University of Pittsburgh, Pittsburgh, PA, the Cooper Institute in Dallas, TX, and the Stanford University in Palo Alto, CA. The Administrative Coordinating Center and the Data Management and Quality Control Center are at Wake Forest University School of Medicine.

The LIFE study assesses the combined outcome of major mobility disability defined as the incapacity to walk 400 m, or death, which will be the primary outcome of the full-scale study. This outcome has not been used in previous randomized, controlled trials, and therefore, a pilot study is needed to assess its incidence rate. Secondary outcomes include ADL disability, major fall injuries and cardiovascular events. LIFE explores the effects of the intervention on physical performance measures, cognitive function, health-related quality of life, and use of health care services. In addition, LIFE explores and performs cost-effectiveness analyses of the intervention.

This pilot study will yield the necessary preliminary data to design a definitive Phase 3 randomized, controlled trial. By providing a conclusive answer regarding whether physical activity is effective for preventing major mobility disability or death, the results of the full-scale trial will have relevant clinical and public health implications, and will fill an important gap in knowledge for practicing evidence-based geriatric medicine.

2. Background and rationale

2.1. General overview

The life expectancy of older Americans continues to increase, with persons aged ≥70 years representing the fastest growing segment of the US population.[1] While prolongation of life remains an important public health goal, of even greater importance is that extended life should involve preservation of the capacity to live independently and to function well.[2] Therefore, identification of **proven interventions to prevent disability** is a major public health priority.[3] Mobility and activities of daily living represent tasks that are necessary for the maintenance of basic independent functioning.[4;5] The inability to perform these activities marks a serious decline in functional health, conferring increased risk of institutionalization and death.[6]

Most older adults are sedentary,[7;8] and most of these individuals are mobile and free of disability, but are at high risk for loss of mobility, which, in turn, is a key predictor of further decline and of increased risk of mortality. It is these individuals who would represent the target population for the intervention.[9-11]

2.2. Causes of Physical Disability in Older Persons

In most cases, physical disability is directly caused or aggravated by acute events (stroke and hip fracture) and chronic conditions (heart failure, coronary heart disease, diabetes and arthritis).[12;13] In contrast, some individuals with no clear connections to a single disease experience progressive decline in physical function, with subsequent development of age-related physical disability. As diverse as the etiologies of physical disability are, sarcopenia (a progressive loss in skeletal muscle mass and strength) is hypothesized to represent a common pathway that is associated with the initial onset and progression of physical disability in many individuals.[14] Low levels of cardiorespiratory fitness also contribute to functional limitations.[15;16]

2.3. Health Benefits of Physical activity on Chronic Disease and Disability

Physical activity may benefit a number of morbid conditions that underlie disability, including cardiovascular disease,[17] risk of falls,[18;19] respiratory diseases,[20] cancer,[21] diabetes,[22;23] osteoporosis[24] and obesity.[25;26] **Physical inactivity is one of the strongest predictors of physical disability** among older persons.[27;28] Longitudinal observational studies reveal that regular physical activity not only extends longevity, but also reduces the risk of physical disability in later life.[7;29-32] Of the 6,200 older persons free of baseline disability in the EPESE studies, those with a low level (lower tertile) of regular physical activity were 1.8 times more likely to develop ADL[4] or mobility disability over 6 years than those with a high level (upper tertile) of physical activity.[7;33] The benefit of physical activity on physical function may be mediated by a direct effect on impairments such as reduced muscle strength,[34] low cardiorespiratory fitness[16] and impaired balance,[35] or by prevention of frequently disabling diseases. In a cohort of Finnish men and women aged 75 years, those involved in a high level of everyday physical activity (household chores, walking and gardening) showed significantly less decline in knee extension strength and grip strength after 5 years, as compared to those who were sedentary.[34]

Several RCTs have demonstrated the beneficial effects of physical activity programs in diseased or frail older adults. In FAST,[25] a RCT conducted at WFUHS and University of Tennessee Memphis among 439 community dwelling older adults with knee osteoarthritis, self-reported physical function was significantly improved among those participating in an 18-month aerobic physical activity training or resistance physical activity training program, as opposed to those participating in a successful aging program. The FAST physical activity programs also significantly improved objective physical

performance, walking speed and postural sway (balance).[36] In other studies, patients with chronic obstructive pulmonary disease[37] or heart failure[38] improved physical function and distance walked in 6 min after a physical activity program,[39] frail older adults experienced beneficial physical health effects from structured physical activity programs, and a strengthening physical activity program among frail nursing home patients significantly improved functional mobility, gait speed and muscle strength.[40;41]

In healthy older adults, the beneficial physiological effects of a structured physical activity program targeted towards older people have been conclusively demonstrated. Regular physical activity that emphasizes aerobic conditioning and/or strength training increases aerobic capacity,[42] muscle strength[42-47] and endurance.[44] Despite these findings, it remains unclear whether the positive effects of physical activity interventions can be sustained for a sufficient duration of time and maintained at adequate intensity to prevent a **clinically significant disability outcome**, thereby **prolonging autonomy**. Addressing this question requires new data from an intervention study with a sufficiently large sample size, a long follow-up time and appropriate disability outcome measures.

Evidence also exists that **physical activity may benefit** the secondary outcomes of interest in this study, including **cardiovascular disease, cognition, psychological symptoms, and sleep**. In physically capable older men, walking <0.25 miles per day was associated with a two-fold higher risk of incident coronary heart disease over a 2- to 4-year period, compared to men walking more than 1.5 miles per day.[48] Recent evidence supports the likelihood that physical activity can have a beneficial effect on the brain and on cognitive functioning. In animal models, physical activity increases levels of brain-derived neurotrophic factor and other growth factors, stimulates neurogenesis, increases resistance to brain insult and promotes gene expression that may benefit brain plasticity processes.[49] A recent RCT demonstrated selective improvement in executive control processes[50] after 6 months of aerobic physical activity. Further work is needed, however, to clarify the effect of longer-term physical activity on early cognitive decline. Physical activity improves mood in the short term, especially among those who are already depressed,[51] and RCTs of up to one year have shown improvements in symptoms of anxiety and depression among older persons involved in both high- and low-intensity training programs.[52] Conversely, a recent observational study in older persons failed to show a protective effect of vigorous physical activity in patients experiencing depression $\geq$5 years,[53] and long-term effects of physical activity on depressive symptoms and anxiety remain to be demonstrated in clinical trials. Physical activity-related improvements in sleep complaints in persons up to age 75 have been demonstrated in trials running up to 4 months[54] but, again, the longer-term impact of physical activity on sleep, and the effect in persons aged >75 years remains to be investigated.

2.4. Report of the Surgeon General on Physical Activity and Health – Gaps in Evidence

The Surgeon General's report on physical activity and health emphasizes the importance of physical activity at all ages and documents the wide range of health benefits that result from physical activity.[55] The report stresses that moderate intensity physical activity such as walking can be quite effective in improving health, and it recommends 30 minutes of this activity on most, if not all, days of the week. The report suggests that to attain these specific benefits, endurance exercises should be supplemented with strength-developing exercises at least twice per week. The intervention is entirely compatible with the Surgeon General's report, recommending a goal of 150 minutes per week of moderate physical activity, adding strength training, and addressing the special needs of an older population.

Consistent with the findings presented in the review noted above, the report points

to “promising evidence” that physical activity in older adults may preserve the ability to maintain independent living and reduce the risk of falling. While this statement relies on clinical trial evidence regarding the effects of physical activity on impairments such as decreased strength and balance, evidence supporting the beneficial effects of physical activity on **maintenance of independence** is entirely based on observational studies. These latter studies are especially prone to bias, since healthier older people are much more likely to be physically active, and statistical adjustment for level of comorbidity in observational studies is never fully adequate. Most such studies do not comprehensively assess disease status and almost none can adjust for the severity of all diseases that may be present. Thus, residual confounding is highly likely in even the best-conducted observational studies, and the corresponding data **cannot provide definitive evidence regarding whether physical activity can prevent the onset of disability in older people**. Furthermore, in persons who already have impairments and functional limitations (and who reflect the target population for our intervention), diseases causing these impairments could lead to eventual disability; even if these impairments improve with physical activity. It is therefore critical that a RCT be conducted to evaluate the Surgeon General report’s proposed benefit of physical activity in preventing disability. This would have a large public health impact on strategies for reducing dependence in older populations. In addition, findings that a large subset of RCT participants especially vulnerable to disability could be identified and successfully targeted for disability prevention would provide important information to supplement the current Surgeon General’s recommendations.

2.5. Need for a Definitive Trial

There are no proven interventions to prevent the onset of ADL[4] or major mobility disability in older persons. The Systolic Hypertension in the Elderly Program (SHEP) trial has shown a benefit of antihypertensive treatment on cardiovascular events and death,[56] but not on ADL disability,[57;58] and the results of growth hormone trials were also disappointing.[59] Physical activity is an extremely promising intervention, but evidence regarding prevention of mobility and ADL disability derives only from secondary data analyses. The benefits of physical activity have only been demonstrated in the context of change in intermediate measures such as disability scales and performance scores, or muscle strength.[25]

Several examples in medicine that relate to the pharmacological treatment of arrhythmias (CAST),[60] hypertension (ALLHAT),[61;62] coronary heart disease (BHAT),[62;63] and hormone replacement (HERS,[64] WHI)[64;65] demonstrate the need of relying on large long-term randomized controlled trials of adequate scope to modify clinical practice, suggesting that results from trials on surrogate outcomes may not always apply to generalized prevention of events.[61;62;65] Although there is strong evidence supporting the benefits of physical activity, concerns remain regarding whether physical activity interventions in older persons can be sustained for a sufficient duration of time and maintained at adequate intensity to actually improve clinically significant outcomes over the long-term. In addition, physical activity interventions in frail elderly persons may have adverse consequences. Conclusive evidence is lacking concerning whether physical activity interventions can reduce the risk of onset of major mobility disability or death over the long-term in the general older population, and whether the benefits outweigh the potential risks.

2.6. Information Needed Prior to Fielding a Definitive trial

While several studies consistently suggest a benefit of physical activity on disability and function, definitive evidence is lacking that physical activity prevents the onset of

disability (including mobility disability) in older persons. A Phase 3 randomized, controlled trial (RCT) is needed, but preliminary data to estimate the sample size for such a trial are currently insufficient. Additional feasibility data also should be gathered before such a trial can be effectively designed and implemented, including refining sample size calculations to demonstrate the feasibility of a full-scale trial and refining/developing recruitment, procedures, materials and organizational infrastructure.

3. Overview of Trial Design

The LIFE study conducts a **multicenter single-blind pilot RCT** involving physical activity vs. a successful aging program, with a follow-up of at least one year in 400 non-disabled, community-dwelling persons age 70-<90 years. The goal of this pilot study is to gather preliminary data for planning a full-scale Phase 3 RCT to assess whether a long-term structured physical activity program reduces the risk of the combined outcome of major mobility disability or death.

The **inclusion criteria** are (1) age 70 to <90 years; (2) summary score <10 on the EPESE short physical performance battery;[66] (3) sedentary lifestyle; (4) ability to complete the 400 m walk test without an assistive device; (5) successful completion of the behavioral run-in; and (6) willingness to be randomized to either treatment group. The **exclusion criteria** reflect conditions that may interfere with the conduct of the physical activity program. LIFE plans to recruit 65% women and 25% minorities.

3.1. Rationale for Major Design Decisions

3.1.1. Selection of Primary Outcome

After a thorough evaluation of possible alternative approaches LIFE has selected as the primary outcome for the full-scale trial **time to the onset of the combined outcome of major mobility disability or death**. This outcome is adjudicated as described below. The objective component of the **major mobility disability** outcome is defined as the inability to complete a 400 m walk test within 15 minutes without sitting and without the use of an assistive device (including a cane) or the help of another person. Individuals who complete the walk in more than 15 minutes have an extremely slow pace (<0.45 m/sec), which would make their walking capacity of little utility in daily life.[67] Selecting a higher cut point, such as 30 or 60 minutes, makes the objective assessment impractical and does not add to the clinical significance of the outcome. Major mobility disability is assessed every six months by staff that are **blinded** to the intervention. Criteria for selection of this objectively measured mobility outcome include its face validity and public health relevance. Older persons who lose mobility are less likely to remain in the community, have higher rates of subsequent morbidity and mortality, have more hospitalizations, and have poorer quality of life.[66;68-71] The underlying premise is that major mobility disability for most older persons is a potentially preventable chronic condition rather than an irreversible consequence of aging and comorbidity. For those that are unable to attend a clinic session to perform the 400m walk, we have defined several alternative criteria that also comprise major mobility disability (see section 8.4.1. Adjudication Of The Major Mobility Disability Outcome).

The **decision to include death** in this composite outcome is based on the following factors: (1) the death rates for the intervention and control groups may differ, thereby leading to bias; (2) the intervention may reduce mortality[72-75] and (3) if the intervention actually leads to increased mortality, a primary mobility outcome that did not include death would mask the potential negative effect on mortality.

The requirement of **not using an assistive device**, i.e., a cane, is incorporated into the definition of major mobility disability, for conceptual and practical reasons. The transition from ability to inability to walk 400 m without personal help or without an assistive device is clinically meaningful. An intervention that diminishes or delays the need for a cane, for example, would likely be quite appealing to many older persons. Bias could be introduced into the results if high-income persons or participants in the intervention group were more likely to obtain an assistive device and complete the 400 m walk test because of the device. Inherent in the selection of this outcome is that use of a cane to walk 400 m would represent an exclusion criterion.

Primary hypothesis to be tested in the full scale study:

Compared to random assignment to a successful aging program, random assignment to a long-term structured physical activity program reduces the risk of the combined primary outcome (major mobility disability or death) in community living frail older persons.

3.1.2. Selection of Secondary Outcomes

LIFE uses this pilot study to address important clinical and public health questions that relate to the secondary and tertiary aims. Indeed the pilot study may have sufficient power to detect significant differences for some tertiary outcomes. This pilot study will furnish the necessary preliminary data to design and implement a definitive Phase 3 RCT that would address the following hypotheses:

Secondary hypotheses to be tested in the full scale study:
Compared to random assignment to a successful aging program, random assignment to a long-term structured physical activity program:

1. Reduces the risk of onset of disability in activities of daily living (ADLs)[4]
2. Reduces the risk of serious fall injuries
3. Reduces the risk of cardiovascular events
4. Improves cognitive function and health-related quality of life
5. Reduces the utilization of health care services and is cost-effective.

3.1.3. Selection of Interventions

The physical activity program includes aerobic, strength, flexibility, and balance training. LIFE focuses on **walking** as the primary mode of physical activity for preventing/postponing the combined outcome of major mobility disability or death, given its widespread popularity and ease of administration across a broad segment of the older adult population.[55;76] Other forms of endurance activity (e.g., stationary cycling) are, however, utilized when regular walking is contraindicated medically or behaviorally. Each session is preceded by a brief warm-up and followed by a brief cool-down period. In light of current clinical guidelines, participants are instructed to complete **flexibility** physical activities following each bout of walking. Moreover, following three bouts of walking each week, participants are instructed during the initial phase of the program to complete a 10-minute routine that focuses primarily on **strengthening exercises.** As has been done in other strengthening programs for older adults,[26;77] supplementary instructional materials (e.g., videotapes, printed materials) are supplied to participants in this group, to reinforce the strength training occurring during setting-based instruction, so that it can be generalized to the home environment. **Balance training**[25] is introduced during the second month of the two-month adoption phase of the program as a complement to the endurance and strength components. In addition, the intervention involves encouraging participants to increase all forms of physical activity throughout the day. This may include activities such as leisure sports, gardening, use of stairs as opposed to escalators, and leisurely walks with friends.

Intensity of training. The participants are introduced to the intervention exercises in a structured way such that they begin with **lighter intensity and gradually increase** over the first 2-3 weeks of the intervention. LIFE promotes walking for physical activity at a **moderate intensity**. LIFE relies on **ratings of perceived exertion** as a method to regulate physical activity intensity.[78;79] Using Borg's scale,[80] that ranges from 6 to 20, participants are asked to walk at an intensity of 13 (activity perception SOMEWHAT HARD). They are discouraged from exercising at levels that approach or exceed 15 (HARD) or drop to a rating of 11 (FAIRLY LIGHT) or below.

The intervention consists of a general weekly walking goal of 150 minutes. This is

consistent with the public health message from the Surgeon General's report that moderate physical activity should be performed for 30 minutes on most if not all days of the week (150-210 total minutes). This goal is **approached in a progressive manner** across the first 3 months of the trial. There are multiple ways that the goal can be achieved, based on the physical abilities and constraints of each participant.[25;81] In light of the heterogeneity of the target population (with respect to physical capabilities and health status), this pilot study allows to more specifically define the variability in participants' ability to reach this weekly target, to estimate the dose-response relationship between incremental increases in weekly physical activity and changes in the primary and secondary outcomes, and to better specify the level of ongoing behavioral instruction needed to achieve such changes.

3.1.4. Selection of Study Population

LIFE plans to recruit sedentary and physically impaired, but ambulatory, community living older persons age 70 to <90 years. The specific inclusion and exclusion criteria are summarized below. These criteria are intended to select a population that is at higher risk of experiencing the major mobility disability outcome, would most likely benefit from the physical activity intervention, and would most likely comply with the intervention and assessment protocols. This age group is selected because it is at high risk of major mobility disability,[66] and it may have a sufficiently long life expectancy[1] to participate in a full-scale RCT, which would have a duration of 3 to 4 years.

3.2. Objectives of Pilot Study

The **objective** is to conduct a **pilot, single-blind RCT** (400 participants followed for at least one year at four sites) to compare a moderate intensity physical activity program to a successful aging program in sedentary persons aged 70-<90 years who are at risk of disability. This enables to address the aims listed below, all of which are of critical importance for designing a full-scale study.

Primary aims:

1. To obtain data that allow a more accurate projection of the sample size needed for a full-scale study by using the incidence rates of the combined outcome of major mobility disability (defined as being unable to walk 400 m without the use of an assistive device or adjudicated evidence of inability to walk 400m) or death and the drop-in, drop-out and loss to follow-up rates.
2. To provide internal validity verification of the efficacy of the physical activity intervention by assessing its effects on the Established Populations for Epidemiologic Studies of the Elderly (EPESE)[69] physical performance score, the 4 m gait speed, the 400 m gait speed, and a self-reported disability scale.
3. To assess protocol feasibility and participant adherence and retention in the intervention group (stepped-care approach to physical activity) and in the control group (successful aging program), to refine these protocols, and to assess their replicability and quality control across multiple sites.
4. To assess the rates of intercurrent illness that may compromise adherence to the intervention and to assess the feasibility of a physical activity protocol to accommodate these events.
5. To assess the feasibility and yields of recruiting an at-risk cohort from diverse communities and ethnic subgroups, and to refine the recruitment strategies.
6. To assess the psychosocial and health-related early predictors of response and adherence to the physical activity intervention so that participants requiring increased efforts to maximize adherence can be readily identified.

7. To optimize the multicenter infrastructure needed to conduct the full-scale study, including: 1) establishing a prototype for the infrastructure for the main study 2) developing and refining study forms, 3) developing a web-based communications system, 4) programming a data management system, 5) preparing study documents (including intervention materials and a manual of operations), 6) establishing a study-wide system for quality control, and 7) developing a comprehensive system to monitor and ensure participant safety.

Secondary aims:

To assess in the pilot study the outcome rates and loss to follow-up rates of the secondary outcomes (listed below). This information will be used to calculate power tables that are based on the projected sample size for the full-scale study and to determine the hypothesized effect size of the intervention on these outcomes. The secondary outcomes of interest include:

1. Onset of self- or proxy- reported and objectively assessed disability in activities of daily living (ADLs);[4]
2. Serious fall injuries;
3. Combined cardiovascular events; and
4. Acute care hospitalizations and nursing home admissions.

Tertiary aims:

1. To **assess the variance** of the tertiary outcomes (listed below), which are measured as continuous variables, and to **explore the short-term effect** of the intervention on these outcomes. This information will be used to calculate power tables that are based on the projected sample size for the full-scale study and on the hypothesized longer-term effect size of the intervention on these outcomes, which include:
    a. Cognitive function measures;
    b. Health-related quality of life (HRQL), as reflected by depressive symptoms, anxiety, energy and fatigue level, sleep, and pain; and
    c. Nursing home and acute-care hospitalization length of stay.
2. To assess feasibility of, refine instruments for and conduct **cost-effectiveness analyses** of the intervention and health care utilization.

3.3. Sample Size Considerations

For the LIFE pilot study, a sample of **approximately 400 participants** is recruited across 4 Field Centers.

The first primary aim involves estimation of the event rate within the successful aging program intervention. With approximately 200 participants in each of the intervention groups, if the observed event rate is less than 30%, we will be able to place 95% confidence intervals with a maximum width of 12.7% around the estimate of the 1-year rate of the combined outcome of major mobility disability or death. The maximum width of 90% confidence intervals around this estimate will be 10.6%. This level of precision is sufficient to rule out situations in which endpoints are too rare (e.g. 10%/year incidence) to make the full-scale trial feasible. We expect, given our assumptions, to observe a lower incidence rate in the physical activity intervention group than health education group. For example, if the underlying one-year incidence rate in the health education group is 25% and the physical activity intervention is associated with a 20% lowering of incidence, the probability that the observed incidence rate in the physical activity intervention group in our pilot study will be lower than the health education group is 0.88.

Intervention effects on EPESE short physical performance battery score/gait speed (4 m, 400 m), self-reported disability: The second primary aim involves an investigation of the internal validity associated with four endpoints that have previously been reported to be affected by physical activity interventions, namely physical performance measures, gait speed (4m, 400 m or 6 min walk) and self-reported disability. [82-85] Using data from the WHAS and EPESE studies, we have obtained baseline means and standard deviations for physical performance (EPESE score) and gait speed after restricting the sample by age (70-85), disability [no inability to walk a half mile (EPESE) or quarter mile (WHAS)], no regular physical activity, and EPESE scores below 10 (Table 3.3.a.).

Table 3.3.a. Descriptive statistics for EPESE score and gait speed m/sec

Outcome	WHAS (N=305 Women)	EPESE (N=470 Men)	EPESE (N=891 Women)
EPESE Score	6.30 (SD=1.97)	7.13 (SD=1.78)	7.06 (SD=1.78)
Gait Speed (4 m)	0.666 (SD=0.203)	0.581 (SD=0.179)	0.571 (SD=0.163)

The LIFE Study plans to recruit 65% women. Thus, using averages of the variances from the data in Table 3.3.a, we will assume an overall combined SD of 1.8 for EPESE score and 0.18 m/sec for 4-meter gait speed for our calculations. The relative effect of the physical activity intervention at 12-months follow-up will be estimated using a contrast from a repeated measures analysis of covariance (with baseline scores as covariates for follow-up measures). For the analysis of covariance, the variance of the mean difference between physical activity and education groups is reduced by a factor of $(1-r^2)$, where r is the correlation between the baseline and 12-month outcome measurements. Within the WHAS study, the correlation between baseline and one-year measures of 4-meter gait speed and EPESE scores were 0.56 and 0.58, respectively. Based on these assumptions, the width of the 95% confidence interval about the mean difference in EPESE score and 4-meter gait speed will be 0.58 and 0.058, respectively. If The LIFE Study assumes an education group mean of 7.0 for EPESE score and 0.60 for 4-meter gait speed, these widths represent 8.3% and 9.7% of the education intervention group means.

After restricting the samples using the above criteria, similar calculations were performed to obtain descriptive statistics for 400-meter gait speed, as measured in HABC (815 men, 827 women), and a self-reported disability scale used in the FAST study (56 men, 131 women). For the 400-meter walk, the estimated baseline speed for the 400-meter walk was 1.18 m/sec (SD=0.18). For the disability score, the estimated baseline score was 2.0 (SD=0.65). The correlation between initial and 12-month measurements for gait speed was 0.45; whereas, both the 9- and 18-month correlations for the self-reported disability score were approximately 0.55. For calculations, The LIFE Study assumes that the 12-month correlation is also 0.55. Based on these assumptions, the width of the 95% confidence interval about the mean difference in 400-meter gait speed and self-reported disability is 0.058 and 0.21. If The LIFE Study assumes an education group mean of 1.18 m/sec for 400-meter gait speed and 2.0 for self-reported disability, these widths represent 4.9% and 10.5% of the education group means.

Power for EPESE score, gait speed (4-meter, 400-meter), self-reported disability hypothesis tests: This pilot study has excellent power to detect the projected intervention effects on EPESE scores and gait speed.

Table 3.3.b. Power for differences in physical activity and health education intervention group means at 12-months (n=400, α=0.05)

Difference As A Percent of Within-Group SD					
20%	21%	22%	23%	24%	25%
0.67	0.71	0.75	0.79	0.82	0.85

In Table 3.3.b., we provide the power to detect various percent differences (differences between means as a % of the within-group SD), assuming a two-sided probability of Type I error of 0.05 and n=400. A correlation between baseline and follow-up measurements of 0.55 is assumed. If the within group SD is 1.8 and a follow-up education group mean is 7.0 for the EPESE score, the power to detect a 0.45 difference in means between groups (6.4% of the projected mean in the education group) exceeds 0.85. For 4-meter gait speed, if the within group SD is 0.18 m/sec and the education group mean is 0.60 m/sec, the power to detect a 0.045 m/sec difference in means between groups (7.5% of the projected mean in the education group) also exceeds 0.85. For 400-meter gait speed, if the within group SD is 0.18 m/sec and the education group mean is 1.18 m/sec, the power to detect a 0.035 m/sec difference in means between groups (3.8% of the projected mean in the education group) exceeds 0.85. For disability, if the within group SD is 0.65 and the education group mean is 2.0, the power to detect a 0.163 difference in means between groups (8.1% of the projected mean in the education group) exceeds 0.85.

4. Study Population

The eligibility and ineligibility criteria for the LIFE Study identify participants who are not currently disabled but have moderate to high risk for occurrence of mobility disability and for whom the intervention is safe.

The coordinating center monitors the distribution of the recruited cohort with respect to age, gender, ethnicity, score on the Short Physical Performance Battery (SPPB) and other factors expected to influence the incidence rate of the trial's primary outcome. Based on this monitoring activity, targeted recruitment strategies may be developed to ensure that the study cohort is racially and ethnically diverse and has a range of age and physical performance adequate to evaluate the results of this pilot study.

4.1.1. Targeting Populations at High Risk of Disability

Targeting the non-disabled but high-risk segment of the older population for a physical activity program aimed at reducing disability has many advantages. These persons are in the middle of the functional spectrum and are neither so disabled that a physical activity program may not offer help nor so highly functional that their already very low risk of becoming disabled would not be appreciably affected by the intervention. They may be at a transitional stage in the pathway to disability, so that a well-focused intervention could be extremely effective in pulling them back from the brink of disability onset and lead to additional years of disability-free life.

Most of the older population is non-disabled and an important goal in this segment of the population is to prevent or postpone the onset of disability. However, there is a great deal of heterogeneity in the non-disabled portion of the older population and any strategy to prevent disability should take the very broad range of health status into account. Some older non-disabled persons are already very active and vigorous while others are sedentary and may actually have impairments and functional limitations that indicate an elevated risk of disability. The eligibility criteria in this study are aimed at identifying persons who are sedentary, have functional limitations, as assessed by a battery of physical performance tests, but who have not yet developed disability, as documented by their ability to walk 400 meters without the use of an assistive device. Targeting this subset of the population makes it possible to recruit a non-disabled but at risk population for a clinical trial of disability prevention. This is a large segment of the older population in which successful prevention of disability onset, in this case through a physical activity program, would have a major public health impact.

4.1.2. Establishing Eligibility

Eligibility is established in a multi-step screening process. The first step is a telephone screen to assess specific inclusion and exclusion criteria. This is followed by an interviewer assessment, including the administration of the SPPB, the 400 meter walk test, the MMSE and an interview. Finally, the potential participant receives an examination by the study physician, who determines if conditions are present that meet exclusion criteria. Eligibility criteria are as follows:

Gender Men and women are eligible. The LIFE Study endeavors to recruit men and women in rough proportion to their representation in the catchment area population.

Age Individuals aged 70-<90 years old are eligible. This age group is selected because it is at high risk of major mobility disability,[66] and it may have a sufficiently long life expectancy[1] to participate in a full-scale RCT, which would have a duration of 3 to 4 years.

Ethnicity All ethnic groups are eligible for the study. The LIFE Study goal is for a study

cohort that is at least 25% from minority populations (primarily African Americans and Hispanic Americans).

Residency Participants must be planning to reside in the area for at least 9 months in the next year.

Functional Status Summary score <10 on the EPESE physical performance battery.[66] Ability to complete the 400 m walk test within 15 minutes without sitting and without the use of an assistive device (including a cane) or the help of another person. The LIFE study goal is a target of 40% of randomized participants to have a score of < 8.

Cognitive functioning Persons are eligible if they do not report a diagnosis of dementia or score < 21 on the Mini-Mental State Exam. Persons that score < 21 will be advised by the research staff to take the results to his/her PCP for additional review since our testing is for research purposes only. In our previous studies with physical activity interventions such as FAST and ADAPT, the same inclusion criteria of score of 21 or greater was used. The participants were able to understand and perform the required study procedures.

Physical activity and exercise Sedentary lifestyle, i.e., has spent less than 20 minutes per week in the past month getting regular physical activity. Physical activity includes activities like: brisk walking, jogging, weight lifting, cycling, aerobics, and dancing.

Chronic disease status The LIFE Study recruits individuals both with and without chronic diseases, except for specific conditions described in the exclusion section that may be life-shortening or prevent the participation in a physical activity intervention.

Willingness to participate Participants must be willing to give informed consent, be willing to be randomized to either Physical Activity or the Successful Aging Program intervention, and to follow the protocol for the group to which they have been assigned.

Run-in Participants must successfully complete the behavioral run-in before they are randomized and join the trial.

4.2. Exclusion Criteria

Individuals are excluded from participation from the study for any of the following reasons: 1) the potential participant may have difficulty adhering to either intervention, 2) participation may be unsafe, 3) the participant has serious health conditions that would interfere with the intervention goals, and/or 4) the participant is already physically active to a degree that the adoption of an activity program would be of little additional benefit.

In many cases, participants may have conditions that would preclude participation in the study that could resolve. Therefore, we also define a set of temporary exclusions. Participants with such exclusions may be re-contacted later during the recruitment period for further evaluation.

4.2.1. Exclusion Criteria for Factors that May Limit Adherence to Interventions or Affect Conduct of the Trial

- Unable or unwilling to give informed consent or accept randomization in either study group.
- Current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder

- Current consumption of more than 14 alcoholic drinks per week.
- Plans to relocate to out of the study area or plans to be out of the study area for more than 3 months in the next year
- Failure to complete the run-in for tracking physical activity (see section 4.6)
- Self-reported inability to walk two blocks
- The use of a walker or assistive device to complete the 400 m walk
- Another member of the household is a participant in the Life Study.
- Residence too far from the intervention site.
- Difficulty in communication with study personnel due to speech or hearing problems.
- Mini-Mental Status Exam < 21
- Other medical, psychiatric, or behavioral factors that in the judgment of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol

4.2.2. Exclusion Criteria for Underlying Diseases Likely to Limit Lifespan and/or Affect the Safety of the Interventions

- Severe arthritis (either osteoarthritis or rheumatoid arthritis)
- Cancer requiring treatment in the past three years, except for non-melanoma skin cancers or cancers that have clearly been cured or in the opinion of the investigator carry an excellent prognosis (e.g., Stage 1 cervical cancer)
- Lung disease requiring either steroid pills or injections or the use of supplemental oxygen
- Development of chest pain or severe shortness of breath on a 400 m self-paced walk test
- Cardiovascular disease (including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history or cardiac arrest, use of a cardiac defibrillator or uncontrolled angina)
- Parkinson's disease or other serious neurological disorder.
- Renal disease requiring dialysis
- Other illness of such severity that life expectancy is considered to be less than 12 months.
- Conditions not specifically mentioned above may serve as criteria for exclusion at the discretion of the clinical site

Current Physical Activity Exclusion Criterion

- Having spent 20 or more minutes per week over the past month getting regular physical activity.

Temporary Exclusion Criteria

- Uncontrolled hypertension (systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 110 mmHg).
- Uncontrolled diabetes with recent weight loss, diabetic coma or frequent insulin reactions.
- Stroke, hip fracture, hip or knee replacement, or spinal surgery in the past 6 months.
- Serious conduction disorder (e.g., 3rd degree heart block), uncontrolled arrhythmia, or new Q waves or ST-segment depressions (>3 mm) on ECG.
- Myocardial infarction, major heart surgery (i.e. valve replacement or bypass surgery), stroke, deep vein thrombosis or pulmonary embolus in the past 6 months.

- Undergoing physical therapy
- Currently enrolled in another randomized trial involving lifestyle or pharmaceutical interventions

5. Recruitment and Retention

5.1. Recruitment

The goal of the study is to enroll 400 participants, approximately 100 at each of the 4 clinical sites. Participants are recruited over a 9 month period with a goal of overall minority participation of at least 25%. Recruitment in the Life Study also has a recruitment target of at least 40% of participants with baseline SPPB (Short Physical Performance Battery) EPESE scores of 7 or below. To facilitate recruitment of ethnic minorities, minorities are not part of this recruitment target restriction. All recruitment related activities are overseen by the Recruitment, Adherence and Retention Committee. The Committee coordinates press and media and assists the sites in the preparation of recruitment materials. Each clinical site develops a site-specific recruitment plan to accommodate the variability across centers in catchment area characteristics, media market outlets, and access to older participants. Recruitment strategies include the use of radio and television advertisements, direct mail, and presentations at health fairs, senior centers, medical clinics, and churches. Participants in previous studies may also be approached and ineligible participants are asked for friends who might be eligible. All recruitment materials are reviewed by the appropriate field center IRB before being used.

5.1.1. Screening Process

The purpose of the staged screening process is to identify and verify eligible participants at a series of contacts achieving the objectives of an informed consent process, complete baseline measurements and procedures, and randomize participants into the LIFE study. Interested participants first are screened by phone. The interview is designed to exclude individuals who are clearly ineligible or unlikely to benefit from participation in the study. At the first screening visit, the remainder of medical exclusions is assessed, including those based on lower extremity physical function. At the second clinic visit, the ability of the participant to successfully complete the behavioral run-in is assessed and a final eligibility determination is made prior to randomization. The exclusion criterion likely to have the largest impact is having a score on the short physical performance battery (SPPB) 10 or above. To save clinic time and expense, this test can be administered off-site or in a modular form during the screening process.

5.2. Retention and Drop-out Recovery

5.2.1. Identifying Secondary/Proxy Contacts

Although not a criteria for enrollment in the trial, LIFE attempts to identify a proxy respondent for all participants. A proxy respondent and two additional contact persons are identified and may be contacted to provide supplemental information on the participant.

5.2.2. Retention Promotion Efforts

During screening, participants are informed about which test results they receive and when these tests are performed during the course of the study. In general, screening test results are available immediately, whereas follow-up results (performance measures, blood pressure) are not made available until the end of the study (unless findings indicate a possible abnormal value requiring health care attention).

Before enrollment, preventive measures are taken to minimize participant non-compliance related to data collection. Because the study requires a dedicated commitment to examination schedules, only those subjects who appear likely to follow the study protocol are enrolled. During a one-week **behavioral run-in** period (prior to randomization), prospective participants ate asked to **self-monitor specific behaviors** (such as diet and physical activity), to attend a clinic visit, and to complete mock forms. Participants who fail these simple preliminary tasks are not considered for randomization.

The judgment of Field Center staff is essential in determining overall eligibility with respect to adherence. Providing clear, easy-to-follow, written instructions for returning for follow-up visits is important. Reviewing these instructions with the participant periodically during follow-up is a priority, especially if demonstrated compliance problems exist. Involving the subject's spouse or other family members in these reviews can be useful. Attempts are made to maintain continuity of follow-up care, so that, whenever possible, the same staff member sees the subject throughout the study. Every attempt is made to make all clinic visits pleasant. Minimizing waiting time and providing parking space, free transportation for the clinic assessment visits, and comfortable waiting room facilities makes the visits more pleasant, thereby enhancing participant retention to follow-up appointments.

During the follow-up phase, participants attend two to four clinic visits. If they are unable to come to the clinic, home or institutional visits are scheduled. Telephone or proxy interviews are scheduled if in-person visits cannot be completed. Attendance at scheduled visits is documented by completion of the follow-up Visit and Missed Visit forms. Field Centers are advised to keep detailed records of rescheduled and broken appointments for each participant. Participant retention is monitored, and efforts are made to identify those individuals who need support and encouragement. Records of participants consenting to only a portion of the follow-up procedures, i.e., partial compliance, are also are maintained. Summary reports of such difficulties help to identify problems. Critical review of such problems may offer potential solutions.

5.2.3. Drop-out Recovery Efforts

Algorithms are developed to address non-attendance at the clinic. These involve procedures (discussed below) that facilitate documentation of these cases, and formulate how best to rectify the attendant problems. The following procedures are implemented (as appropriate in each Field Center) to carefully document and monitor missed clinic or home visits:

- Preparing for the next visit at the end of each current visit by making the appointment and giving instructions for the next visit.
- Sending out pre-visit reminders.
- Establishing a mechanism to chart and monitor local clinic attendance, so that clinic staff would be immediately alerted to a missed visit.
- Immediately contacting participants (usually by telephone) when they miss a visit.
- Planning clinic action to rectify the problem within the scope of clinic services.
- Rescheduling the visit within the same window, if possible. Examinations that fall outside of the target window remain important and are used in all analyses. These examinations are assigned to whichever target visit would be the closest in time. If it becomes clear that a visit corresponding to a particular set of forms (e.g., a 6-month visit) is not completed, a Missed Visit form is filled out.

Some randomized participants may not actively participate in the study, perhaps by not adhering to the intervention and/or not attending the clinic. This may be due to a number of reasons, such as family objections to participation, or participant decision. Regardless of the reason(s), these participants are followed until the end of the study, and clinic staff attempts to make contact at the 6th, 12th, and 18th month of the trial and at the close-out visit. These contacts are intended to remind the participant that they are welcome to fully rejoin the study at any time. Considerable effort is expended to collect main outcome data at appropriate times.

The following guidelines promote adherence to the protocol, in terms of intervention adherence and clinic attendance. The availability of local clinic resources determines

which techniques are is used.

- **Participant-staff relationship**. A key element contributing to participants' continued commitment to the trial involves fostering personal relationships between study subjects and individual members of the staff.
- **Continuity of care**. In general, participants' appointments should be scheduled so that they can be seen by the same clinic staff members during each visit.
- **Clinic environment**. The clinic environment which is warm and pleasant, and oriented to the comfort of the participant.
- **Participant-staff communications**. Good and consistent communication is essential. Instructions are clear and interactions are friendly and individualized. The participant is reminded of the benefits of study participation. Written reminders about clinic appointments further enhance communication efforts. Unmasked clinic staff meets regularly with intervention staff to reinforce the importance of consistency of communications across intervention groups.
- **Convenience and accessibility**. An easily accessible clinic location, availability of transportation, and convenient clinic hours all serve to facilitate study adherence. Field Centers make study visits as easy as possible for participants, a factor critical to the success of the study. All sites take steps to ensure that clinic attendance is not compromised by a lack of transportation, unsuitable hours of clinic operation, or any similar circumstance. If necessary, participants are reimbursed for or are provided transportation to the clinic assessment visits.
- **Time in clinic**. Total clinic visit time is kept to a minimum, consistent with maintaining quality. If waiting is necessary, the situation is explained to the participant and, if possible, an offer is made for the participant to see another staff member, or to reschedule the visit. On the other hand, participants are not rushed or made to feel unwelcome. Clinic staff is trained to take time to visit with participants.
- **Appointment reminders**. Appointment reminders are used to prompt participants to come for clinic visits. These written reminders are mailed to participants so that they receive them one to two weeks before their scheduled visit date.

5.3. Monitoring Recruitment and Retention

The Recruitment, Adherence and Retention Committee routinely monitors screening and recruitment yields, and compares them to preset gender and ethnic minority benchmarks for each site. If these benchmarks are not attained, the main reasons for exclusion of subjects are analyzed and the recruitment strategies are modified accordingly. The Recruitment, Adherence and Retention Committee may also recommend changes in the protocol, if needed. Reports on recruitment are generated and are reviewed by the Steering Committee, the Data and Safety Monitoring Board, and the Project Office.

5.3.1. Retention and Efforts to Maintain Contact with Inactive Participants

Retention is promoted by:

1. examining and attempting to remove barriers (e.g., by addressing parking and other transportation issues, adjusting clinic hours);
2. incorporating a variety of methods to promote contact with all participants and provide social support for all participants, including those in the Education arm;
3. providing all staff and investigators who have contact with LIFE participants with training and regular re-training in motivational methods; and

4. ensuring that participants' concerns are identified and addressed before they express a desire to reduce their involvement in the study.

Efforts to Maintain Contact with Inactive Participants

LIFE has the goal of maintaining some form of contact (e.g., phone, e-mail) with participants who are unable to continue full engagement in the study and to foster some form of continued contact (e.g., even an agreement to allow future contact) with participants who are inactive in the study. The greatest importance is given to attending semi-annual assessment visits; even participants who are unwilling to continue attending intervention sessions are strongly encouraged to attend the assessment visits.

5.3.2. Monitoring and Quality Control of Recruitment and Retention

The coordinating center collects data to monitor recruitment and retention activities, the number of potential participants contacting each site, how potential participants indicate that they heard about the study, the yield at the various screening steps, and follow-up rates. Regular web-based reports are available to clinical centers and the LIFE Recruitment and Retention Committee. Members of this committee maintain regular phone contact with clinic staff to:

1. review recruitment goals and yields for all centers participating on each call,
2. review the recruitment plan and progress in achieving the objectives outlined in the plan,
3. share successful and unsuccessful recruitment methods, and
4. review retention.

If centers encounter difficulties in recruitment, the Recruitment and Retention Committee (or a subgroup it designates) provides a graduated set of assistance responses that are based on the degree of recruitment shortfall. If retention becomes a problem for a clinic, a graded response of assistance that is based on clinic-specific retention issues is provided.

6. Measures and Procedures

6.1. Informed Consent

Before individuals may participate in any screening procedures, informed consent must be obtained. Verbal consent is acquired prior to the administration of the telephone screen. Clinics are allowed to elect, as their IRB requires, to use either a single consent procedure to cover consent for participation in the entire study or a staged consent procedure in which they are asked to provide initial consent to participate in the screening followed by, for those who qualify, later consent to participate in the remainder of the study. Model consent forms are provided in Appendix C.

6.2. Measures

6.2.1. 400 Meter Walk Test

The primary outcome for the full-scale trial is time to the onset of the combined outcome of major mobility disability or death. The objective outcome of major mobility disability is defined as the inability to complete a 400 m walk within 15 minutes without sitting and without the use of an assistive device (including a cane) or the help of another person. Major mobility disability is assessed every six months by staff that is blinded to the intervention.

For each follow-up clinic visit, participants and their proxies are also independently asked a distinct set of mobility-related questions that serve as surrogates for the 400 meter walk test. Participants are asked these questions prior to the 400 meter walk test, while proxies are asked these questions over the phone or face-to-face within 72 hours of the 400 meter walk test.

6.2.2. Short Physical Performance Battery (SPPB or EPESE Battery)

The SPPB, originally developed for the Established Populations for the Epidemiologic Study of the Elderly (EPESE) is a brief performance battery based on timed short distance walk, repeated chair stands and balance test (as described by Guralnik et al.,[66]).[68;69;86-88] We also test the capacity to put on and button a blouse/shirt. The battery is administered by trained examiners. The measurement goal for this battery is to assess lower extremity functional limitations, which indicate functional abilities and are a strong measure of risk for future disability. The test takes about 10-15 minutes to administer and can be done in the home or the clinic setting. The battery has an excellent safety record. It has been administered to over 10,000 persons in various studies and no serious injuries are known to have occurred. The components of the battery are as follows:

Walking speed. Walking speed is assessed by asking the participants to walk at their usual pace over a 3 or 4 m course. Participants are instructed to stand with both feet touching the starting line and to start walking after a specific verbal command. Participants are allowed to use walking aids (cane, walker, or other walking aid) if necessary, but not the assistance of another person. Timing begins when the command is given, and the time in seconds needed to complete the entire distance is recorded. The faster of two walks is used to compute walking speed.

Chair stands. The repeated chair stands test is performed using a straight-backed chair, which is placed with its back against a wall. Participants are first asked to stand once from a sitting position without using their arms. If they are able to perform the task, they are then asked to stand up and sit down five times, as quickly as possible. The time to complete the task is recorded.

Standing balance. For the test of standing balance, participants are asked to maintain balance in three positions, characterized by a progressive narrowing of the base support: feet together (side by side position), the heel of one foot beside the big toe of the other foot (semi tandem position), and the heel of one foot in front of and touching the toes

of the other foot (tandem position). For each of the three positions, participants are timed to a maximum of 10 seconds. Scores are summed for the measure of balance for a range of 0 to 30 seconds.

Quantile summary performance score. Each of the three performance measures is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. For the test of balance, participants are assigned a score of 1 if they can hold a side-by-side standing position for 10 seconds, but are unable to hold a semi-tandem position for 10 seconds; a score of 2 is assigned if they can hold a semi-tandem position for 10 seconds, but are unable to hold a full-tandem position for 3 seconds; a score of 3 is assigned if they can stand in a full-tandem position for 3 seconds but less than 10 seconds; a score of 4 is assigned if they can stand in a full-tandem position for 10 seconds.

Four categories are computed for walking speed and chair stands, according to cut points that are based on quartiles of the time to perform each task assessed in the EPESE.[66] The time of the faster of two walks is scored as follows: For 4-meter walk > 8.7 sec = 1; 6.21 to 8.70 sec = 2; > 4.82 to 6.20 sec = 3; < 4.82 sec = 4; For a 3-meter walk > 6.52 sec = 1; 4.66 to 6.52 sec = 2; 3.62 to 4.65 sec = 3; < 3.62 sec = 4; a score of 0 is assigned to participants unable to perform the test.. The time required to perform five chair stands is scored as follows: > 16.7 sec = 1; 13.7 to 16.6 m/sec = 2; 11.2 to 13.6 m/sec = 3; < 11.1 = 4. A score of 0 is assigned to participants unable to perform the task. A summary score ranging from 0 (worst performers) to 12 (best performers) is calculated by adding walking speed, chair stands and balance scores. This scale has proven reliable[89] and valid for predicting institutionalization, hospital admission, mortality and disability,[69] and it is used for participant screening and as a secondary outcome**.**[66;68;88;90]

Putting on and buttoning a blouse/shirt. For the task of putting on and buttoning a blouse/shirt the participant is given a blouse/shirt of appropriate size and instructed to put it on and button it as fast as possible without mistakes.[91] This task is performed in the standing position or, for those unable to stand unsupported, in the sitting position. Timing begins when the participant touches the blouse/shirt and ends when the task is completed or after 4 minutes, whichever comes first.

6.2.3. Lateral Mobility Task

The lateral mobility task is a task designed to assess lateral mobility and transfer in older adults that uses simple equipment, is easily transported and exhibits similar measurement properties to the getting into a car task. This task is administered at the first screening visit, and at the 6 and 12 month follow-up at the Wake Forest University Field Center only.

The equipment required for the task includes two sets of standards (high and low), 2 cross bars, a standard chair, step bench, and 9 closed cell foam floor tiles. Participants are positioned so that they are standing in line with the chair, and the lateral part of their left foot is 53cm from the first cross bar. The participant is facing away from the crossbar so that the first movement is a lateral step. Participants are instructed to “step onto the mat with your left foot, step over the bar left foot first, duck under the second bar, and sit in the chair with both feet flat on the step in front of you”. The task is demonstrated by the tester and a practice trial is completed. Timing is initiated as soon as the participant places their left foot in front of first bar on the foam tiles, and finishes when the participant places his/her right foot (or both feet if done simultaneously) on the step. If the participant displaces either bar, the trial is stopped and redone. A record that a failed trial occurred is noted on the scoring sheet along with the bar (low/high) that was displaced. The time to complete the trial, to the nearest 1/10th of a second is recorded and three trials are administered.

6.2.4. Hand Grip Strength

Hand grip strength is a commonly used measure of upper body skeletal muscle function and has been widely used as a general indicator of frailty with predictive validity for both mortality and functional limitation.[92;93] Grip strength in both hands is measured using a hydraulic grip strength dynamometer. If a person reports current flare-up of pain in the wrist or hand, or has undergone fusion, arthroplasty, tendon repair, synovectomy, or other related surgery of the hand or wrist in the past 3 months, the affected side is not tested, and results of the other hand are. Other than possible temporary discomfort during the test itself there are no known risks for the participant.

6.2.5. Self-Reported Physical Function, Activity and Disability

For the purpose of the pilot study, the measure of self-reported function is based on a 25-item, self-report disability questionnaire. This questionnaire, with two additional items, was developed at WFUHS for FAST[25] and has been widely used in physical activity RCTs and observational studies (ADAPT,[94] OASIS[95]). The questionnaire, which is not disease-specific, inquires about perceived difficulties in general activities of daily living during the last month. For each item, respondents answer whether they experience 1) no difficulty, 2) a little difficulty, 3) some difficulty, 4) a lot of difficulty, 5) unable to do or, 6) did not do for other reasons. Answers can be averaged across the items, in order to better assess the overall perceived disability burden by a person. The 23-item questionnaire used in FAST, which was validated by Rejeski et al., consists of five subdomains: mobility, transferring, upper extremity, instrumental and basic ADLs.[4] In factor analysis, all of the loadings for the individual items on the subdomains were in excess of 0.40 and alpha internal consistency reliabilities for the five subscales were excellent: basic ADLs=0.73, complex IADLs=0.84, mobility=0.82, transfer=0.84, and upper extremity=0.72.[96] In addition to being a valid measure, the disability questionnaire has been shown to be responsive to change in our previous physical activity intervention studies among various disease populations.[25;85]

As expected, the average score on the 23-item disability questionnaire was found to correlate at a low to moderate level (correlations between 0.18 and 0.48) with objectively assessed physical performance measures (6-minute walk, a stair climb test and a lift and carry test).[96] This illustrates that these measures are complementary and that they assess different dimensions of physical function. Similar findings have been reported by others.[97;98] A self-reported disability questionnaire assesses subjects' perceptions of their own functional capacity within their own social and physical setting, as opposed to performance measures of functional capability that take place in the "experimental" setting.

Within the 23-item disability questionnaire, LIFE selects specific subdomains for in-depth analyses of a specific disability outcome. For example, the FAST data have been used to focus on basic ADL disability, which is the most severe form of disability that seriously limits older persons' autonomy and introduces dependence.[5;99] Basic ADL disability marks a serious decline in functional health and increases the risk of outpatient care, hospitalization, nursing home admission, and death.[6;9;9-11;100] The basic ADL items included are the same ADL items used and validated by Katz et al,[4] and used by other investigators: eating, transferring from bed to chair, using the toilet, bathing and dressing. Penninx et al. used these items to address the question of whether physical activity may prevent the onset of ADL disability.[99] A similar analytic approach can be done for other types of disability (mobility, upper extremity).

LIFE adds two items to the previously used 23-item questionnaire. These are "walking across a small room" and "walking a quarter of a mile," (about 2 or 3 blocks). These two items have been used previously as the single outcome of interest for studies

on mobility disability.[90;101] ADL disability is also assessed through proxy respondents, when participants are not available for personal interviews.
In addition, for the basic ADLs we plan to also ask whether the participant receives help from another person to complete the task. This allows to calculate a Katz ADL score. Finally, we plan to administer the Late Life Disability questionnaire developed by Dr. Jette and colleagues.[102;103] This instrument includes 16 tasks representing a broad range of disability indicators and was developed using more contemporary psychometric techniques.

Self reported physical activity is monitored by means of the Community Healthy Activities Model Program for Seniors (CHAMPS) Activities Questionnaire a validated questionnaire that takes about 15 min to complete. [104 105] The questionnaire assesses weekly frequency and duration of various physical activities typically undertaken by older adults. This instrument is administered at the second screening visit, and at the 6, 12 and 18 month follow-up visits.

6.2.6. Process Measures

A brief battery of tests is employed to evaluate psychological processes that are theoretically linked to adherence and success with the interventions. These include items related to performance efficacy, barriers efficacy, satisfaction with function, motivation for physical competence, and self-regulatory style. This brief test battery is collected on all participants during scheduled outcome assessments.

6.2.7. Vital Signs

Prior to randomization and subsequently during each semiannual clinic visit, data are collected on sitting blood pressure, heart rate, waist circumference and weight. Body height is measured once prior to randomization. The blood pressure assessments will allow the determination of the incidence of hypertension and serve as basis for a temporary exclusion. The other measures are collected primarily for descriptive purposes.

6.2.8. Medication Inventory

Many older adults use both prescription and non-prescription pharmaceutical products. The use of these products is of interest for several reasons. Their use is an important indicator of overall health, and the nature of the drugs taken is a strong indicator of clinically manifest disease. The response to the intervention may be enhanced or diminished by some drugs. Finally, individuals who use nutritional supplements, herbs or other complementary products may have stronger sense of health self-efficacy, and thus the use of these products could be related to study adherence. All participants are asked to bring all prescription and non-prescription medications taken in the past two weeks to their first pre-randomization screening visit and subsequent follow-up visits. Medications include: pills, tables, drops, salves, injections, creams/ointments, inhalers, suppositories and dermal patches. Non-prescription medications include: vitamins, aspirin, laxatives, dietary supplements, and herbal preparations. The name, strength and formulation of each product are transcribed. These medications are coded according to formulation for use in subsequent data analyses. This method of drug assessment has been shown to be valid in older adults.[106]

6.2.9. ECG

Twelve lead ECG is performed at the initial visit for safety purposes. The ECG is read and interpreted by the study physician at each field center to assess potential exclusion criteria.

6.2.10. Social, Economic and Health Related Questions

For descriptive purposes, data are collected on several participant characteristics, including: age, gender, race, living situation, household composition, marital status, education, smoking, alcohol consumption, employment, occupation, volunteer work, income and chronic conditions.

6.2.11. Cognition

Cognitive function is assessed at baseline and at the 12-month follow-up in participants enrolled at the Wake Forest University School of Medicine site and the Stanford University site.

The LIFE Study evaluates a variety of cognitive functions including memory and executive function using the following assessments:

1. Digit Symbol Test (DSST)[107] as a measure or attention and perceptual speed.[108] Subjects are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 1 minute.
2. Modified Stroop Test[109] as a measure of complex speed of processing. This test consists of three subtasks: color word naming, color naming, and naming of color words printed in a different color.
3. Teng Mini-Mental Status Exam (3MS)[110] as a measure of a broad variety of cognitive measures. This is an expanded 100 point version of the original Folstein MMSE.
4. Rey Auditory Verbal Learning Test (RAVLT)[111] as a measure of verbal learning and memory. A target list of words is presented and participants are asked to recall (both immediate and delayed) as many words as possible.

6.2.12. Health-Related Quality Of Life

The following key components of HRQL are assessed at baseline and after one year of follow-up:

1. Depressive symptomatology is assessed with the Center for Epidemiologic Studies Depression Scale (CES-D),[112] a 20-item scale with four answer categories, queries about depressive symptoms experienced in the previous week.
2. Sleep quality is assessed by means of the 5-item Women's Health Initiative Insomnia Rating Scale,[113;114] which assesses sleep latency, duration, efficiency and disturbances.
3. Energy and fatigue level is assessed by the 6 fatigue and energy items from the Modified Exercise-induced Feeling Inventory.[115] Each item is rated on a 6-point, which focuses on the amount of time that individuals experienced fatigue or energy related feelings during the past week.
4. Pain is assessed using the 12-item pain scale as used in the FAST[25] and ADAPT[94] physical activity trials. This pain scale assesses both the intensity and the frequency of pain during transferring and ambulation/ climbing activities and has been validated in an older disabled sample.[116]

6.2.13. Quality of Well-Being Scale (QWB-SA)

The self-administered version of the Quality of Well-Being Scale (QWB-SA) is used to assess general quality of life and for the subsequent cost-utility analyses.
Participants are asked to complete the questionnaire (described below) at home prior to the second screening visit and each of the follow-up clinic visits. These forms are reviewed

for completeness during the relevant screening/clinic visit. The QWB is a comprehensive measure of health-related quality of life that assesses health symptoms and functioning. The observed level of function and the subjective symptomatic complaints are then weighted by preference, or utility, on a scale that ranges from 0 (dead) to 1.0 (optimum function). The weights were obtained from independent samples of judges who rated the desirability of observable health states. Several studies have shown that the weights do not vary as a function of demographic variables, including race, income, and gender.

The QWB-SA takes about 10 minutes to complete. The assessment covers an extensive list of symptoms including both acute and chronic conditions and psychological well-being is well represented. The questionnaire asks about symptoms and functioning over the previous 3 days, minimizing recall bias, and providing a "point in time" expression of health. The measure has been selected for several multisite NIH clinical trials, including the National Emphysema Treatment Trial (NETT),[117] the Diabetes Prevention Program (DPP), and portions of the Prostate, Lung, Colorectal, and Ovarian screening trial (PLCO). In addition, the QWB has been used in a variety of clinical studies for a range of medical and surgical conditions that include COPD,[118] AIDS,[119] cystic fibrosis,[120;121] diabetes mellitus,[122] atrial fibrillation,[123] lung transplantation,[124] arthritis,[125] cancer,[126;127] schizophrenia,[128] and many other conditions.[129]

6.2.14. Health Care Utilization

Health care utilization is assessed using a self-administered, self- report questionnaire developed at the University of California San Diego. The measure consists of 12 questions that ask about the frequency of various types of health care utilization over the previous 3 months. The questions ask about utilization of hospital days, emergency care, urgent care, primary care, telephone calls, prescriptions, and medical equipment. Health care costs are calculated by multiplying the frequency of each service by the prevailing community charge. The measure has been validated in a clinical trial of patients with chronic obstructive pulmonary disease.[130]

6.2.15. Biological Specimen Sampling and Storage

Blood samples for future assessment of biomarkers in ancillary studies are collected in the early morning, after a 12-hour fast at baseline, 6-month and 12-month assessment visits. The participation in this component of the study is optional. Blood (67 ml per visit) are collected via venipuncture into 2 plain, 3 EDTA-treated, 1 heparin-treated, and 1 citrate-treated vacutainers by a trained phlebotomist. **DNA** to be used for later genetic analyses is extracted from leukocytes collected in the EDTA-treated vacutainers. The participation in DNA studies is optional. All samples are shipped quarterly on dry ice via overnight delivery to the central repository at Wake Forest University School of Medicine. A rationale and justification of ancillary studies using biological samples is provided in the Appendix.

6.3. Study Run-In

All participants complete a one-week run-in period prior to randomization. They are asked to record on a paper log information about number and type of fruits and vegetables taken, and type and frequency of physical activity daily during this period. The logs are then reviewed by a trained interviewer. To pass the run-in, participants must have written entries for at least 6 of the 7 days for both fruits/vegetables and physical activity. The quality of their responses is not rated. The person conducting the review of the run-in can also make a decision not to pass the participant based on clinical judgment. Successful completion of self-monitoring is required for eligibility.

6.4. Randomization

6.4.1. Final Eligibility Assessment

Data related to eligibility (including run-in compliance) and key measures must be entered prior to randomization. A computerized check is performed to confirm that all required elements are entered and are within range prior to randomization. If the eligibility check is not successful (i.e., it shows the participant as ineligible), staff in the clinic confirms that all required data were entered correctly, correct any omissions or errors in the database, and re-initiate the eligibility check. Any corrections that are made to the eligibility screens after the eligibility check is run are documented in the system and reviewed periodically by the Data Management, Analysis and Quality Control Center to ensure compliance with the study protocol. Eligibility is dependent on screening data being collected within a set timeframe: all screening data are to be collected within four months (i.e. the time between the date of the informed consent and the date of randomization cannot exceed four months) and key clinical and performance measures (400-meter walk; weight; behavioral run-in) are to be collected within one month of randomization. The computerized eligibility check does not permit randomization if the dates for these data are outside of these ranges. If a screenee is ineligible, staff determines whether this is may be a temporary condition (e.g., blood pressure out of range or too young of age) and discuss this with the participant. Re-screening can be conducted at a later date in such situations.

The allowable time from the date of randomization to the date of the first individual intervention is one month. The maximum time between the randomization and the start of the first group session is two months. Randomizations are timed at the clinic sites to allow these deadlines to be met. The Data Management, Analysis and Quality Control Center monitors these activities and provide regular reports to the study leadership.

6.4.2. Randomization Algorithm

Each eligible participant is randomized to one of the two arms of the clinical trial (physical activity intervention and successful aging program intervention) according to a variable block-length algorithm that is controlled by the Data Management, Analysis and Quality Control Center. This approach provides a high probability of balance between intervention assignments and makes anticipation of assignments difficult. Randomization is stratified by field center to ensure nearly equal sample sizes for the two intervention groups within each center. This is necessary because the cohorts assembled by the centers differ due to local population characteristics and recruitment plans. Randomization is also stratified on gender to ensure nearly equal sample sizes for the two intervention groups within gender. Randomization assignment is made using a web-based randomization system that is part of the study data management system.

6.4.3. Masking or Blinding

Masking, which is used synonymously with the term “blinding,” refers to structured attempts to limit the disclosure of study data and participant status to as few persons (both study personnel and participants) as possible. It is generally recommended that access to all types of study data be limited. This includes access to clinic and laboratory measurements, intervention group assignment, and measures of adherence to interventions. Many examples exist in the medical literature to demonstrate that knowledge of some aspects of a participant’s status can subjectively lead to differences in how data are collected and interpreted. The assessment team is blinded to the intervention assignment.

7. Interventions

7.1. Intervention Theory and Goals

7.1.1. Intervention Theory

The intervention is based upon a **social cognitive model of acquisition and maintenance of health behaviors**. The social cognitive approach views behavior (including health behavior) as being acquired and maintained through a complex set of behavioral, cognitive, and environmental conditions. Social cognitive intervention strategies are found in a number of studies to be effective with older as well as younger adults, and with programs aimed at physical activity as well as with other forms of health behavior change. Social cognitive theory concepts are combined with strategies derived from recent applications of the Transtheoretical Model to the area of physical activity (e.g., consciousness raising and other cognitive approaches in the preparation and action phases early in the program; reinforcement management and related behavioral approaches in the later phase of the program). These are applied systematically in administering the intervention in this study.

7.1.2. Goals of the Intervention Arms

Participants are randomized to the **physical activity** intervention or to the **successful aging program**. The physical activity intervention is of moderate intensity and consists of aerobic, strength, flexibility, and balance training, with a target duration of 150 minutes per week. However, goals are individualized based on each participant's level of physical fitness and be modified in response to illness, injury, or physical symptoms. Based on our experience, these interventions can be successfully delivered to older individuals, including frail persons, and can result in sustained participation rates and improved physical function.

The purpose of the successful aging group is to control for general levels of staff and participant time and attention, in addition to general secular and seasonal effects that could influence the outcomes of interest.

7.2. Physical Activity Intervention

The physical activity intervention includes aerobic, strength, flexibility, and balance training. **Walking** is the primary mode of physical activity for preventing/postponing the combined outcome of major mobility disability or death, given its widespread popularity and ease of administration across a broad segment of the older adult population.[55;76] Other forms of endurance activity (e.g., stationary cycling) are, however, utilized on a limited basis when regular walking is contraindicated medically or behaviorally. Each session is preceded by a brief warm-up and followed by a brief cool-down period. In light of current clinical guidelines, participants are instructed to complete **flexibility** physical activities following each bout of walking. Moreover, following three bouts of walking each week, participants are instructed during the initial phase of the program to complete a 10-minute routine that focuses primarily on **strengthening exercises.** Strength training will focus primarily on lower extremity physical activities by using variable weight ankle weights and will be followed by a brief lower extremity stretching.

Supplementary instructional materials are supplied to participants in this group, to reinforce the strength training occurring during setting-based instruction, so that it can be generalized to the home environment. **Balance training**[25] is introduced during the adoption phase of the program as a complement to the endurance and strength components. In addition, the intervention involves encouraging participants to increase all forms of physical activity throughout the day. This may include activities such as leisure sports, gardening, use of stairs as opposed to escalators, and leisurely walks with friends.

Intensity of training. The participants are introduced to the activities of the

physical intervention in a structured way such that they begin with **lighter intensity and gradually increase** over the first 2-3 weeks of the intervention. LIFE promotes walking for exercise at a **moderate intensity** and relies on **ratings of perceived exertion** as a method to regulate physical activity intensity.[78;79] Using Borg's scale,[80] that ranges from 6 to 20, participants are asked to walk at an intensity of 13 (activity perception SOMEWHAT HARD). They are discouraged from exercising at levels that approach or exceed 15 (HARD) or drop to a rating of 11 (FAIRLY LIGHT) or below. Lower extremity strengthening exercises are performed (2 sets of 10 repetitions) at an intensity of 15 to 16 using Borg's scale for the strength training component of the program.

7.2.1 Contact Mode and Frequency

The intervention consists of a general weekly walking goal of 150 minutes. This is consistent with the public health message from the Surgeon General's report that moderate physical activity should be performed for 30 minutes on most if not all days of the week (150-210 total minutes). This goal is **approached in a progressive manner** across the first 3 months of the trial. There are multiple ways that the goal can be achieved, based on the physical abilities and constraints of each participant.[25;81] In light of the heterogeneity of the target population (with respect to physical capabilities and health status), this pilot study allows to more specifically define the variability in participants' ability to reach this weekly target, to estimate the dose-response relationship between incremental increases in weekly physical activity and changes in the primary and secondary outcomes, and to better specify the level of ongoing behavioral instruction needed to achieve such changes.

Table 7.2.1. Intervention staff contacts for physical activity group

Week	Center-Based Physical activity	Additional Behavioral Group Counseling Session	Telephone Counseling Contact
Adoption: 1-8	3 times each week	1 Orientation session 3 individual sessions 10 total group behavioral contacts, immediately following a scheduled center-based physical activity session	1 time each month
Transition: 9-24	2 times each week		1 time each month
Maintenance: 25 – end of the trial	Offered Once per week		1 time per month

7.2.2. Participant assessment at baseline

As undertaken in other programs with older adults,[131-133] each participant randomized to the physical activity group receive a 45-minute individualized, face-to-face **introductory session**, during which time the program is described, questions are answered, and results from each individual's baseline assessment is utilized to tailor the program with respect to physical activity progression, to optimize safety and participation.

When participants first enter the physical activity intervention, their **demographic and contact information is** entered into a structured data window that is part of the computerized tracking system. In addition, the computer prompts interventionists to complete **session cards** for participants at each scheduled visit. These session cards include information on attendance, the specific goals for the physical activity prescription,

and the amount of physical activity completed during the visit. In addition, on a weekly basis, interventionists enter the number of steps taken each day during the previous week (self-monitoring using a step counter) and the total number of minutes of physical activity performed each day of the previous week (recorded in logs). In this manner, LIFE can track and promote physical activity that is occurring both at the center and off site.

7.2.3. Intensive Contact Phase

For the first eight weeks, three **center-based** physical activity instruction sessions per week are conducted in a supervised setting. These sessions are used to initiate the walking program and to introduce participants to the strength, stretching, and balance portions of the program in a safe and effective manner. The supervised setting allows instructors to better tailor the program to individual needs and abilities early on, so as to prevent early dropout and to facilitate the building of self-efficacy and support, which have been found to be key to long-term physical activity maintenance.[134] These physical activity sessions involve 40-60 minutes of physical activity instruction.

It is important to implement a stepped-care approach for both prescribing physical activity and proactively promoting adherence to the intervention during the course of the trial. Our initial exercise prescriptions are individualized, based on participants' baseline levels of endurance capacity, strength, balance, and behavioral readiness for the used regimen. Once participants are randomized, the stepped-care model is implemented with the assistance of a computerized tracking system.

7.2.4. Transition Phase (weeks 9-24)

During weeks 9-24 of the program, the number of **center-based** sessions is reduced to two times each week. These are supplemented by **home-based** endurance/ strengthening/ flexibility exercises as a means of promoting physical activity in multiple settings. This is a key feature of sustained physical activity participation among older as well as younger adults.[76] Appropriate community based exercise facilities (e.g., YMCAs; senior centers) are identified for those persons preferring to undertake center-based activities on a more frequent basis throughout the week.

7.2.5. Maintenance Phase (week 25 through the end of trial)

The Maintenance phase consists of:

• Once-per-week **center-based** group physical activity sessions offered to each participant.

• Monthly brief **telephone contact** with each participant, to evaluate progress and provide continuing problem-solving and support around barriers to adherence.

• Quarterly project **newsletters**, used to promote ongoing support and participation and to provide ongoing information related to physical activity participation and adherence.

7.2.6. Educational Modules

The participants receive all of the written material provided from the health education modules provided to the participants in that arm of the study.

7.3. Successful Aging Program Intervention

7.3.1. Contact Mode and Frequency

The successful aging program arm meets in small groups, one time each week for

the first 24 weeks of the intervention. Monthly contacts are offered for the duration of the study. Telephone calls are made after each missed visit to problem-solve barriers to attendance and to encourage regular participation.

7.3.2. General Content and Structure of Intervention Modules

The Successful Aging Program group is based on **successful aging workshop series.** Participants receive information on a variety of topic areas of relevance to older adults (e.g., how to effectively negotiate the health care system, how to travel safely, recommended preventive services and screenings at different ages, where to go for reliable health information, etc.). The program includes an experiential component, in which participants learn how to actively 'take charge' of their health in seeking out appropriate medical information and services.

In addition, to these educational offering a short instructor led program (5-10 minutes) of **upper extremity stretching exercises** is performed during each class. The rationale for this "placebo exercise" activity is that it helps foster adherence to this arm of the study and increase the perceived benefit of the Successful Aging workshop series to the participants without directly affecting the study outcomes.

7.4. Strategies for Keeping Participants Involved in the Intervention

7.4.1. Adherence and Monitoring

Adherence to all scheduled intervention contacts is recorded by interventionists into a tracking system. Overall and site specific reports on adherence are posted on the web and periodically updated. In addition, the Lifestyle Resource Core monitors these adherence reports and provides monthly feedback to each site.

7.4.2. Strategies for Promoting Adherence in The Physical Activity Group

During the **adoption and transition phase** (first 6 months) the primary behavioral techniques include:

1) **Personalized feedback and setting of individualized goals**, based on functional testing that occurs during the initial center-based physical activity session, and based on determination of an individualized physical activity program that is tailored to physical performance test results. Additional regular feedback on level of activity is obtained via use of a pedometer.[135;136]
2) **Specific structuring of expectations** concerning the effects of physical activity, to ensure that subjects' expectations are reasonable and realistic.
3) **Consciousness raising** and similar experiential processes related to the problems of under-activity, and the benefits of adopting a more active, heart-healthy lifestyle (e.g., self-reevaluation processes)[137]
4) The use of a staff-participant **contract** to clarify goals and increase initial participant commitment to the goals. This contract, read and signed by the participant and staff member following random assignment to the physical activity group, restates the responsibilities of both the participant and project staff with respect to the study, and is used to note the specifics of the first several weeks of the intervention (e.g., days, location).[138]
5) Frequent **individual instruction** (via telephone and through the scheduled center-based sessions), support, goal-setting, and feedback with a trained staff person throughout the intervention period, tailored to facilitate each individual's ongoing behavioral participation as well as performance level.
6) Provision of all center-based **exercise equipment** (e.g., exercycles), as deemed appropriate.
7) Distribution of easy-to-read **written materials** to prompt regular and appropriate

participation in the physical activity programs.

8) Instructions to maintain a simple daily **activity log or calendar***,* which details the intensity (rating of perceived exertion),[80] duration, frequency of activities being undertaken, and the number of steps recorded on the digi-walker*.* Such logs have been used extensively in previous studies of older adults and have been found to be brief and easy to complete by older men and women across periods spanning 12 to 24 months.[131-133;139;140] To reduce participant burden and costs associated with mailing physical activity logs back to the clinic, participants record their physical activity behaviors on a simple, easy to use magnetic calendar, which is affixed to the refrigerator. Participants subsequently report this recorded information to clinic staff during each monthly intervention telephone call. This approach has proven to be successful in other physical activity studies that we have undertaken.
9) Instruction in the use of **visual prompts** to encourage and reinforce successful change.[76]
10) Monitoring of **immediate disincentives** to adherence (e.g., discomfort, perceived inconvenience) on the activity logs/calendar, and active brainstorming with staff members via telephone to minimize them.
11) Introduction to **relapse prevention** strategies via telephone, mail, and setting-based contacts by identifying and planning for high-risk situations such as illness, in which early relapse from physical activity programs is likely. This also includes instruction in problem-solving methods and skills to help individuals develop and apply strategies, so that they may overcome barriers to attaining their physical activity goals.

During the **maintenance phase,** which runs from the 6-month visit until the end of the trial, the primary behavioral techniques include:

1) **Regular updating of behavioral and performance-based goals,** to ensure that goals remain realistic yet challenging.
2) Continued **logging** of target behaviors.
3) Further development of plans to keep the regimen **flexible***,* with respect to location, scheduling, and other issues, to accommodate preferences as well as periodic fluctuations in motivation and schedules.
4) Increased instruction in and use of **self-rewards** and other self-control, reinforcement management strategies for behavioral maintenance.[134]
5) Increased practice in the application of subject-initiated **relapse prevention and problem-solving strategies***,* with relevant feedback and support provided by the intervention staff through telephone and center-based contacts.
6) Continued use of **stimulus control** strategies (e.g., visual prompts) to promote maintenance.
7) Continued receipt of **social support** via regular staff telephone, mail, and setting-based contacts.

7.4.3. Strategies to Enhance Participation Rates in The Successful aging program

The following behavioral strategies, which have been used successfully to promote sustained participation in previously studied health education control groups,[132] parallel the behavioral strategies to be used in the physical activity group. These include the following:

During the adoption and transition phase (first 6 months) for the successful aging program group the primary behavioral techniques include:

1) **General feedback** obtained from baseline testing related to overall levels of health and functioning.
2) **Specific structuring of expectations** concerning the Successful Aging curriculum, to ensure that subjects' expectations are reasonable and realistic.

3) **Consciousness raising** and similar experiential processes related to the problems of a poor diet and other health areas (e.g., foot and eye care; medical screening), and the benefits of adopting a healthier lifestyle.
4) Establishing **concrete goals** related to attending the Successful Aging sessions and participating in that intervention throughout the one-year intervention period.
5) A staff-participant **contract** (following randomization) is used to clarify the above goals and expectations and to increase initial participant commitment to the goals. This contract, reviewed and signed by the participant and a staff member, restates the responsibilities of both the participant and project staff with respect to the study, and is used to note the specifics of the first several weeks of the successful aging program intervention (e.g., days, location).[138]
6) Distribution of easy-to-read **written materials** to prompt regular and appropriate participation in the Successful Aging program.
7) All participants assigned to this group are encouraged to attend the Successful Aging Program sessions on a weekly basis, to foster **early 'buy in'** to this intervention group, and to set the stage for continued participation throughout the intervention period. During the latter portion of the initial 6-month period, participants are encouraged to actively participate in choosing topic areas that receive additional focus during the 2nd 6-month period.
8) Similar to the physical activity group, participants assigned to the successful aging program group are encouraged to **track behavior changes** related to nutrition and other areas; they are given relevant homework assignments to complete prior to the next class meeting (e.g., trying specific healthful recipes; undergoing simple pantry checks in their homes; food label reading activities).
9) Participants who miss a scheduled meeting are contacted via telephone by a study interventionist to encourage continued participation in this group and to use **problem-solving** skills to overcome potential barriers to continued participation. All participants in this study group additionally receive a brief, monthly telephone call to encourage continued study participation.

During the **maintenance phase** (6th month through the end of the trial), participants in the **successful aging program** continue to receive support from study intervention staff that relates to participation in the monthly Successful Aging meetings. Those participants who miss a scheduled meeting are contacted to encourage continued participation in this group and to use problem-solving skills to overcome potential barriers to continued participation. Participants are encouraged to actively 'take charge' of their ongoing program experience, with respect to topic areas of interest, guest speakers, etc.

7.4.4. Protocol for Managing Illness/Injury and Other Health Problems

If physical activity is reported to have been suspended due to a hospitalization, injury or other health reason, the participant is asked to come to the center for re-evaluation to determine the level of physical activity for restarting, once it is determined that the health event has resolved. If the health event remains unresolved, monthly calls are made to reassess whether criteria for restarting are met, as described below.

Restarting a suspended physical activity program. Evaluation for restarting physical activity depends on the functional impact of the illness and any activity limitation prescriptions that may have been provided by the participant's health care team, including the primary care physician, surgeon, consultants, or therapists.

a. If, after the illness episode, the participant is able to leave the home and walk independently outside the home with no more assistance than a straight cane, and if there is no prescribed activity or weight bearing-limitation or therapy, reevaluation is

done at the Field Center, and a new physical activity prescription begins. The same protocol as was used for the baseline program prescription and progression is used.

b. Regardless of ability to leave the home, if after an acute illness and suspension of physical activity the participant is under prescribed activity or weight bearing limitation or rehabilitative treatment, re-evaluation is made at the end of the activity limitation prescription or treatment course.
c. If the physical activity is specifically limited due to chest pain or dyspnea, physical activity is suspended and is not restarted without definitive treatment by the participant's health care provider. In some of these cases, the primary care physician may refer the participant to a medically supervised rehabilitation program. When this occurs, the intervention staff attempts to obtain information on what the participant is doing in the rehabilitation program so that this information can be added to study records.
d. If the participant remains unable to leave the home under the conditions prescribed above, and is nearing the end of a six-month assessment window, a home examination is done at the required interval to assess for study endpoints. A similar protocol is used for the control group.

Individualizing restart of physical activity after illness or injury episode. The physical activity program is adapted to the assessed level of ability. This is the same protocol as the baseline starting protocol for individualizing the start of physical activity. A special remedial program is provided for those who fall below the original starting criteria for enrollment.

Individualizing goals when physical activity is reduced because of illness or injury. If there is an illness episode that does not meet the above criteria for suspension of the physical activity program, reduction in physical activity may still occur, and is detected by either the tracking system, observation by staff, or self-report at a center visit. Physical activity goals are re-adjusted on an individual basis. Re-assessment or need for special attention and individualization is performed at the field center. All injuries are reported to the Medical Safety Committee. Rehabilitation staff and primary care physicians may also be consulted as needed.

8. Participant Safety and Confidentiality

The study monitors the medical safety of participants. One aspect of this monitoring is to evaluate potential volunteers at screening to determine whether it is safe for them to participate in the planned intervention. Another aspect is monitoring of safety during study assessments. A third area is safety during physical activity, both supervised and unsupervised. Also, if a volunteer has a medical or surgical illness, the safety of continuing or resuming participation in interventions is ascertained by the medical staff at the local center in cooperation with the participant's primary care physician, Finally, the study monitors adverse events, assess their potential relationship to the intervention and report events to the Data Safety Monitoring Board (DSMB).

8.1. Data Safety Monitoring Board

A **Data Safety Monitoring Board (DSMB)** is established, with responsibility to monitor all aspects of the study. The **Medical Safety Committee** reports to the DSMB for issues related to participants safety.

The DSMB has the following charges:

- The initial task of the DSMB is to review the entire study protocol and the informed consent form with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing of subject records, and quality control and analysis plans, and to identify needed modifications. The DSMB then identifies the relevant data parameters and the format of the information to be regularly reported.
- Review data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, forms completion, intervention effects, gender and minority inclusion and subject safety.
- Identify problems relating to safety over the course of the study. Inform study PI via written report, who, in turn, ensures that all Field Center PIs receive this report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- Make recommendations regarding recruitment, treatment effects, retention, compliance, safety issues and continuation of the study.
- Send the Program Administrator and PI written reports following each DSMB meeting. These reports may address all (blinded) issues reviewed by the DSMB. The PIs then send the DSMB report to their respective IRBs.
- The study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs.
- At any time, the DSMB may recommend discontinuation of any component/treatment group of the study for any of the following reasons:
    1) Compelling evidence from this or any other study of an adverse effect of the study treatment(s) that is sufficient to override any potential benefit for the interventions to the target population.
    2) Compelling evidence from this (or any other) study of a significant beneficial effect of the study treatment(s), such that its continued denial to other study group(s) would be unethical.
    3) A very low probability of addressing the study goals within a feasible time frame.
- The DSMB may convene an executive session at any time.

Finally, the NIA makes the final decision on whether or not to accept the DSMB's recommendation about discontinuation of any component of the study. Any serious

adverse events that might be due to the study intervention are reported to the DSMB, the IRB and to the Project Office.

8.2. Medical Problems Detected During the Study Assessments

Medical problems that increase risk of study participation are assessed through structured telephone interviews and in person physical examinations during the initial subject evaluation, prior to randomization. The goal of these assessments is to detect conditions by history, such as recent major surgery, symptomatic conditions such as angina or weight bearing pain and asymptomatic conditions, such as valvular heart disease or abdominal aortic aneurysms. Such persons are excluded from further participation and are referred to their primary physician for further care.

8.3. Safety Considerations for Study Assessments

All study assessments are done by trained and certified staff. Safety precautions are taken during the 400 m walk test by applying standardized stopping criteria. If the participant reports chest pain, tightness or pressure, significant shortness of breath or difficulty breathing, or feeling faint, lightheaded or dizzy the test is stopped. During the baseline 400 m walk tests, a fully stocked crash cart is available with all necessary emergency equipment (drugs, defibrillator, airway management), and practice codes are conducted with staff every other month to handle medical emergencies. On-site staff trained in advanced cardiac life support, is available to deal with medical emergencies. Also, institutional and community EMS services are activated if needed.

It is anticipated that some medical problems occur during the course of the study while some participants are in the clinic. The following is a summary of a plan of action based on level of acuity of the problem.

Emergent problems and problems that are life threatening or require life saving attention should be dealt with using the local Emergency Medical System (EMS). Clinical staff may provide basic life support as an interim measure when appropriate until EMS personnel arrive. CPR training is recommended but is not required. The study staff is responsible for notifying the participant's family or designated contacts and the participant's primary care provider.

Urgent medical problems and problems that require immediate attention but that do not require life saving attention are dealt with by taking measures to ensure the participant's comfort and offering first aid, as appropriate. Disposition plans should be made with the participant, clinic staff, investigators, family, and primary care provider. The clinic staff may arrange transportation of the participant to another medical care site for definitive care. The primary care provider and family or designated contacts should always be notified.

General medical problems or those problems that require attention when feasible should be dealt with by contacting the primary care provider. The clinic staff should follow the primary care provider's directions regarding disposition and follow-up. The participant should be advised regarding the primary care provider's instructions and documentation of the problem and actions should be placed in the participant's record on a progress note. A follow-up letter to the primary care provider documenting the problem and actions taken should be sent by clinic staff.

8.4. Safety Considerations for the Physical activity Intervention

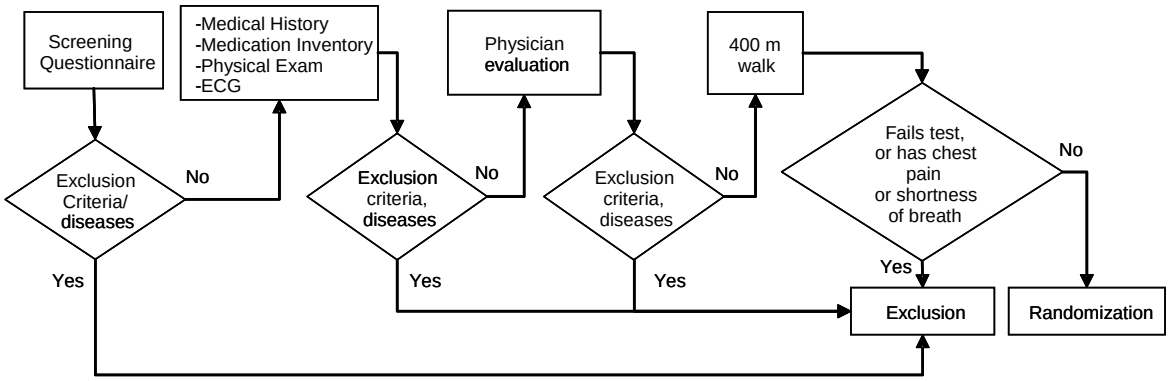
Appropriately designed and implemented physical activity interventions have been shown to be safe and efficacious in older adults.[25;141] The literature on physical activity training in the frail elderly in nursing homes contains no reports to date of serious cardiovascular incidents, sudden death, myocardial infarction, or exacerbation of

metabolic control or hypertension.[142] Also, researchers at the Cooper Institute and the University of Florida have conducted over 26,000 assessments of maximal dynamic strength without one single cardiovascular event.[143] A recent review concluded that an appropriately prescribed resistance physical activity program is a safe form of physical activity for the majority of the population and is associated with minimal risk of cardiovascular events, even in those with previous myocardial infarction or chronic congestive heart failure.[144]

8.4.1. Pre-Physical activity Safety Screening

Appropriately designed and implemented moderate-intensity physical activity interventions, as are being utilized in this study, have been shown to be safe and efficacious in older adults.[54] To maximize the **participants' safety** we follow a standardized screening protocol (Figure 8.4.1.). Accordingly, all potential participants undergo **screening for cardiovascular and other major diseases** by means of a health questionnaire, ECG and physical exam. Those with overt cardiovascular diseases (or other severe diseases) that meet the exclusion criteria as determined by the study physician are excluded. Next, otherwise eligible persons undergo the **400 m walk** test. According to a protocol to evaluate cardiovascular reserve similar to the one suggested by Gill et al.,[145] persons who develop chest pain or substantial shortness of breath during the 400 m walk test are also excluded. Those who are not excluded are randomized to the physical activity intervention group or to the successful aging program.

Figure 8.4.1. Algorithm for screening morbid conditions



Participants do not undergo physical activity stress testing. This decision is based on the following considerations:

- The **recommendations** published in by Gill et al.[145] advised that a screening protocol based on a simple cardiovascular reserve test, similar to the one described above is more suitable for screening older adults than a protocol based on stress physical activity testing.
- The American Heart Association (AHA) and the American College Sports Medicine (ACSM) **joint position statement** advised that "apparently healthy persons of all ages and asymptomatic persons at increased risk may participate in moderate-intensity physical activity without first undergoing a medical examination or a medically supervised, symptom-limited physical activity test".[146]
- The **AHA Scientific Statement** on Exercise Standards for Testing and Training by Fletcher et al., advised that "for older, apparently healthy persons desiring to participate in a low to-moderate intensity activity such as walking, an exercise test may not be required", and that "the role of exercise testing among the elderly (>75

- years) as a guide to identifying the high-risk patient for primary prevention requires further study".[78]
- The majority of older persons (>75%) are **unable to satisfactorily complete** a treadmill exercise test,[147] which makes its utility as a screening tool in the elderly population questionable.
- Older persons have a **high prevalence of ECG abnormalities**,[148] which diminish the diagnostic accuracy of treadmill exercise testing.[149]
- Participants with potential cardiac contraindications to the physical activity program are identified and excluded by means of the **screening** process described above.
- Physical activity of **moderate intensity** is conducted in a **supervised environment**.
- A maximal or near maximal exercise test on a treadmill is an **unpleasant, if not frightening experience**, for sedentary and unfit adults (unpublished data from WFUHS and Cooper Institute). Requiring an exercise stress test may deter older persons from participating in the trial.
- Regular exercise and physical activity **may actually reduce the overall risk of MI and death** among older persons,[48;150] possibly through improvements in cardiac risk factors and overall fitness.[79]

In summary, exercise stress testing provides little additional information, is not necessary to protect the safety of participants, and that is disliked by sedentary and unfit participants. The physical activity intervention protocol also requires that the center-based sessions at the beginning of the study include careful monitoring of cardiac and other signs and symptoms by trained staff.

8.4.2. Safety Measures During Physical activity

Center based interventions are conducted at a central location and all sessions are conducted and supervised by **trained interventionists,** who monitor potential adverse experiences and symptoms. During the physical activity sessions a defibrillator and on-site trained staff are available to deal with medical emergencies. Also, institutional and community EMS services are activated if needed. As indicated previously, participants are taught the importance and proper method of **warming-up** prior to and **cooling-down** following structured activity sessions. If at any point during a physical activity session, participants develop chest pain, shortness of breath, or dizziness, they are instructed to rest and to contact the center and their physicians if these symptoms persist or recur with further physical activity. The implementation of three supervised center based physical activity instruction sessions per week for the first eight weeks, two supervised center-based sessions per week for the remainder of the first 6 months is consistent with the recommendations published by Fletcher et al. for older adults who may have stable cardiovascular disease.[78]

Blood pressure and heart rate are monitored before and after the walking activity at each center-based intervention session, and during the walking at weekly intervals. Blood pressure and heart rate are measured during the walking at each center based session in participants who had experienced any of the following during a previous physical activity session:

- Resting blood pressure systolic $\geq$ 200 mm Hg or diastolic $\geq$ 100 mm Hg
- Decrease in diastolic blood pressure $\geq$20 mm Hg during the activity
- Increase in systolic blood pressure to $\geq$250 mm Hg or in diastolic blood pressure $\geq$115 mm Hg during the activity
- Resting heart rate $\geq$120 bts./min or $\leq$ 45 bts./min
- Increase in heart rate $\geq$90% of age predicted maximum
- Unusual or severe shortness of breath

- Chest pain or discomfort, or heartburn
- Palpitations
- Light headedness, dizziness or feeling about to faint
- A physical activity session had to be discontinued because of other symptoms, excluding musculoskeletal symptoms (e.g., knees, ankles, hips), reported by the participant.

If any of the above occurs, the individuals are instructed to seek their physician's permission before continuing with the physical activity program.
Very few persons are expected to drop out for this reason based on previous experience and cardiac-based exclusion criteria.

Procedures to minimize discomfort include **warm-up and cool-down activities** that include cycling and flexibility exercises. The participants are also introduced to the intervention activities in a structured way, such that they begin with **lighter resistance and gradually increase** over the course of the first 2-3 weeks of the intervention. During the intervention visits, participants are **supervised at all times and instructed** on correct physical activity techniques. Participants are instructed to talk with the interventionists about any muscle soreness.

If for any reason the participant reports an injury, chest pain, shortness of breath, or dizziness, they are referred to their doctor, or the study physician calls the doctor or other health care provider. The participating institutions are in compliance with NIH policies regarding physical injuries resulting from experimentation of human subjects. Trained technicians administer all tests, with an emphasis on the well being of the participant. In addition, specific criteria for **suspending or stopping physical activity** are developed to adjust the program for **intercurrent illness**.

8.5. Adverse Events

Serious adverse events are defined to include: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences if they might jeopardize the participant or might require medical or surgical intervention to prevent one of the outcomes in the definition. An example of this in LIFE is an injurious fall resulting in a fracture that occurred during walking for physical activity.

For LIFE purposes, an **adverse event or experience** is defined as any health-related unfavorable or unintended medical occurrence that happens during the process of screening or after randomization. Certain adverse events may be protocol-defined outcomes (serious fall injury). Minor adverse events are defined as conditions that may be unpleasant and bothersome to the participant, such as sore muscles, but that do not require discontinuing the study intervention or components of the intervention. Examples of minor adverse events include but are not limited to the following: anxiety, fatigue, decreased appetite, insomnia, dizziness, muscle or joint stiffness, muscle strain or soreness, ankle or knee pain, foot pain, and other minor symptoms that may have restricted the participant's usual activities for at least ½ day like a head cold, flu or allergy problems. Minor adverse events should be reported on an annual basis to each site's own IRB.

Potential adverse events for study related activities and interventions are explained to each participant by trained study personnel during the informed consent process. Each participant is instructed to report the occurrence of an adverse event at scheduled data collection times (scheduled clinical exams or phone interviews). Participants also have

access to study clinic personnel at other times to report serious adverse events or concerns about the safety of participating in the LIFE study

Cardiovascular events are assessed using standard protocol measures including ECGs. When a cardiovascular event has occurred, a study physician decides whether it is permissible for the participant to continue interventions. If the LIFE interventions are discontinued for safety reasons, they may be resumed after consultation with the participant's primary care physician.

Serious fall injuries and fractures are assessed using standard protocol measures, including radiographs and hospital records. When a serious fall injury or fracture occurs, a study physician decides whether it is permissible for the participant to continue interventions. If the LIFE interventions are discontinued for safety reasons, they may be resumed after consultation with the participant's primary care physician.

In the LIFE safety monitoring system, participants who report adverse events to any staff person at any time are referred to unmasked medical staff responsible for identifying, recording, and managing these events. Safety-related events are reported in a timely fashion as required by the Data and Safety Monitoring Board and the IRBs responsible for the study. Interventionists and other staff reporting or managing adverse events for safety purposes do not at any time communicate information regarding these events to study assessment personnel.

LIFE maintains an event outcome database that is completely separate and distinct from the safety monitoring system for the intervention group. This is necessary because many of the LIFE staff members are not be masked to intervention assignment, and it is critical that the identification and reporting of serious adverse events for safety reasons not bias the study's collection of outcome data. Thus, for outcome purposes, all LIFE participants are systematically queried at clinic visits or on clinic phone calls scheduled according to the protocol to capture outcome data on study outcomes, medical events, or adverse experiences. This separate outcome database contains solely those adverse events that are reported through these regularly scheduled event interviews conducted by designated outcome assessment staff that are masked to intervention assignment.

8.6. Confidentiality

The information below relates to all collaborating performance sites for the study. Data is used only in aggregate and no identifying characteristics of individuals are published or presented. Results of testing are sent to participant's private physicians if participants agree to this. Alert values for all medically relevant procedures (e.g., ECGs) are developed, and a system is in place to alert study physicians and participants' private physicians, depending on the urgency of the values.

Confidentiality of data is maintained by using research identification numbers that uniquely identify each individual. Safeguards are established to ensure the security and privacy of participants' study records. The information collected from participants in this study has a low potential for abuse, since the data do not address sensitive issues. Nevertheless, appropriate measures are taken to prevent unauthorized use of study information. The research ID number is used. The research records are kept in a locked room in the Field Center. The files matching participants' names and demographic information with research ID numbers are kept in a separate room and are stored in a locked file that uses a different key from that of all other files. Only study personnel have access to these files. After the study is completed, local data are stored with other completed research studies in a secured storage vault.

In compliance with the Health Insurance Portability and Accountability Act (**HIPAA**) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, LIFE accesses personal health information

and **medical records** only after receiving signed **informed consent.** Participants' medical records are obtained, reviewed and abstracted. Such records are in a locked cabinet that is separate from other files cabinets and that uses a different key from that of all other files.

Biological samples repository

LIFE complies with the OHRP requirements and guidelines related to the research use of stored biological samples as stated in "Issues to consider in the research use of stored data or tissues" from the OPRR. (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm). The repository is subject to the oversight of the WFUSM IRB which reviews and approves the protocol, training documents, and an informed consent document.

Use of stored blood samples by other investigators. Blood samples may be used by investigators other than the investigators of the current study. The use is limited to non-commercial purposes.

Storage and disposal of biological material. DNA and other blood components are stored at WFUHS for up to 20 years after study completion after which time all samples will be destroyed. All specimens have numerical samples IDs with no personal identifiers.

9. Feasibility Evaluation and Stopping Rules

9.1. Feasibility Evaluation of Definitive Trial

The LIFE Study pilot is designed to provide information that informs the development of feasibility criteria for the planned definitive trial. Critical to this is quantifying relationships between measures of adherence and principle trial outcomes. These relationships allow the identification of benchmark levels of adherence that appear necessary to produce desired levels of outcomes.

No explicit feasibility criteria are established for The LIFE Study pilot, however the progress of The LIFE Study group and the study's potential of attaining its goals is regularly evaluated by the Data and Safety Monitoring Board. This committee reviews and provides feedback to the NIA on the overall performance of the study group, including its success with respect to goals for recruitment, retention, and data quality.

9.2. Stopping Based on Safety Concerns

At each meeting, the DSMB reviews data on adverse events and other safety issues to make an overall recommendation to the NIH concerning the safety of continuing The LIFE Study pilot. Consistent with NIH policy, each Field Center Principal Investigator receives a report summarizing the DSMB review of the adverse event data. Field Center Principal Investigators are responsible for providing this report to the IRB.

10. Assessment Schedule and Outcomes Ascertainment

10.1. Summary of Baseline and Follow-Up Assessments

The schedule of clinic visits, procedures and assessments is summarized in Table 10.1. Further details of the procedures and assessments schedule are summarized in Appendix D.

Pre-randomization screening visits. The preliminary phone screen focuses on inclusion and exclusion criteria. Those who qualify are invited for the first two clinic visits (Visits 1 and 2.) At Visit 1, participants are asked to give the informed consent before any study procedures are performed. Participants are administered the SPPB EPESE[69] battery and the 400 m walk to further assess study eligibility. A personal interview is administered, which focuses on medical history, inclusion and exclusion criteria, socio economic, and health-related factors, physical activity and physical disability questionnaires. Medication use is assessed. Participants undergo measurement tests for blood pressure, pulse rate, anthropometric measures, cognitive testing, a physical exam, and a physician evaluation. The 400 m walk test is administered after the study physician has reviewed all medical assessments, including physical exam, medical history, medication use, and ECG. The 400 m walk can be administered either at the end of Visit 1 or at Visit 2. Participants who meet entry requirements are then invited to join the study and, if they agree, receive detailed instructions for the one-week behavioral run-in. During this period, prospective participants are asked to self-monitor specific behaviors, such as diet, to respond to a clinic visit, and to complete mock forms similar to those used in various phases of data collection. Compliance with the behavioral run-in is assessed at Clinic visit #2. Participants who fail the preliminary tasks are not considered for randomization. Those that continue to qualify have an ECG and a blood draw for assays to be done in future studies. Questionnaires including the HRQL and tests of physical performance are also administered.

To ensure blinding of the assessment staff to intervention assignment, the randomization is performed by staff members that are not involved in the assessments.

Clinic follow-up visits occur every six months as summarized in Table 10.1. To minimize participant burden, HRQL questionnaires, hand grip strength and blood collection are assessed only at the 6- and 12-month follow-up visit. Cognitive function batteries are assessed only at the 1-year visit at Wake Forest and Stanford. The 18-month visit is done only in participants who are recruited early in the study.

The **close-out** visit occurs for participants who did not receive a follow-up visit in the past three months. Every effort is made to conduct the study visits in the clinic. If participants are unable to come to the clinic according to the time frame of 8 week window, the assessments are done in home or institution visits. If participants are not available for in-person visits, personal or proxy telephone interviews are conducted.

End-point Follow-up. Those achieving end-point at the last visit are re-contacted 6 months later to look at persistence of end-point status.

Safety monitoring. Safety is assessed at each clinic visit by in-person interviews and by means of quarterly telephone interviews.

Table 10.1. LIFE Assessments Schedule

Table of Assessments Schedule

Visit type	Scr	Scr	Rnd	Tel	Fu	Tel	Fu	Tel	Fu/Cls	End	Nsv
Visit Code		SV1	SV2	F03	F06	F09	F12	F15	F15/F18		
Clinic or Home Visit number		1	2		3		4		5	6	
Telephone call	1			2		3		4			
Week number		-2	0		26		52		78	65-91	
Activity/assessment Month number		-0.5	0	3	6	9	12	15	15/18	18/21/24	
Form name											
Verbal Consent	x										
Telephone screener	x										
SPPB Consent		x									
SPPB Battery		x			x		x		x		x
Informed Consent		x									
Contact Information		x									
Demographic, social, economic		x									
BP, Radial Pulse and Weight		x			x		x		x		x
Waist Circumference		x			x		x				
Body Height		x									
Medication inventory		x			x		x				
Medical, hospital admission history		x									
ECG		x									
Physical exam		x									
Disability Questionnaire		x		x	x	x	x	x	x	x	x
400 M Walk Test *		x			x		x		x	x	x
Process measures		x			x		x				
MMSE Exam		x									
Quality of well being (CEA)			x		x		x				
Health care utilization (CEA)			x		x		x				
Study Eligibility Checklist (Run-In Review)			x								
Phlebotomy/Blood Processing			x		x		x				x
CHAMPS battery			x		x		x		x		
Grip strength			x		x		x				
Lateral Mobility Task			x		x		x				
Blouse/Shirt Test			x		x		x		x		x
Health Related Quality of Life (HRQL)			x		x		x				
Late Life Disability Questionnaire			x		x		x				
400 M Walk Proxy					x		x				
Proxy ADL Questionnaire					x		x				
Assistive Device Questionnaire							x				
Updated contact information					x		x		x		x
Cognitive Tests			x				x				

* The 400 m walk test can be administered either at the end of SV1 or at SV2

10.2. Primary Outcome Measure: Major Mobility Disability or Death

The primary outcome for the full-scale trial is time to the onset of the combined outcome of major mobility disability or death. Mobility disability is determined by the objective 400m walk or by adjudicated evidence that the individual could not perform the 400 m walk. The objective component of major mobility disability is defined as the inability to complete a 400 m walk test within 15 minutes without sitting and without the use of an assistive device (including a cane) or the help of another person. Individuals who complete the walk in more than 15 minutes have an extremely slow pace (<0.45 m/sec), which would make their walking capacity of little utility in daily life.[67] Major mobility disability is assessed every six months by staff who are blinded to the intervention.

10.2.1. Time Frame For Follow-Up Assessments Of The Major Mobility Disability Outcome

The primary and secondary outcomes are assessed at baseline and at semiannual follow-up visits. Participants receive a modest payment for each assessment and are provided with transportation to the assessment clinic as needed. If the participant is unable or unwilling to come to the clinic, the assessment is done in the participant's home or institution. Every effort is made to personally interview and assess all participants. Telephone interviews are conducted in the event that personal assessments are not possible. Some flexibility is needed to account for occasions when participants are not readily available to complete the outcomes assessment, e.g., during acute care hospital admissions. To minimize the possibility of missing an assessment, the following protocol is followed:

1. At the time of enrollment, 2 persons are identified (names, addresses, phone numbers) who do not live with the participant and who would likely know the whereabouts of the participant if he/she could not be contacted for a follow-up assessment;
2. For each follow-up assessment, LIFE allows a 4-week window for completion on each side of the "anniversary" date (for a total of 8 weeks); the time between assessments is no shorter than 5 months and no longer than 7 months;
3. If the participant is acutely ill, is in the hospital, has a temporary condition that interferes with walking capacity (for example, ankle sprain or foot surgery), or is otherwise unavailable, LIFE attempts to complete the assessment at another time within the 8-week window; if possible, LIFE waits at least one week after an acute illness or hospital discharge to complete the assessment;

Since participants who are acutely ill may subsequently die, LIFE attempts to determine their self-reported major mobility disability during the initial contact, to minimize potential losses to follow-up; this information is used if the participant subsequently dies or refuses to complete the follow-up assessment. Proxy respondents are also used during follow-up to assess the mobility status.

10.2.2. Persistent Mobility Disability

Participants who achieve the mobility disability outcome during the "final" assessment (i.e. at 12 or 18 months) are reassessed six months later (i.e. at 18 or 24 months) to determine whether the mobility disability is persistent. This reassessment includes only the 400-meter walk test and self-reported function and disability.

10.3. Secondary Outcome Measures

These outcomes of interest include **physical performance, disability, cognition, health related quality of life, falls, cardiovascular disease, and cost-effectiveness**.

10.3.1. Self-Reported Function And Disability

For the purpose of the pilot study, the primary measure of self-reported function is based on the 25-item, self-report disability questionnaire described earlier.

In addition, for the basic ADLs the participant is also asked whether the participant receives help from another person to complete the task. This allows calculation of a Katz ADL score. Finally, the Late Life Disability questionnaire developed by Dr. Jette and colleagues is administered.[102;103] This instrument includes 16 tasks representing a broad range of disability indicators and was developed using more contemporary psychometric techniques.

10.3.2. Short Physical Performance Battery (SPPB or EPESE Battery)

The SPPB, originally developed for the Established Populations for the Epidemiologic Study of the Elderly (EPESE) is a brief performance battery based on timed short distance walk, repeated chair stands and balance test (as described by Guralnik et al.)[66;86;68;69;87;88]. The capacity to put on and button a blouse/shirt is also tested. For the task of putting on and buttoning a blouse/shirt, the time to perform the task is measured as well as the capacity to perform the task is assessed. These tasks are also used to objectively assess the capacity to perform basic activities of daily living. The time for performing the lateral mobility task is also assessed at the Wake Forest site only.

10.3.3. Serious Fall Injuries

Serious fall injuries include only those falls that result in a clinical, non vertebral fracture and/or lead to hospitalization. Falls that meet these criteria are associated with the greatest morbidity and costs.[151] Criteria for serious fall injuries do not include other adverse consequences of falls, e.g., non-fracture injuries that do not lead to hospitalization, restricted activity, fear of falling, etc.

10.3.4. Cardiovascular disease outcomes

Combined cardiovascular events, including **acute myocardial infarction, stroke, hospitalization for heart failure, coronary artery bypass surgery, coronary artery angioplasty or stent placement, abdominal aortic aneurysm rupture or repair, carotid endarterectomy, and cardiovascular death, are** assessed by abstraction and review of medical records.

Incident hypertension is also ascertained as a secondary outcome. This is ascertained at the quarterly clinic visits by a question regarding new physician diagnosis of hypertension, self report of a new medication for hypertension or by three consecutive visits with BP over 140 systolic or 90 diastolic. **Change in blood pressure** is also assessed as a continuous variable.

10.3.5. Cognition

Cognitive function is assessed at baseline and at the 12-month follow-up in at the Wake Forest University site and at the Stanford site. The LIFE Study evaluates a variety of cognitive functions including memory and executive function using the following assessments:

1. Digit Symbol Test (DSST)[107] as a measure or attention and perceptual speed.[108] Subjects are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 1 minute.
2. Modified Stroop Test[109] as a measure of complex speed of processing. This test consists of three subtasks: color word naming, color naming, and naming of color words printed in a different color.

3. Teng Mini-Mental Status Exam (3MS)[110] as a measure of a broad variety of cognitive measures. This is an expanded 100 point version of the original Folstein MMSE.
4. Rey Auditory Verbal Learning Test (RAVLT)[111] as a measure of verbal learning and memory. A target list of words is presented and participants are asked to recall (both immediate and delayed) as many words as possible.

10.3.6. Health-Related Quality Of Life

1. The following key components of HRQL is assessed at baseline, 6 months and after one year of follow-up:
2. Depressive symptomatology is assessed with the Center for Epidemiologic Studies Depression Scale (CES-D),[112] a 20-item scale with four answer categories, queries about depressive symptoms experienced in the previous week.
3. Sleep quality is assessed by means of the 5-item Women's Health Initiative Insomnia Rating Scale,[113;114] which PSQI assesses sleep latency, duration, efficiency and disturbances.
4. Energy and fatigue level is assessed by the 6 fatigue and energy items from the Modified Exercise-induced Feeling Inventory.[115] Each item is rated on a 6-point, which focuses on the amount of time that individuals experienced fatigue or energy related feelings during the past week.
5. Pain is assessed using the 12-item pain scale as used in the FAST[25] and ADAPT[94] physical activity trials. This pain scale assesses both the intensity and the frequency of pain during transferring and ambulation/ climbing activities and has been validated in an older disabled sample.[116]

10.3.7. Cost Effectiveness

Quality-adjusted life years (QALYs) are used for cost-effectiveness analysis.[152-154] QALYs integrate mortality and morbidity to express health status in terms of equivalents of well-years of life.

Although there has been considerable interest in measuring cost effectiveness of treatments in old age, the validity of most general preference weighted measures has not been well evaluated in this field. One exception is the **Quality of Well-being Scale (QWB)**, which has been used in several trials with seniors.[123;125;127;152-160] Studies using the QWB suggest that physical activity interventions may produce benefits for older adults at a cost comparable to many widely advocated programs.[161] In this pilot study, the QWB-SA is used as a general outcome measure. In addition to the ease with which QALYs can be calculated from the QWB-SA, the measure allows for specific areas of clinical improvement to be identified among its 58 acute and chronic symptoms.

10.3.8. Acute Care and Nursing Home Admission and Length of Stay

Acute care and nursing home admission and length of stay is assessed by means of self report to questionnaires assessed during follow-up visits and telephone interviews and by reviewing medical records.

10.4. Outcome Adjudication Procedures

10.4.1. Adjudication of the Major Mobility Disability Outcome

Final determination regarding when study participants reach the major mobility disability outcome is made by the Outcomes Committee, using an adjudication process. Final assignment of endpoint requires unanimous agreement by the committee which reviews cases at least every 6 months during the pilot phase. In most instances, the outcome of major mobility disability is readily apparent from the results of the 400 m walk performance test. All subjects who attempt but do not complete 400 m in 15 minutes or

less are categorized (on the day of the assessment) **mobility disabled**. Any individual requiring an alternative assessment has all available records summarized and reviewed by the committee, for determination of disability status. These alternative contacts may include a home visit, telephone interview with participant or proxy, or review of hospital records.

The process of review of all alternative contacts is sensitive to cases of possible disability and minimizes loss-to-follow-up by making use of all available information. The criteria for adjudication of these potential cases as mobility disabled are designed to maximize specificity and minimize bias. There may be some cases where only self-report or proxy-report may be available. LIFE has designed an interview that is quite specific, as compared to performance testing. No self- or proxy-report instrument is perfectly sensitive and specific; hence the primary method of outcomes assessment must be based on objective performance. Those with inadequate information for a definite diagnosis of major mobility disability are considered to be non-disabled for mobility. Some may become mobility disabled by the subsequent visit. Every effort is made to obtain follow-up contact within the required time window using the same methods in both cases and controls. All outcomes assessments are performed by researchers who are blinded to group assignment. The committee is also blinded to intervention assignment. This approach is similar to methods used for adjudication of cardiovascular disease, cancer, dementia, fracture and other health outcomes in RCTs.

Hierarchical Adjudication of Major Mobility Disability

Definite: ANY of the Following:

(1) Primary
Unable to complete 400-meter walk in 15 minutes

(2) Alternative (in home or clinic)
Unable to walk 4 meters without assistance of another person or mobility aid (e.g. cane, walker) OR Unable to complete 4-meter walk test in 10 seconds or less, i.e. gait speed less than 0.4 meter/sec

(3) Alternative (telephone or in home)
(a) Self report of inability to walk across a room (12 ft) without the assistance of another person

Operationally, this criterion is met based on an affirmative response to one or more of the following 2 questions:

(i) respondent answers "unable to do" when asked, "During the past month, how much difficulty have you had walking across a small room because of your health?"

(ii) respondent answers "Yes" to "Do you usually receive help from another person when you walk across a small room";

OR

(b) Proxy report of inability to walk across a room (12 ft) without the assistance of another person

Operationally, this criterion is met based on an affirmative response to the following question:

(i) proxy answers “Yes” to “Does (participant) usually receive help from another person when he/she walks across a small room”;

(4) Alternative (medical record)
Documentation of inability to walk across a room (12 ft) without the assistance of another person or mobility aid (e.g. cane, walker); example of descriptors include: bed-bound or wheelchair-bound, obtunded or moribund, etc.

Possible: Meets Criterion for #1 OR #2

Results for #1 AND #2 also evaluated

(1) Surrogate questions: participant
Answers Yes to Q1 and No to Q2 and Q3
1. Because of a health or physical problem, do you have any difficulty walking a distance of one mile, that is about 8 to 12 blocks?
2. Could you walk up and down every aisle in a grocery store without sitting down to rest or leaning on a cart?
3. Do you think you could walk a quarter of a mile now without sitting down to rest?

(2) Surrogate questions: proxy
Answers No to Q1 and Q2
1. In the past two weeks, has the participant done any walking outside the home? This would include walking in your neighborhood or in other parts of the city/town, walking in the mall or at the gym?
2. Could the participant walk the entire length of an indoor shopping mall without sitting down to rest?

Alternative adjudication approaches may be explored during the conduction or at the end of the LIFE pilot study.

10.4.2. Death

The fact and date of death are confirmed by death certificate. Cause is determined from hospital records, death certificate and informant interview information and coded into major categories of death.

10.4.3. Cardiovascular Disease Outcomes

Cardiovascular disease outcomes are assessed by administration of the outcomes assessment questionnaire at each follow-up contact by staff who are masked to group assignment. The following conditions are assessed by this questionnaire. In addition, all hospital records are screened for codes or diagnoses that might indicate the presence of an unreported CVD event. All deaths are reviewed for cause and adjudicated as a cardiovascular death or other cause. Finally outcomes may be reported as adverse events. Adverse events reported during the routine follow-up visits that are also study outcomes are reported and investigated through the outcomes adjudication process. Adverse events reported during intervention contacts are not investigated as outcomes to avoid ascertainment bias.

Recurrent vs. incident CVD events is classified on the basis of the baseline medical history. The baseline medical history includes questions as to self-report of a

physician diagnosis of any of the above CVD events.

Cardiovascular disease outcomes:

- Acute Myocardial infarction
- Stroke
- Hospitalized Congestive Heart Failure
- Coronary artery bypass surgery
- Coronary Artery angioplasty or stent placement
- Abdominal aortic aneurysm rupture or repair
- Carotid endarterectomy
- Cardiovascular death

The cardiovascular disease events data must be of the highest quality. There are three critical elements: (1) clear and unambiguous definitions for the different types of events; (2) proper training of investigators to apply these definitions and (3) central adjudication for all reported events, to achieve consistency across participating centers. Combined cardiovascular events, including acute myocardial infarction, stroke, hospitalization for heart failure, coronary artery bypass surgery, angioplasty, aneurysm, carotid endarterectomy, and cardiovascular death, are assessed by abstraction and review of medical records. Silent myocardial assessed by ECG was proposed initially but has been dropped as an outcome. Similarly to other large trials, all events are adjudicated by using standardized algorithms.[56]

10.4.3 Fractures

Clinical fractures[162] are defined as fractures involving any skeletal site (except vertebral) that occur after randomization, are diagnosed because of fracture-related symptoms, are reported to the investigators, and are documented by a definite radiologic diagnosis (radiographs, bone scan, etc.). These fractures are ascertained using a protocol[162] that was originally developed by the FIT (Fracture Intervention Trial) investigators and is now being used in the Osteoporotic Fractures in Men Study.

Data are collected on all hospital admissions. These data are reviewed by an expert physician at the coordinating center, who is masked to treatment group, and who identifies hospital admissions that are primarily attributable to a fall injury, including: fractures, head injuries resulting in loss of consciousness, joint dislocations and other serious joint injuries, severe lacerations, serious internal injuries (e.g., retroperitoneal hematoma) and the major sequelae of aging (rhabdomyolysis, dehydration, and hypothermia).

10.5. Ancillary Studies

Proposals of ancillary studies are subject to review by the Emerging Science Committee. The rationale for ancillary studies involving biological samples is presented in the Appendix H.

10.6. Tracking Health Care Utilization and Vital Status, and HIPAA Compliance

In compliance with the **HIPAA** and the DHHS' Standards for Privacy of Individually Identifiable Health Information, LIFE accesses personal health information and **medical records** only after obtaining **informed consent**. Social security number, Medicare number, date of birth, and health insurance information is collected. A proxy respondent and two contact persons are also identified.

Abstraction of hospital records. Participants are asked to notify study personnel about any hospitalization or serious illness. At each clinic visit or telephone contact, participants are questioned about interim hospitalizations. Periodic searches of the Medicare files are conducted to identify hospitalizations missed by regular surveillance. Since any hospitalization may potentially result in changes in activity level or performance, LIFE abstracts minimal information on all hospitalizations (discharge diagnoses, procedures, and length of stay). Hospitalizations are reviewed to assess study outcomes. Cardiovascular events are confirmed by review of ECGs, laboratory results and procedures. For fractures, type of fracture and treatment are verified by review of the medical record. Reports of **death** through regular surveillance or via databases searches are tracked by collecting death certificates and relevant medical records, including autopsy reports if available. For all medical record reviews, standard forms are completed by trained abstractors.

11. Data Management and Quality Control

11.1. Data Management

11.1.1. Field Centers-Screening, Randomization, and Follow-Up Visits

An internet-based, web browser application is used to manage screening, randomization and follow-up visits in this project. Clinics access the study web site and initiate the interactive randomization page. Entry into this area is password protected and encrypted. Once security requirements have been satisfied, a series of questions establish identifying and eligibility information, and a participant identification number is issued. When the randomization session is complete, an e-mail process is spawned and a record of the transaction is sent to the clinic coordinator and the project manager at the DMAQC indicating that the participant has been properly appended to the database.

The ‘Participant Tracking System’ (PTS) is a fully integrated tracking and notification system that advises clinic staff about participant follow-up windows and projects clinic and laboratory workload. Participant tracking begins at randomization and continues automatically throughout the project by integrating participant follow-up data with predetermined follow-up "windows." Reports about protocol deviations are automatically generated and transmitted to the clinic via e-mail attachments. These data are available in the study web site.

11.1.2. Data Entry, Verification and Quality Control

Clinic data coordinators review each set of completed forms for accuracy and completeness. During data entry, key variables are checked for accuracy with the assigned range checks. A review is required for any data entered outside of preset ranges. Override capabilities exist; however these are flagged for review upon receipt by the DMAQC. Through communication with the clinic coordinators, the DMAQC project manager reconciles any responses that continue to be questionable. A random verification pass is performed to detect error patterns and logic flaws. Also, a sample of key forms is double-keyed for entry verification and identification of problem fields/forms.

11.1.3. Core Repository

Biological specimens are sent on a fixed schedule to the Core Repository. The clinic logs each shipment, specifying participant ID and visit sequence in a computerized format. This information includes dates for specimen/test acquisition as well as shipping.

11.1.4. Database Closure

Upon study completion, after all clinic and laboratory data have been collected and filtered through the appropriate quality control procedures, the database is certified. The database is taken off-line and archived. The final datasets are certified and issued version numbers to synchronize analytic efforts, after which they are distributed in accordance with Steering Committee and Institute policy.

11.2. Management of Administrative Data

A Web-based administrative tracking and monitoring system facilitates the flow of information and increases the level of communication within LIFE. Its Web site includes the Study Directory, meeting times and locations, minutes, data reports, IRB status of projects, and other procedural, technical or administrative documents.

11.3. Quality Control (QC)

QC is a shared responsibility of all investigators. The DMAQC takes a vigorous lead in assuring the quality of study databases. The quality and eventual acceptance of all studies depend on issues such as: maintaining randomization integrity, accurately assessing participant eligibility, recording dropouts and adherence, measuring outcome variables without bias, preventing premature release of results, monitoring and assessing protocol adherence, and avoiding biases in the analysis of the results. QC procedures are devised to monitor screening, data collection, follow-up, clinical measurements, collection of forms, data entry procedures, implementation of interventions and overall scientific and leadership operations.

12. Statistical Considerations

12.1. Introduction and Aims

The LIFE pilot study has been designed to investigate the feasibility of a full-scale trial comparing a physical activity intervention of moderate intensity versus a successful aging program intervention in sedentary persons aged 70-<90 years. The LIFE pilot study recruits approximately 400 persons aged 70-<90 years and involves four clinical sites.

The first six primary aims of the LIFE pilot study require statistical analysis. These aims are:

Primary aims:

1. To obtain data with which to project more accurately the needed sample size of the full-scale study by using the rates of major mobility disability (defined as incapacity to walk 400 meters or death), drop-ins, drop-outs, and losses to follow-up.

2. To provide an internal validity verification of the efficacy of the physical activity program by assessing its effects on the Established Populations for Epidemiologic Studies of the Elderly (EPESE) physical performance score, the 4-meter gait speed, the 400-meter gait speed, and a self-reported disability scale.

3. To assess the feasibility, rates of participant adherence and retention, standardization, and quality of the physical activity and health education interventions across the four clinic sites.

4. To assess the rates of intercurrent illnesses that may compromise adherence to the interventions and to examine the feasibility of the intervention protocols to accommodate these events.

5. To assess the feasibility and yields of recruiting this at-risk population in diverse communities and ethnic subgroups, and to refine the recruitment strategies.

6. To assess the psychosocial and health-related early predictors of response and adherence to the physical activity intervention so that the participants who may require increased effort to maximize adherence can be readily identified.

The secondary aims of the LIFE pilot study are to assess the outcome rates and loss to follow-up rates of the outcomes listed below. This information is used to calculate power for determining the sample size of the full-scale study and to select the relative effect size of the physical activity intervention. The secondary outcomes of interest are the following:

1. Onset of self- or proxy- reported and objectively assessed disability in activities of daily living (ADLs);

2. Serious injuries from falls;

3. Combined cardiovascular events; and

4. Acute care hospitalizations and nursing home admissions.

Additional aims of the LIFE pilot study are to assess the variance of the tertiary outcomes

listed below measured and to explore the short-term effect of the intervention on these outcomes. This information is used to calculate power for the full-scale study and to estimate the relative effect size of the physical activity intervention on these outcomes. These outcomes are the following:

1. Cognitive function measures;

2. Health related quality of life (HRQL) assessed by means of depressive symptoms, anxiety, energy and fatigue level, mood, sleep, and pain; and

3. Nursing home length of stay, acute care hospitalization length of stay, and use of health care services.

The LIFE study also assesses the cost-effectiveness of the intervention and health care utilization.

12.2. Analysis Plans

Primary aim 1: *To obtain data with which to project more accurately the needed sample size of the full-scale study by using the rates of major mobility disability (defined as incapacity to walk 400 meters (through objective or adjudicated evidence) or death), drop-ins, drop-outs, and losses to follow-up.*

The 1-year rate of major mobility is estimated as the proportion of participants who were unable to do the 400-meter walk at either 6-months or 12-months or who have died. Ninety-five percent confidence intervals are placed on the rates calculated among participants randomly assigned to each intervention condition. Sensitivity analyses are performed by calculating rates both with and without proxy reports included and through the use of propensity score methods to adjust for non-response. We also estimate the proportion of: education intervention participants who “drop-in” to the physical activity condition through the initiation of a physical activity program, physical activity condition participants who “drop-out” of the intervention, and participants who are completely lost to follow-up. These rates are estimated at 6-months, 12-months, 18-months, and close-out. We examine the consistency of measures and their variances across important subgroups, which allow developing and contrasting recruitment goals for the full-scale trial.

The marginal incidence distributions for the two components of the primary outcome measure (400-meter walk and death) are estimated separately and estimates for the proper cumulative incidence function and the associated confidence intervals for these are constructed. We explore how these components of the primary outcome separately relate to other secondary outcomes and persistent mobility disability by intervention arm to provide additional information as to whether congruous intervention effects are observed for both components of the endpoint.

The following secondary variables are explored for potential use in defining composite endpoints for the full trial:

1. Inability to walk 4 meters without assistance of another person or mobility aid (e.g. cane, walker) *OR* inability to complete 4-meter walk test in 10 seconds or less, i.e. gait speed less than 0.4 meter/sec
2. Self report of inability to walk across a room (12 ft) without the assistance of another person or mobility aid (e.g. cane, walker) *AND* Proxy report of inability to walk across a

room (12 ft) without the assistance of another person or mobility aid (e.g. cane, walker)
3. Documentation of inability to walk across a room (12 ft) without the assistance of another person or mobility aid (e.g. cane, walker); example of descriptors include: bed-bound or wheelchair-bound, obtunded or moribund, etc.
4. Surrogate questions to participant and proxy

To explore the use of the above alternative components of a composite endpoint, a series of supportive secondary analyses are conducted. Specifically, we:

- Determine the sensitivity/specificity of proxy-reports in comparison to observed measures of 400-meter walk performance;
- Evaluate the inter-relationships that measured and self-/proxy-reports have with other measures of disability and risk factors for disability;
- Compare actual measures of performance to adjudicated proxy- and self-report status;
- Estimate the concordance and uncertainty (measurement error) of the adjudication process and identify factors that may predict this discordance for use in developing analysis plans for the full trial; and
- Characterize differences between participants with full and incomplete ascertainment in order to develop plans for potential stratification designs for the full study.

Primary aim 2: *To provide an internal validity verification of the efficacy of the physical activity program by assessing its effects on the Established Populations for Epidemiologic Studies of the Elderly (EPESE) physical performance score, the 4-meter gait speed, the 400-meter gait speed, and a self-reported disability scale*.

Follow-up measures of EPESE physical performance score, gait speed (4 m, 400 m), and self-reported disability obtained at the 6-month, 12-month, 18-month and close-out visits, are compared using mixed effects analysis of covariance models. An estimate of the effect size at 6-, 12-, 18-month and close-out visits is obtained by using a contrast to estimate the difference between mean levels of each outcome between education and intervention groups at each time point. The analyses contain factors used to stratify randomization (e.g. gender), the baseline measure of the outcome, and the intervention group assignment. Further analyses explore for linearity in the trends of response over time.

Primary aim 3: *To assess the feasibility, rates of participant adherence and retention, standardization, and quality of the physical activity and health education interventions across the four clinic sites.*

These analyses focus on both randomized groups. Regression analyses are performed to link changes in the primary and secondary outcomes to the variability in individuals' participation levels in progressing through the program to 150 min. /week of walking. Logistic regression and survival analyses are used for discrete outcomes, such as retention.

Primary aim 4: *To assess the rates of intercurrent illnesses that may compromise adherence to the interventions and to examine the feasibility of the intervention protocols to accommodate these events.*

For analysis of trends in discrete outcomes such as illness at 6-, 12-, and 18-month follow-up and close-out visits, we use both marginal and transitional models for repeatedly measured discrete outcomes. Transitional models allow focusing on rates of intercurrent illness. Both types of models are fit using generalized estimating equations (GEEs) that account for the dependency between repeated measures. Should missing observations pose a problem for these analyses, weighted transitional GEE models are used to look at the sensitivity of estimates to missing observations. We also generate event rates per person-years of follow-up using Poisson regression to generate confidence intervals. These rates help us anticipate safety issues in the full-scale trial and help us design substudies related to cost (we are able to project the volume of hospital records that may be involved).

Primary aim 5: *To assess the feasibility and yields of recruiting this at-risk population in diverse communities and ethnic subgroups, and to refine the recruitment strategies.*

Recruitment yields are calculated by site and ethnic sub-group for all visits leading up to the randomization visit. Such yields are compared to monthly benchmarks that are set according to the trial timeline. Logistic regression are used to determine characteristics of eligible individuals that were randomized vs. those that were eligible, but chose not be participate in the study.

Primary aim 6: *To assess the psychosocial and health-related early predictors of response and adherence to the physical activity intervention so that the participants who may require increased effort to maximize adherence can be readily identified.*

To identify potentially manageable socio-demographic, psychosocial, and health-related factors related to participation in the screening process, agreement to random assignment, acceptance and adherence to the intervention, we collect brief indicators of relevant information at each stage of the study recruitment process. Additionally, persons who meet study eligibility criteria, but who decline to participate or drop out during the trial phase, are given a semi-structured exit interview designed to ascertain both the reasons for disinterest and suggestions for improvement. Regression analyses are used to relate these variables to response and adherence to physical activity.

Secondary Aims:

Data are gathered to assess the outcome rates and loss to follow-up rates associated with the secondary outcomes listed below. This information is used to calculate power and target the relative effect size for the full-scale study. The secondary outcomes of interest are the following: (1) Onset of self- or proxy- reported and objectively assessed disability in activities of daily living (ADLs), (2) Serious fall injuries, (3) Combined cardiovascular events, (4) Nursing home admissions, and (5) Acute care hospitalizations. Estimates of event rates are obtained for each of these outcomes. All estimates are obtained using an intent-to-treat approach. Sensitivity of estimates to loss-to-follow-up is obtained through the use of propensity score techniques. We also use transitional models to investigate the persistence of major mobility disability across 6-month visits.

Other Aims:

We assess the effect of the intervention on the following outcomes measured as continuous variables: (1) Cognitive function, (2) Quality of life assessed by means of

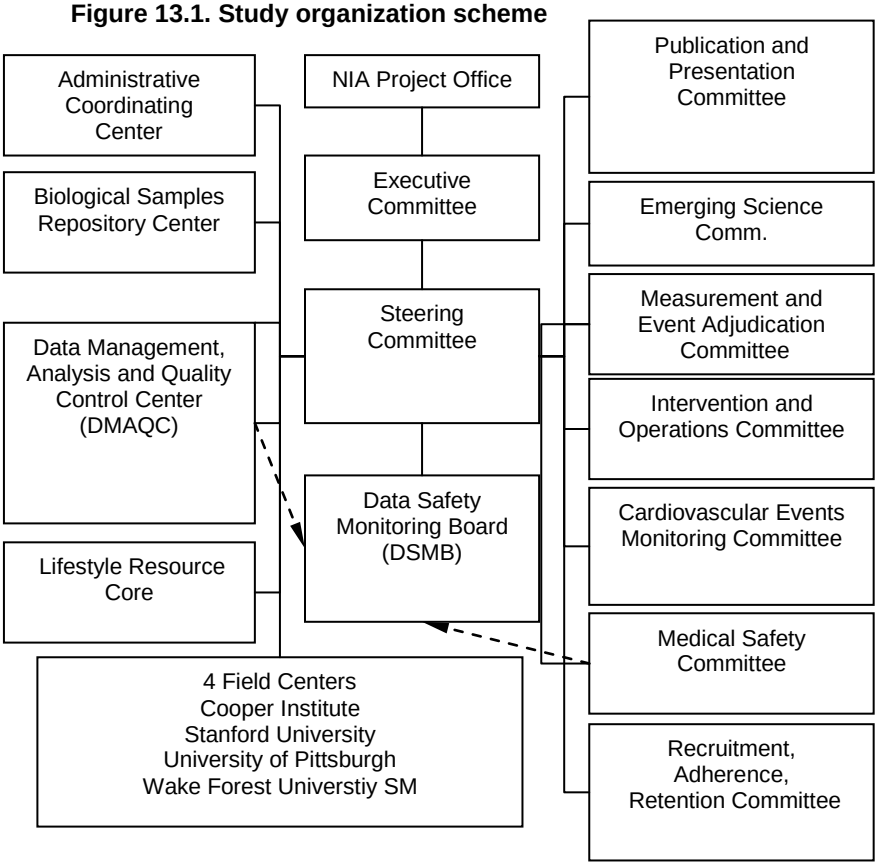
depressive symptoms, anxiety, energy level, sleep, and pain, (3) Nursing home length of stay, acute care hospitalization length of stay, and use of home care services. Mixed effects models, as described for primary aim 2, are used to analyze these repeatedly measured tertiary outcomes. When necessary, transformations of the outcome variables are used to obtain homogeneity of variance and normality of outcomes. Variances obtained from these analyses are used to compute power and target relative effect sizes for the full- scale study.

Cost-effectiveness analyses are conducted following the guidelines of the Panel of Cost-Effectiveness in Health and Medicine. The ratio of direct costs of the physical activity intervention to the amount of QALYs produced is calculated. Health care costs are estimated and differences between the intervention and education groups are calculated to examine whether any cost-offset may occur. The study takes a societal perspective. The study uses the health education intervention as the comparator for all cost-effectiveness analyses. Results are described as the incremental cost-effectiveness over the comparator. Sensitivity analyses are conducted to examine whether the cost-effectiveness results change as a function of any estimates or assumptions made in the process. Decision modeling is used to estimate long-term cost-effectiveness beyond the 1-year time horizon for which data collection is planned. Future costs and health are discounted at a rate of 3% for any calculations or projections beyond the first year of follow-up.

13. Trial Organization

Several centers, cores and committees support key components of the study and ensure its successful conduct and completion (Figure 13.1.).

Figure 13.1. Study organization scheme



The **Steering Committee,** which is charged with the overall governance of study conduct, consists of selected investigators of the Field Centers and other support Centers, and the NIA Project Officers. The Steering Committee approves the final protocols and manuals of operations, supervises the overall execution of the trial, generates and approves study policies, considers modifications of the protocol and study operations, plans and drafts study-related publications, and plans the protocol for the full-scale study. The Steering Committee appoints and charges the subcommittees described below. All major scientific decisions are determined by majority vote of the Steering Committee.

The **Executive Committee** includes the Co-chairs of the Steering Committee, the NIA project officer and one Field Center PI. The Executive Committee functions as the main liaison between the study investigators and the NIA, is responsible for negotiating budgets, the fiscal management of the trial, allocating resources based on pre-set budgets and on performance of individual Field and Support Centers, and evaluating and reporting on progress, timeline benchmarks and deliverables.

The **Administrative Coordinating Center** performs the following tasks:

- Development and monitoring of subcontracts with all sites, matching timelines and deliverables
- Coordination of meetings and conference calls for Committees and Sub-Committees:
- Development of the Manual of Operations (MOP), protocol and intervention materials

- Update the MOP, protocol and intervention materials
- Development of the questionnaires and forms jointly with the DMAQC Center and with relevant sub-committees of the Steering Committee (see below)
- Development of study recruitment materials, jointly with a Centralized Media Group
- Development of systems for communication among Steering Committee and sub-committee members
- Mailing of materials to the Field Centers
- Tracking of equipment and supplies
- Coordination of training and certification of Field Center staff.

The Data Management, Analysis and Quality Control Center (DMAQC) performs the following tasks:

- Development of sample size and statistical analysis plans, including stopping guidelines
- Development of the centralized web-based data management system
- Development and maintenance of the study wide web-based tracking and monitoring system
- Development of the decentralized participant tracking system
- Development of the randomization protocol and procedures
- Development of systems for obtaining data from the ECG reading center
- Generating data quality reports for study sites, Steering Committee and DSMB meetings
- Participating in presentation of blinded and unblinded data to the DSMB
- Monitoring of adverse events
- Monitoring of all QC aspects of data collection, including measurement and intervention reliability
- Reviewing of proposed ancillary study protocols
- Participation in writing teams for manuscripts
- Establishing procedures for ensuring safety and confidentiality of records to meet HIPAA guidelines
- Establishing procedures for archiving and backup of data
- Participation in meetings and calls for all committees

The **Lifestyle Resource Core** serves as the primary group responsible for monitoring the fidelity and quality control of the intervention, training and certifying all project intervention staff involved in the intervention protocols and in operation of the computerized tracking system, and assisting interventionists with problem solving and related adherence strategies throughout the course of the intervention. The team reviews tracking system reports, operates e-mail and phone-based contact systems for assistance with the intervention protocol and provides advice on dealing with problems that arise in delivering the intervention.

The **Biological Samples Repository Center** coordinates and standardizes the collection, processing and short-term storage of blood samples across all Field Centers; coordinates the shipping of biological samples to the centralized repository; ensures the safe and secure long-term storage of the samples; performs genomic DNA extraction and storage; devises training and quality control procedures for the biological samples processing and storage at the Field Centers; and ships the biological samples to the investigators for ancillary study assays.

The **Field Centers** recruit study participants, administer the physical activity intervention and the health education control, ensure retention and adherence of study participants, perform all study related assessments (including complete tracking of outcomes during follow-up), and enter the data into the web-based data entry system. The Field Centers work with all other centers, cores and committees to ensure the accurate implementation of the study protocol and the successful conduct and completion of the trial. The Field Center investigators participate in the study committees, manuscript writing and planning of the full-scale study.

The **Publications and Presentations Committee** (P&P) (a) encourages production of high quality publications and presentations in a timely fashion, (b) encourages broad participation by the study investigators in publications and presentations, and (c) assures accurate maintenance of a database on study publications.

The **Emerging Science Committee** monitors the literature, scientific meetings and input received from colleagues on the cutting-edge science related to topics that are relevant to the project, and advises the Steering Committee on emerging scientific issues that may affect the conduct and future directions of the study. The Committee also reviews plans for ancillary study proposals, including those that involve utilization of biological samples.

The **Measurement and Event Adjudication Committee** refines the assessment protocols, and works closely with the DMAQC Center and the Field Centers to ensure the quality control procedures. The Committee also works with the Cardiovascular Events Monitoring Committee on matters related to such events. The Committee refines and implements strategies for the outcomes tracking and adjudication.

The **Intervention and Operations Committee** finalizes and refines the intervention protocols, and works closely with the DMAQC Center and the Field Centers to ensure the QC procedures and training for the intervention. The Committee develops the Intervention Manual, refines and implements strategies to monitor compliance, and together with the Recruitment, Adherence and Retention Committee, refines and implements strategies to enhance adherence to the intervention.

The **Cardiovascular Events Monitoring Committee** implements protocols for monitoring and ascertaining cardiovascular events, and ensures that the data on cardiovascular disease events are of the highest quality. The committee implements the following: (1) a clear and unambiguous definition of the different types of events; (2) proper training of investigators to apply these definitions and (3) central adjudication for all reported events, in order to achieve consistency across participating centers.

The **Medical Safety Committee** reviews masked study data related to the overall safety of study participation, develops safety reports for the Data and Safety Monitoring Board, addressws IRB issues (related to participant safety) that may arise, reviews clinical practice-related issues and oversees the clinical safety of all study participants.

The **Recruitment, Adherence and Retention Committee** refines and optimizes protocols and strategies for recruitment, adherence and retention of study participants.

A **Data Safety Monitoring Board (DSMB)** monitors all aspects of the study, including those that require access to any blinded data.

14. Study Timeline

The overall duration of the funding period for this pilot study is four years (Table 14.1). The first six months are dedicated to setting up the study, including subcontracting with the field centers, finalizing the manual of operations, standardization of the procedures, development of the web-based data entry and tracking system, training of the field centers, and staff recruitment.

Table 14.1. Trial timeline

Funding Year	Year 1				Year 2				Year 3				Year 4			
Funding year quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Calendar Year	**2003**	**2004**			**2005**				**2006**				**2007**			
Calendar year quarter	**3**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**
Activity																
Centers subcontracts	x															
Manual of operations finalized		x														
Procedures standardization		x														
Web based data entry and tracking system		x														
Field centers training		x														
Recruitment material		x														
Field Centers staff recruitment		x														
Participants recruitment			x	x	x											
Intervention and follow-up			x	x	x	x	x	x	x							
Close-out visit									x							
Data analyses			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Publications preparation						x	x	x	x	x	x	x	x	x	x	x
Preparation of the full scale trial protocol and application										x	x	x	x	x	x	x

Participant recruitment begins in the third quarter of the first funding year and continues for three additional months in the second funding year (Total 9 months of recruitment). All participants are followed for at least one year. Year four is dedicated to data analyses, publications and preparation for the full-scale study.

15. Participating Sites

15.1 Clinical Sites

The Cooper Institute
Dallas, Texas

Stanford University
Stanford, California

University of Pittsburgh
Pittsburgh, Pennsylvania

Wake Forest University Health Sciences
Winston-Salem, North Carolina

15.2 Coordinating Center

Wake Forest University Health Sciences
Winston-Salem, North Carolina.

15.3 Federal Sponsors

National Institutes of Health, National Institute on Aging

15.4 Central Resource Centers

Data Management, Analysis and Quality Control Center (DMAQC)
Wake Forest University Health Sciences
Winston-Salem, North Carolina

Cardiovascular Disease Monitoring
Wake Forest University Health Sciences
Winston-Salem, North Carolina

Biological Samples Repository and DNA Extraction Facility
Wake Forest University Health Sciences
Winston-Salem, North Carolina

Cost Effectiveness Analysis Center
University of California, San Diego
San Diego, California

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Appendix A

Definition of Terms and Abbreviations

ACSM	American College Sports Medicine
ACT	Activity Counseling Trial
ADAPT	Arthritis, Diet and Activity Promotion Trial
ADL	Activities of Daily Living
AHA	American Heart Association
ALLHAT	Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial
BHAT	Beta-blocker Heart Attack Trial
BP	Blood Pressure
CAST	Cardiac Arrhythmia Suppression Trial
CES-D	Center for Epidemiologic Studies Depression Scale
CHAMPS	Community Healthy Activities Model Program for Seniors
CHF	Congestive Heart Failure
CPR	Cardio Pulmonary Resuscitation
CVD	Cardiovascular Disease
DMAQC	Data Management, Analysis and Quality Control
DPHS	Department of Public Health Sciences
DSST	Digit Symbol Test
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EMS	Emergency Medical System
EPESE	Established Populations for Epidemiologic Studies of the Elderly
FAST	Fitness and Arthritis in Seniors Trial
FDA	Food and Drug Administration
FIT	Fracture Intervention Trial
HABC	Health Aging and Body Composition Study
Health ABC	Health Aging and Body Composition Study
HERS	Heart and Estrogen/progestin Replacement Study
HIPAA	Health Insurance Portability and Accountability Act
HRQL	Health Related Quality of Life
IADL	Instrumental Activity of Daily Living
IRB	Institutional Review Board
LIFE	Lifestyle Interventions for Independence in Elders
Look AHEAD	Action for Health in Diabetes
MMSE	Mini Mental Status Exam
NIA	National Institute on Aging
NIH	National Institutes of Health
NYHA	New York Heart Association
OASIS	Observational Arthritis Study in Seniors
PI	Principal Investigator
PTS	Participant Tracking System
QC	Quality Control
QWB-SA	Quality of Well-Being Scale
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomomized Controlled Trial
SHEP	Systolic Hypertension in the Elderly Program

SPPB	Short Physical Performance Battery
TONE	Trial of Nonpharmacologic Interventions In The Elderly
WFUHS	Wake Forest University Health Sciences
WHAS	Women's Health and Aging Study
WHI	Women's Health Initiative

Appendix B

Definition of the Primary and Other Outcome Measures

Primary Outcome Measure: Major mobility disability or death

The primary outcome for the full-scale trial will be time to the onset of the combined outcome of major mobility disability or death. Mobility disability is determined by the objective 400m walk or by adjudicated evidence that the individual could not perform the 400 m walk. The objective component of major mobility disability is defined as the inability to complete a 400 m walk test within 15 minutes without sitting and without the use of an assistive device (including a cane) or the help of another person.

Other Outcome Measures

Serious Fall Injuries

Serious fall injuries will include only those falls that result in a clinical, non vertebral fracture and/or lead to hospitalization.

Cardiovascular Death

The following shall all be defined as cardiovascular death:

- Fatal myocardial infarction. Death within seven days of the onset of documented myocardial infarction.
- Congestive heart failure. Death due to clinical, radiological or postmortem evidence of congestive heart failure without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock to be included.)
- Death after invasive cardiovascular intervention. Death associated with the intervention, i.e., within 30 days of cardiovascular surgery or within seven days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment, or other invasive coronary or peripheral vascular intervention.
- Documented arrhythmia. Death due to bradyarrhythmias or tachyarrhythmias not associated with an acute cardiac ischemic event.
- Death following non-cardiovascular surgery. Death due to cardiovascular causes as within 30 days of surgery or other invasive procedure.
- Stroke. Death due to stroke occurring within seven days of the signs and symptoms of a stroke. (Categories include ischemic stroke, primary intracerebral hemorrhage, subarachnoid hemorrhage, and stroke of unknown type etiology.)
- Other cardiovascular diseases. Death due to other vascular diseases including pulmonary emboli and abdominal aortic aneurysm rupture.
- Presumed cardiovascular death Presumed myocardial infarction, stroke, or other presumed cardiovascular disease cause that did not meet criteria for myocardial infarction, stroke, or other specific cardiovascular disease diagnosis; death certificate consistent with myocardial infarction, stroke, or other cardiovascular cause without other underlying or immediate cause.
- Rapid unexplained cardiovascular death. Unexplained death presumed to be due to ischemic cardiovascular disease or possible stroke of undetermined type, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease and without clinical or postmortem evidence of other etiology.

NOTE: A rapid or sudden unexplained death that does not meet criteria sufficient to classify the etiology as cardiovascular will not be classified as such. Such deaths will be counted in secondary outcome measures of total mortality as sudden death etiology unknown.

Myocardial Infarction

Q-wave myocardial infarction. Myocardial infarction is defined as death of part of the myocardium due to an occlusion of a coronary artery from any cause. The algorithm for classification includes, in comparison to the last ECG, presence of at least one new significant Q wave on a standard 12-lead ECG as defined by the ECG Central Reading Center, and at least one of:

1. Typical symptoms (e.g., typical ischemic chest pain for less than 20 minutes), or
2. Significant elevation of serum enzymes – presence of any one of the following criteria:
    a) elevation of serum troponin (T or I) to a level that indicates myocardial necrosis in the laboratory performing the test
    b) elevation of serum CK MB to twice the upper limit of normal for the laboratory that performed the test
    c) total serum CK at least twice the upper limit of normal for the laboratory that performed the test
    d) Elevation of other enzymes not specified here that become accepted by the scientific community as diagnostic of myocardial infarction shall be added as the Steering Committee deems appropriate.

NOTE: This definition includes as a myocardial infarction a participant with any elevated level of troponin. This is because these participants have an impaired clinical outcome.

Aborted myocardial infarction a diagnosis of aborted myocardial infarction must meet all of the following criteria:

1. Symptoms and ECG evidence for acute myocardial infarction at presentation;
2. Intervention (e.g., thrombolytic therapy procedure) is followed by resolution of ECG changes; and
3. All cardiac enzymes are within normal limits.

NOTE: Participants having ECG findings of acute myocardial infarction and elevated enzymes shall be classified as acute myocardial infarction.

Non Q-wave myocardial infarction Significant elevation of cardiac enzymes with or without characteristic pain in absence of new significant Q wave.

Silent (unrecognized) myocardial infarction. Development of new significant Q waves without other evidence of myocardial infarction (the date of event will be assigned halfway between the date of discovery and last normal /baseline ECG).

Probable non Q-wave myocardial infarction Presence of new and persistent ST-T changes (more than 24 hours in duration) on the ECG with characteristic symptoms of ischemic chest pain without documentation of enzyme elevation.

1. Persistent ST-segment depression $\geq$ 0.05 mV (0.08 seconds after the J-point)in at least two leads in a given location, not known to be old and not in the setting of LVH, or
2. Persistent T-wave inversion $\geq$ 0.3 mV (or pseudonormalization $\geq$ 0.1 mV above the

isoelectric line) in at least three leads not known to be old and not in the setting of LVH.

Non-fatal myocardial infarction after cardiovascular invasive interventions. Myocardial infarction associated with the intervention within 30 days of cardiovascular surgery or within seven days of cardiac catheterization, arrhythmia ablation, or angioplasty, atherectomy, stent deployment or other invasive coronary, or carotid, or peripheral vascular interventions

Non-fatal myocardial infarction after non-cardiovascular surgery Myocardial infarction occurring within 30 days of non-cardiovascular surgery or other invasive procedure.

NOTE: Hospitalized angina that does not meet criteria for any of these myocardial infarction classifications will not be an official outcome for LIFE but will be recorded for the database.

Stroke

The minimum criterion for definite or probable stroke is evidence of sudden or rapid onset of neurological symptoms lasting less than 24 hours or leading to death, in the absence of evidence for a nonstroke cause. Exclusionary conditions for stroke include major brain trauma, neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, vasculitis involving the brain, peripheral neuropathy, hematologic abnormalities, or central nervous system infections. Stroke can be further subdivided into the following etiologies:

Ischemic stroke A diagnosis of definite ischemic stroke requires

1. autopsy or surgical evidence of a nonhemorrhagic (ischemic) infarct of the brain (cerebral thrombosis or cerebral embolism); or
2. evidence from the hospital record of one major or two minor neurologic signs or symptoms lasting at least 24 hours or until the participant died without CT or MRI scan, or lumbar puncture evidence of blood; or
3. deficit lasting more than 24 hours with evidence of brain infarction (mottled cerebral pattern or decreased density in a compatible location). A nonvascular etiology must be absent.

A probable ischemic stroke is defined as one major or two minor symptoms of sudden onset lasting more than 24 hours and CT or MRI findings within the first 48 hours were negative or nonspecific, with no sign of hemorrhage; and a lumbar puncture was done, was traumatic or yielded clear, colorless spinal fluid.

Primary intracerebral hemorrhage A diagnosis of definite primary intracerebral hemorrhage requires

a) an area of increased density indicative of intracranial hemorrhage identified by CT or MRI; or
b) the demonstration of an intracerebral hemorrhage at autopsy or surgery or in the absence of a technically adequate CT or MRI; or
c) the presence of one major or two minor symptoms of sudden onset lasting more than 24 hours, bloody (nontraumatic) or xanthochromic spinal fluid, and evidence from cerebral angiography of a vascular mass without evidence of aneurysm or arteriovenous malformation.

A probable intracerebral hemorrhage is defined as a decreased level of consciousness or coma lasting at least 24 hours and a nontraumatic lumbar puncture with bloody or

xanthochromic spinal fluid, and no or inadequate CT or MRI.

Subarachnoid hemorrhage A diagnosis of definite subarachnoid hemorrhage requires either

1. angiographic identification of a saccular aneurysm as a source of bleeding and bloody or xanthochromic spinal fluid; or
2. CT or MRI findings indicating a blood clot in the fissure of Sylvius, between the frontal lobes, in the basal cisterns, or within a ventricle, with no associated intraparenchymal hematoma; or
3. Autopsy or surgical procedure that uncovered a bleeding saccular aneurysm.

A probable subarachnoid hemorrhage requires

1. angiographic evidence of a saccular aneurysm identified as the source of bleeding and the lumbar puncture was not done, was traumatic, or was missing; or
2. within a few minutes or hours onset there was evidence of a severe headache, meningeal irritation (neck stiffness), depressed or loss of consciousness, or retinal hemorrhages, and the spinal fluid was bloody or xanthochromic.

Stroke of unknown type etiology This is defined as a definite stroke of unknown etiology when CT, MRI, or autopsy is not done. Information is inadequate to diagnose ischemic (infarction), intracerebral hemorrhage, or subarachnoid hemorrhage.

Major stroke symptoms are hemiparesis of two or more body parts, homonymous hemianopia, or aphasia. Minor stroke symptoms are diplopia, vertigo or gait disturbance (both together are one minor symptom), dysarthria, dysphagia, dysphonia, or unilateral numbness of two or more body parts.

Non-fatal stroke after cardiovascular invasive interventions Stroke associated with the intervention within 30 days of cardiovascular surgery, or within seven days of cardiac catheterization, arrhythmia ablation, angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

Non-fatal stroke post non-cardiovascular surgery Stroke occurring within 30 days of non-cardiovascular surgery or other invasive procedure.

Total Mortality
Death by any cause (including cardiovascular disease) contributes to the secondary outcome measure.

Coronary Artery Bypass Grafting and/or Percutaneous Coronary Angioplasty/Stenting
In general, the original report of the procedure should be reviewed rather than accepting references in discharge summaries to results of the diagnostic or therapeutic procedures. If the original full reports are not available, convincing reference to the procedure results in the discharge summaries will be acceptable.

Hospitalization for Congestive Heart Failure (CHF)
Criteria for CHF were adapted from the Women's Health Initiative (WHI). Information necessary to apply the Framingham Heart Study (FHS) criteria will also be collected. LIFE

will identify only in-patient diagnoses of heart failure. The adapted criteria for CHF are:

a) CHF diagnosed by physician and receiving medical treatment for CHF (for instance, diuretics, digitalis, vasodilators, beta-blockers or ACE inhibitors) while hospitalized
b) Pulmonary edema \ congestion by chest x-ray
c) Dilated ventricle or poor left ventricular function (e.g., wall motion abnormalities) by echocardiography, radionuclide ventriculogram (RVG)/multigated acquisition (MUGA), or other contrast ventriculography, or evidence of left ventricular diastolic dysfunction.

For subjects said to have "heart failure," reviewers will check all criteria that apply. This approach has the advantage of permitting easily a range of analyses based on definitions of heart failure that include "soft" criteria (#1 only) or various types of "hard" criteria (#2-3). In general, the original report of the procedure should be reviewed rather than accepting references in discharge summaries to results of the diagnostic or therapeutic procedures. If the original full reports are not available, convincing reference to the procedure results in the discharge summaries will be acceptable.

The NHLBI recommends the Framingham criteria as the "standard" criteria for epidemiologic studies. For Framingham, CHF is defined as the presence of two major criteria or one major and two minor criteria. The major criteria are: paroxysmal nocturnal dyspnea or orthopnea, neck-vein distension, rales, cardiomegaly, acute pulmonary edema on CXR, S3 gallop, increased venous pressure > 16 cm of water, circulation time > 25 sec, heptojugular reflux, or weight loss on CHF Rx of 10 lb in five days; and the minor criteria include ankle edema, night cough, DOE, hepatomegaly, pleural effusion, vital capacity decreased from one third of maximum, tachycardia (rate of < 120), or pulmonary vascular engorgement on chest x-ray. The Framingham investigators have updated their criteria to include laboratory tests such as ejection fraction, cardiac index, filling pressure, valvular heart disease, and left ventricular hypertrophy. The current Framingham algorithm now integrates the clinical and laboratory measures.

Though the adapted WHI criteria will be used to adjudicate heart failure, the Framingham criteria have been reviewed and incorporated into the LIFE data collection forms. The only exceptions are those that are not available in contemporary medical records or those that require autopsy results: (1) increased venous pressure (> 16 cm water); (2) decrease in vital capacity by one-third; (3) pulmonary edema, congestion, cardiomegaly, or left-ventricular hypertrophy on autopsy. With the data collected, we will be able to reconstruct the Framingham definition of heart failure.

Carotid Endarterectomy

In general, the original report of the procedure should be reviewed rather than accepting references in discharge summaries to results of the diagnostic or therapeutic procedures. If the original full reports are not available, convincing reference to the procedure results in the discharge summaries will be acceptable

Peripheral Vascular Disease

The options for peripheral vascular diagnosis include:

1. Surgery, angioplasty, or thrombolysis for peripheral vascular disease;
2. Amputation of one or more toes or part of the lower extremity because of ischemia or gangrene; or
3. Surgical or vascular procedure for abdominal aortic aneurysm.

Appendix C

Model Consent Forms

Main Consent Form

LIFE Study: Model script to obtain verbal informed consent for the phone screen

Thank you for calling [**name of institution**] to find out more about the Lifestyle Interventions for Independence for Elders research study. My name is [**interviewer's name**]. The goal of the LIFE study is find out how older people can make changes in their lives that will help them to remain independent members of their communities for a longer period of time. This study is for people 70 to <90 years of age who would probably benefit most from the program, that is, people who don't regularly exercise or receive counseling to improve health practices. The study lasts up to 2 years, and those participating will be asked to join one of two groups: one group will get help to become more physically active and the other group will attend a special program that will provide information on good ways to stay healthy and independent. As part of the study there will be a number of medical and physical tests, and tests of mood and memory. A small sample of blood will also be collected.

Do you think you might be interested in being a part of the study?

{If NO}: Thank you for your time. If you change your mind you can call me back at XXX-XXXX or ask about the LIFE Study.

{If YES}: Before enrolling people in the LIFE study, we need to see if they are eligible. So what I would like to do now is to ask you a number of questions about your health and health habits to see if you can be in the study. You may not feel like you want to answer some of the questions. If so, let me know. Your participation is voluntary. You do not have to answer any questions if you don't want to. You should know that any information you might share including your name and address will be kept strictly confidential and will be kept under lock and key.

Do I have your permission to ask you these questions?

{If NO}: Thank you for your time. If you change your mind you can call me back at XXX-XXXX or ask about the LIFE Study.

Model Consent for the Short Portable Performance Battery Screen (Off-Site)

Lifestyle Interventions and Independence for Elders: LIFE Study

The LIFE study is a research study to find out how older people can make changes in their lives that will help them to remain independent members of their communities for a longer period of time. The study lasts up to 2 years, and those participating will be asked to join one of two groups: one group will get help to become more physically active and the other group will attend a special program that will provide information on good ways to stay healthy and independent. As part of the study there will be a number of medical and physical tests, and tests of mood and memory. Samples of blood will also be collected.

Based on your answers on the phone questionnaire you may be eligible to be in the LIFE study. At this point, however, I would like you to do a short test of physical ability. This test is used to identify people who are most likely to benefit from the study. If you agree to do this test, it does not commit you to be in the study. The test is used to find out if you can go on to the next step of the enrollment process. Before you decide whether or not you want volunteer to be in the LIFE study you will be provided with a full description of the study along with the risks and benefits of participating in it. You will also have an opportunity to ask any questions you might have about the study before making your decision.

The test has three parts: I will see how long it takes you to walk about 13 feet, how long it takes you to stand up from a chair five times without using your arms, and I will see if you can stand in certain ways while keeping your balance. I'll show you what to do and will be nearby to steady you if you need it. The test takes about 5 minutes to complete.

The benefit of doing this test is to find out if you qualify for moving on in the screening process. The only risk associated with this test is a slight risk of losing your balance. I will be here to help you if you are unsteady.

The LIFE study is sponsored by the National Institutes of Health.

There is no cost to you for doing this test.

The results of this test will be kept confidential. Your test result will be combined with others, but your personal results will not be released by the study unless required by law.

Taking part in this test is voluntary. Not doing this test will not result in any penalty or loss of benefits to which you are entitled. However, if you do not do this test you will not be eligible to participate in the LIFE study.

For questions about the study or in the event of a research-related injury, contact the study investigator,

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, you should contact the Chairman of the IRB at

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

Signatures

I agree to this screening test. I have had a chance to ask questions about being in this test and LIFE 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.

_____	
Subject Name (Printed)	
_____	_____
Subject Signature	Date
_____	_____
Person Obtaining Consent	Date

WAKE FOREST UNIVERSITY®
SCHOOL of MEDICINE
THE BOWMAN GRAY CAMPUS

Consent to Participate in Research

LIFE Study: Lifestyle Interventions and Independence for Elders

Sponsor: **National Institute on Aging**
Principal Investigator:

Invitation:

You are invited to participate in this clinical research study because you are:
- between the ages of 70 and 89 years-old, and
- available for to participate in a successful aging program or regular physical activity program.

LIFE is a clinical research study that involves offering lifestyle programs to participants and then collecting information about the effects these programs might have on health and well-being. This information will be used to develop the best possible programs in the future for enhancing improving independence and improving health in older adults in the future.

This consent may contain words that you do not understand. Please ask our study staff to explain any words or information that you do not clearly understand. If you would like to have this form read to you, please ask and the study coordinator will read this form to you.

Purpose
This research study will assess 2 different programs that are designed to enhance improve independence and to improve your health. Measures of health will include physical performance, functional abilities, and, if they occur, fall injuries and other illnesses. The 2 programs being tested are a physical activity program and a successful aging program. Each person will participate in only 1 of the 2 programs. The study will last up to 2 years.

Number of People Who Will Take Part in the Study

A total of 400 men and women will participate in the study. Study sites include Wake Forest University in North Carolina, the University of Pittsburgh in Pennsylvania, Stanford University in California, and The Cooper Institute in Texas. There will be 100 participants at each site.

Procedures

If you agree to participate in this study you will be asked to complete up to 2 screening visits to see if you qualify for the study. If you do qualify, you will be randomly assigned to 1 of 2 groups, a successful aging group or a physical activity group. ***Random assignment means your group assignment is determined by chance, like flipping a coin. You will not be able to choose one group over the other.***

During the time you are participating in the study, there will also be several health follow-up visits either by phone or at the Geriatric Research Center at the J. Paul Sticht Center on Aging located at the Wake Forest University Medical Center.

There may be from 4 to 7 health follow-up visits depending upon when you start the study. If you need transportation to the screening visits or health follow up visits it will be provided. We will not provide transportation to the group programs sessions. Details are provided below on: A) screening; B) randomization and the two study programs; and C) health follow-up visits. We will make every effort to follow the visit procedures in the order they are outlined below; however, it may be necessary at times to make changes to accommodate schedules.

A. Screening Visits

If you are reading this informed consent, you have already signed a preliminary consent and completed a number of physical tasks that include:

1) Standing up from a seated position in a chair 5 times in a row;
2) Standing in 3 positions to assess your balance;
3) Walking for a short distance (about 13 feet);

Now you are ready to complete the next part of the first screening visit.

Screening Visit 1

For this visit you will go to the Geriatric Research Center located at the Wake Forest University Medical Center. At this visit you will learn about the study in more detail. You will be given time to ask questions and get satisfactory answers about the study. Then, you will be asked to sign this informed consent form if you are interested in participating in the study.

Next, we will measure your blood pressure, pulse rate, height, weight, and waist circumference, and then ask you some questions about your ability to do daily tasks. If you continue to qualify, we will ask you to participate in a test of your memory and concentration, ask you some questions about your medical history,

complete an electrocardiogram (ECG) - a painless test that measures the electrical activity of your heart, and give you a physical exam. We will have asked you to bring in all of your medications and other health products that you have used over the previous 2 weeks. We will review what you have brought in and record the names of the medications and health products. The total amount of time for this visit will be about 2 to 2 ½ hours.

The tests you will complete will help us determine if you qualify for the study and whether it is safe for you to participate. If you continue to qualify and still wish to participate, we will ask you to keep track of your physical activity and some of the foods you eat for 1 week, and to complete a questionnaire at home about your health and your healthcare use. We will ask to you to return for a second screening visit at the end of the week.

You will be asked if you would like to participate in the optional fasting blood draw that will be performed at the second screening visit and at the 6 month and 12 month health assessment follow-up visits. You will have time to ask questions and get satisfactory answers before you make your final decision. Your blood will be drawn by a trained LIFE study coordinator during the following regularly scheduled visits: Screening Visit 2, your 6 month visit, and your 12 month visit.

Screening Visit 2

We will ask you to bring the diet and physical activity log and the questionnaire about your health and healthcare use that you completed in the last week. We will then review this information to determine if you are still qualified.

If you agree to participate in the blood draw, you will be asked to fast for 12 hours before your appointment. We ask that you do not eat anything or drink anything but water. You will have about 4 tablespoons of blood drawn from a vein in your arm. After your blood test is complete, we will give you a snack. Following your snack, you will complete the rest of your visit.

Next you will have a DXA scan. A DXA is a painless scan that measures the thickness of your bones and muscles. For more information about radiation exposure in having a DXA, please see the risk section of this document.

Next, we will then ask you to walk about ¼ mile on our indoor walking course at your own pace. After your walk, if you continue to qualify, we will ask you to complete some simple tests of daily physical activities, such as buttoning a shirt. We will ask you some questions about your daily activities and to complete some questionnaires to measure your mood, memory, and concentration. We will collect contact information on two persons who keep up with your whereabouts in case we are unable to contact you, and on someone who is in close contact with you that can answer questions about your ability to walk.

Finally, we will ask you to provide written permission to contact your physician for a copy of your medical records. This visit will last about 1½ to 2 hours.

If you qualify for the study, and still wish to participate, you will be told which of the 2 study groups you will join. Since your group assignment is determined by chance, neither you nor anyone on our study staff will choose which group you will join. Neither you nor the study staff can change your group assignment.

B. Randomization and the Program Groups

A member of the study staff will help you make your first appointment with your study group. You will be assigned to 1 of 2 groups:

1. Successful Aging Group:

In this group you will receive a series of classes, discussions and demonstrations that will provide up-to-date information and cover topics relevant for older adults including information on medications, foot care, traveling, nutrition, and communicating with health care professionals. You will also participate in some upper body stretching activities.
In Months 1-6, sessions will be held once each week and will last for approximately 1 hour.
In Months 7 - through the end of your study participation, attendance at one session per month is required. These sessions will last approximately 1 hour. Also beginning in Month 7, a monthly phone interview will be conducted by a staff member to provide ongoing support and encouragement to you regarding healthy lifestyle behaviors.

2. Physical Activity Group:

In this group you will receive a fitness program consisting primarily of moderate intensity walking activities, lower body strengthening exercises, flexibility, and balance training. For safety, your physical abilities will be evaluated before beginning the program. Your sessions will be planned according to the following schedule, but please note that changes or variations may be necessary due to staffing and facility requirements:

In Months 1-2, group physical activity sessions will occur 3 times per week and last 40 - 60 minutes. These will be held at the main campus at Wake Forest University. In addition, group-based skills training programs will be held for 30 minutes once a week.

In Months 3-6, the group physical activity sessions will decrease to 2 times per week. Home-based physical activity lasting for approximately 1 hour will be required 1 or more times per week. In addition, the group-based skills training will also continue one time per week.

In Months 7 to the end of the study, the group physical activity sessions will be reduced to 1 time per week. Home based physical activity will be increased to 2 or more times per week. You will receive a monthly phone call

from a staff member to review problems and concerns and problem solve barriers to physical activity.

C. Follow-up Visits

Three-month, 9 month and 15 month follow-up phone interview:
One of our staff members will contact you by phone for a 25-minute interview to ask you about how you are doing and to record any health problems you might have experienced.

However, for some people, the study will end near the fifteen-month time. If this is true for you, we will ask you to make an appointment for a 1-1½ hour visit at the Geriatric Research Center, instead of doing the phone interview.

***Six-month, 12- month, and 15 or 18 month follow-up clinic assessment visit*:**

We will ask you to make an appointment for a 2.5 hour follow-up visit at the Geriatric Research Center. At the six and twelve month visits, you will be asked to fast before your appointment. Please do not eat any food or drink anything but water for 12 hours before this appointment. We will collect 4 tablespoons of blood from a vein in your arm. We will provide a snack for you before you continue with your visit procedures.

We will measure your blood pressure, pulse rate, weight, and waist circumference, and then ask you some questions about your ability to do daily tasks. We will ask you to bring any medications and health products you may have taken over the previous two weeks. We and we will record the names of the medications you have taken. them.

We will also ask you to complete a number of physical tasks just like you completed during your screening visit.
s. We will also ask about your mood, overall health, quality of life and about any health problems you might have experienced.

Prior to your 6 and 12 month visits, we will mail you a questionnaire to ask you to complete at home about your health and healthcare use. Also, at your 12 month visit, we will ask you to complete some tests to measure your memory and concentration skills.
At the 12 month visit you will also have a DXA scan just like the one you had at your second screening visit.

24 month visit (if applicable)
We may ask you to come back for a visit that will last about 30-45 minutes. At that visit, we will ask you about your health and ask you to walkcomplete a number of physical tasks such as walking about ¼ mile on our indoor course if you are able.

Alternative Visits

If you are not able to come for one of the follow-up assessment visits, we will ask your permission to visit you at your home. You will complete study procedures and questionnaires similar to your clinic visit.

Possible Risks

There are some potential (possible) discomforts and risks associated with participating in LIFE. You may experience temporary pain, bruising, and a small risk of infection during the blood sample collection process. Only trained staff will be responsible for the collection of blood samples. There is a risk of losing your balance and falling associated with the physical performance-based testing (e.g., the ¼ mile walk test, balance tests, rising from a chair). We will minimize this risk by: (1) safely escorting you to chairs located along the walking course should you become unsteady; (2) following you at a close distance; and, (3) being at your side should you need assistance.

There exists the possibility that certain physical changes may occur during your participation in your physical activity. These include abnormal blood pressure, fainting, abnormal heart beats, and, in rare instances, heart attack, stroke, and death. Every effort is made to minimize these risks by reviewing information about your health and fitness before the testing and activities begin and by closely observing you during the testing procedure. Emergency equipment and trained personnel are available to deal with unusual situations that may arise.

There may be some discomfort in the beginning of the study from increasing your physical activity. The possibilities include, but are not limited to, some muscle and joint stiffness. This stiffness generally subsidesbecomes less bothersome in 1 or 2 days, and is not considered to be serious. You might experience an exercise-related injury such as a strain, sprain, or other injury to your muscles or joints. You might experience minor aliments such as foot pain, anxiety, fatigue, decreased appetite, insomnia, dizziness, or other minor health occurrences such as colds, flu or allergy symptoms. There may be other risks that are currently not foreseeable.

This research study involves exposure to radiation from the DXA scan. The risk of this procedure is small and is similar to that received from clinical x-ray and nuclear medicine studies. The amount of radiation exposure that you will receive from this procedure is equivalent to a uniform whole body exposure of1.5 millirem. Since you will receive 2 DXA scans you will receive a total of 3.0 millirem. This is equal to less than 1% of the amount of background radiation that the average person in the United States receives each year. The annual background radiation the average person receives each year in the United States is 360 millirem. Other than minimal exposure to radiation, there are no risks associated with DXA scans. Please be aware that this radiation exposure is necessary for this research study only and is not essential for your medical care. The potential long-term risk from these

radiation doses is uncertain, but these doses have never been associated with any definite adverse effects. Thus, the risk to you, if any, is estimated to be slight.

Taking part in this research may involve providing information that you consider confidential or private. 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.

Before you start the study, we will ask you to name a person who knows about you and your health. We will ask this person about your ability to walk and if, for any reason, you are not able to answer questions for yourself we will ask this person about any serious health problems you might have experienced.

A committee of health experts who are not connected withcalled the studyData Safety Monitoring Board will be reviewing all study activities at regular intervals to assure that the risks and benefits being described to you are accurate.

Possible Benefits

You will receive health and medical screening examinations and the results will be discussed with you. You will have the opportunity to participate in a physical activity program or successful aging program with professional supervision.
In the future other older adults could benefit from the results of this research. Information gained from this study could lead to improved medical care for them. However, the study staff will not know if there will be benefits to other people until all of the information obtained from this research has been collected and analyzed.

The research that may be done with your blood sample is not designed to help you specifically. There is no personal benefit to you from taking part in this research study. It might help people in the future but it is not known if this will happen. The results of the research done will not be given to you or your doctor. These results will not be put in your health records.

Alternatives to Participation

To obtain health screening evaluations or health related education, you could visit your personal health care provider. You may choose to increase your activity level on your own without enrolling in this study. You may choose to educate yourself about healthful lifestyles on your own.
The choice to let your blood samples be kept for future use is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood samples can be kept for research, you can change your mind at any time. Just contact your study doctor and let him know that you do not want your blood sample used any longer.

Costs to You

There are no costs to you for taking part in this study. All procedures related directly to the study will be paid for by the study. Costs for your regular medical

care, which are not related to this study, will be your responsibility. You are expected to provide your own transportation to all of the group program visits. If needed, we will provide transportation to the Geriatric Research Center for the screening visits and the scheduled health assessment follow-up visits.

Compensation for Study Participation

You will be compensated for your time and transportation costs in the amount of $30 for each screening visit and health assessment visit that you complete at our clinic. The total amount of compensation will not exceed $180. You will receive your compensation by check that will mailed to you after you after you complete the visit. You will need to provide your social security number and sign a federal tax form to receive your compensation. Legally, you can receive compensation only if you are a U.S. citizen, a legal resident alien (i.e., possess a "green" card), or have a work-eligible visa sponsored by the paying institution.

Use and Storage of Blood Samples

As a LIFE participant, you are being asked to participate in a blood sample study. You will be asked to donate a blood sample 3 times during the study. These samples will be stored for up to 20 years under the supervision of Dr. Barbara Nicklas at the Central Blood Repository at Wake Forest University School of Medicine in Winston-Salem, NC. The samples will be used in the future by researchers designated by LIFE to better understand how factors we can measure in your blood relate to physical health, mood, memory and attention, and your responses to the group program. Your name, address, phone number and other personal information will not be disclosed to these researchers.

Some of these samples will be used to look at your genes. Genes contain information about you that you inherited from your parents, and some of these genes may play a role in your health. You may also choose not to participate in the gene portion of the study. All efforts will be made to keep this information (especially genetic information) confidential, but in the unlikely event that this information is released, there is a small chance that it could affect your ability to obtain a job or health insurance.

Please read each of the following sentences and think about your choices. After reading each sentence, place a check mark next to the sentence that describes your choice. If you have questions, please talk to your study doctor or study coordinator.

1. ____ I agree that my blood samples may be kept for use in future research, including gene research, which has been approved by an Institutional Review Board.

2. _____ I agree that my blood samples be kept for use in future research, except for gene research, which has been approved by an Institutional Review Board.

3. ____ I do not agree to have samples of my blood collected.

Significant Findings

You will be told of any significant findings that may occur during the course of this study that could relate to your willingness to continue to participate.

Compensation for Research-Related Injury

If you suffer any adverse experience during the testing, study staff will render first aid and emergency care. The project physician will not provide medical care to you other than during test activities and physical activity supervision. You will need to obtain follow-up care through your primary physician for any concerns that arise as a result of or during the course of the study.

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses.

To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. The Steadfast Insurance Company provides the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim. The Wake Forest University School of Medicine, and The North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call

Voluntary Participation

Participation in the LIFE study is voluntary. You may refuse to participate or may withdraw from the study at any time without penalty. If you decide to withdraw from the study, we request that you notify the Principal Investigator, ____of your decision in writing. At that time, we also request that you complete an exit interview by mail or telephone to determine the reason for withdrawing from the study.

Termination of Study Participation

At the discretion of the Principal Investigator, participants may be discontinued early from this study due to unanticipated circumstances. The investigator and the sponsor reserve the right to terminate the study and discontinue your participation at any time for any reason in order to ensure your safety.

Some possible reasons for withdrawing a participant from the study:

- failure to follow study instructions
- the investigator decides that continuation could be harmful to you
- you need treatment not allowed in the study
- the study is canceled
- other administrative reason

Project Funding

The National Institute on Aging (NIA) funds this project.

Questions

Your signature indicates that the investigators or other members of study staff have answered all your questions about the study and your participation in the study. If you should have additional questions during the course of the study, or if any problems arise, you should contact the Principal Investigator, Steve Kritchevsky, Ph.D. If you have questions about your rights as a research study participant, contact the Chairman, Wake Forest University Health Sciences Institutional Review Board Chairman at

Confidentiality

Only you and the study investigators will have access to your study records and other data obtained from the study, as required by the Privacy Act, 5, U.S.C. 522a. Details from your medical records will be stored on a private computer with an identification number, but your name will not be stored with this information. Information stored on the computer may be seen by LIFE clinic study staff or government staff at the NIA, which fund the study. Your name will not appear in any publications; only group data will be used.
If for any reason you desire to share any and/or all your data with someone else, a signed letter stating your desire to release this information and to whom it should be released will be required.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects. You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Use, Disclosure and Confidentiality of Health Information

Taking part in this research study may involve collecting health information that you consider confidential or private and that directly identifies you. As described in this informed consent document, information from study-related visits, procedures, test, interventions, interactions, questionnaires, or surveys will be collected. In addition, information in your medical/health records may be reviewed and collected. The researchers may also need to discuss your health information with individuals responsible for treating you such as your physician. All the collected information will be used and possible disclosed and re-disclosed to monitor your health status, to measure effects of procedures/interventions, to determine research results and outcomes, and possibly to develop new tests/procedures and commercial products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor the National Institute of Health (NIA) and representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; the General Clinical Research Center, representatives from government agencies such as the Department of Health and Human Services (DHHS) and similar agencies in other countries, other Pepper Center investigators, and the members of the Data Safety Monitoring Board.

All or part of your research related health information may be used or disclosed for treatment, operations or payment related to providing your healthcare. If this research study involves the treatment or diagnosis of a medical condition research related health information may be placed in your medical record and discussed with individuals not involved with the study who are caring for you. This will allow the individuals caring for you to have information about what drugs, tests or procedures you are receiving in the study and treat you appropriately, if you have other health problems or needs. Your research related health information may be disclosed if required by state or federal law. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

Although every effort will be made to keep your research-related information private, absolute confidentiality and protection of your information cannot be guaranteed. If your information is disclosed to a person or entity that is not covered by the federal privacy regulations it may be re-disclosed. Your research-related information may be used or disclosed until the end of the research study. If your research-related information is included in a research database or repository there is no scheduled date at which this information will be destroyed or no longer used. This is because research information continues to be analyzed for many years and it is not possible to determine when this will be complete. You agree to waive access to or review of your research-related information for the period of the

conduct of the research and of the use of the research findings for regulatory purposes. You can access or review your information after this time.

Taking part in this research study is voluntary and you have the right to choose to not sign this form. If you decide not to sign, you cannot participate in this study. You may decide to revoke/end this authorization at any time by providing written notification of your decision. You do this by sending a written notice to the investigator in charge of the study at the following address:

If you decide at any time to revoke your authorization any information already collected will continue to be used to the extent that it has already been relied on for the study, as necessary to maintain the integrity of the research study or as required by law. You will also not be able to continue to take part in the study if you revoke this authorization. Refusing to sign this authorization or deciding to revoke this authorization will not affect you ability to obtain treatment, or payment or eligibility for benefits to which you are entitled. This Authorization has no expiration date. You will receive a signed copy of this form.

Consent to Participate:

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.

Name (Please print) _____

Signature _____

Date _____

Signature of person obtaining consent: _____

Date: _____

Witness: _____

If you decide at any time to end your authorization any information already collected will continue to be used to the extent that it has already been relied on for

the study, as necessary to maintain the integrity of the research study or as required by law. You will also not be able to continue to take part in the study if you revoke this authorization. Refusing to sign this authorization or deciding to rend this authorization will not affect you ability to obtain treatment, or payment or eligibility for benefits to which you are entitled. This Authorization has no expiration date. You will receive a signed copy of this form.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

_____Yes _____ No

If you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in this study will be placed in the NCBH medical record, along with routine medical test results that were obtained at NCBH as part of this study.

Consent to Participate:

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.

Name: (Please print) _____

Signature: _____

Date: _____

Signature of person obtaining consent: _____

Date: _____

APPENDIX D

Summary of Interventions

Intervention staff contacts for physical activity group

Week	Center-Based Physical Activity	Additional Behavioral Group Counseling Session	Telephone Counseling Contact
Adoption: 1-8	3 times each week	1 Orientation session 3 individual sessions 10 total group behavioral contacts, immediately following a scheduled center-based physical activity session	1 time each month
Transition: 9-24	2 times each week		1 time each month
Maintenance: 25 – end of the trial	Offered Once per week		1 time per month

Table Summary of the Successful Aging Program Schedule

Week	Center-Based Workshop	Home activities	Telephone Contact
Adoption: 1-8	1 time per week	NA	1 time each month and as needed to track missed visits
Transition: 9-24	1 time per week	NA	1 time each month
Maintenance: 25 – end of the trial	Offered once per month	NA	1 time per month

Appendix E

Rationale for collection and storage of blood and DNA specimens

Specific Aims

There are several biological mechanisms postulated to lead to physical disability, including declines in alpha-motor neurons and muscle blood flow, decreases in muscle protein synthesis, increases in proteasome activity, declines in growth hormone and other anabolic hormones, increases in production of catabolic cytokines, and other factors acting directly or indirectly on skeletal muscle.[1] The overall goal of the LIFE pilot project blood repository is to guarantee the proper collection, shipping, and central storage of both blood and DNA specimens. These samples will be used for the purpose of conducting future ancillary studies designed to examine the effects of physical activity on circulating biomarkers of some of these pathways and/or to examine how variation in genes of these pathways modulates responses to the physical activity treatment. We will also work with the NIA in making these samples available to outside investigators interested in the effects of physical activity on biological outcomes via the NIA Virtual Human Biospecimen Repository. Dr. Nicklas will have overall responsibility for achieving this goal. She also is prepared to personally apply for additional funding (via NIH R03 or R01, AHA, or Pepper Center pilot study mechanisms), and to assist other individuals in applying for funding to conduct the necessary assays to answer questions requiring the use of these samples. Because of the cost associated with recruitment, conducting the intervention and assessments of physical function, and organization of such a large trial, guaranteed *a priori* collection of specimens is the most efficient and cost-effective means of conducting future research on the mechanistic effects of physical activity.

Background

Aging is associated with declines in physical function that often lead to onset of physical disability and loss of independence. While there seems to be a common pathway of sarcopenia underlying aging-related loss of physical function, little is known regarding the biological factors that are fundamental for the progression of this process. To date, regular physical activity training is the only therapy known to consistently improve physical function in older adults; however, again, there is a paucity of scientific data about the mechanisms by which physical activity results in improved physical function in the elderly. Because there is no definitive, randomized, controlled trial evidence showing that physical activity prevents

the primary endpoint of incident physical disability, the LIFE pilot study is designed to estimate the outcome rates in preparation for a full-scale study. However, even the pilot study will constitute the largest sample of older individuals randomly treated with a physical activity intervention who also undergo a battery of physical (as well as cognitive) assessments. *Thus, this pilot study offers unique opportunities to gain insight into the biological mechanisms underlying the beneficial effects of physical activity for improving physical function in the elderly*. Knowledge of these mechanisms may eventually lead to new therapies for preventing or minimizing aging-related declines in physical function.

There are recent studies that show aging-related loss of physical function is partly influenced by heredity.[2-3] To date, however, there is a paucity of knowledge about which specific genes are true contributors to aging-related declines in physical function. A unique approach to identifying genes involves experimental perturbation of the trait of interest via some intervention (i.e., physical activity training) to examine gene-treatment interactions (e.g., pharmacogenetics). The LIFE study design provides such an intervention. It is likely that there will be responders and non-responders to the physical activity intervention by LIFE participants in the treatment arm, and it is likely that part of this variation in response is due to genetic variation. Procurement of DNA and analyses of genetic polymorphisms could yield significant information regarding inter-individual differences in the success of this treatment. Eventually, this will lead to individually appropriate and more effective treatments for prevention of physical decline.

Preliminary studies

Through the support of our Claude Pepper Older Americans Independence Center and other funded research, we are beginning to explore whether physical activity training alters markers of the above mentioned mechanisms to improve physical function. Below we report some of our findings relative to this work and illustrate how these data have led to new hypotheses which could ideally be tested using blood or DNA samples from LIFE. We also highlight how these results may serve as pilot data for future grant applications for funding to analyze LIFE samples. With this prior work already conducted, we are in an excellent position to immediately apply for additional research support.

We recently measured circulating levels of pro-inflammatory cytokines in a previous trial named ADAPT designed to determine the independent and combined effects of 18 months of dietary-induced weight loss and physical activity on physical function in 316 older ($\geq$ 60 yrs), overweight/obese (body mass index $\geq$ 28 kg/m^2), and sedentary individuals with

knee osteoarthritis. Blood samples taken before and after the 18-month interventions were available for analyses in 214 participants. We found that the diet treatment lowered C reactive protein, interleukin-6, and soluble tumor necrosis factor alpha receptor concentrations.[4] However, *while there was a trend for an effect of the physical activity training to lower these markers of inflammation, the effect was not large enough to be statistically significant* in this retrospective analysis. Power calculations showed that comparing the 53 participants in the physical activity group to the 60 participants in the control group resulted in only 60% power to detect an effect of physical activity on CRP levels (a total of 81 subjects per group would be required for 80% power). Likewise, to detect a physical activity-induced decrease in IL-6 we would need 133 subjects per group. We concluded that a larger study is needed to assess the effects of physical activity on inflammation. With 200 participants per treatment group, LIFE will have sufficient power to allow us to test whether physical activity training lowers these and other markers of inflammation in older individuals.

In the same study, we measured circulating concentrations of the anabolic hormones testosterone, growth hormone, DHEA, and sex steroid hormone binding globulin (SHBG). There were no effects of the physical activity treatment on circulating concentrations of these hormones (with n=60-70). However, there was a significant positive correlation between changes in knee extensor strength and changes in SHBG ($r=0.56$, $P<0.01$) and testosterone ($r=0.39$, $P=0.13$) among exercisers only. Therefore, we would like to follow this up to definitely determine whether physical activity-induced changes in physical function are related to physical activity-induced changes in anabolic hormones.

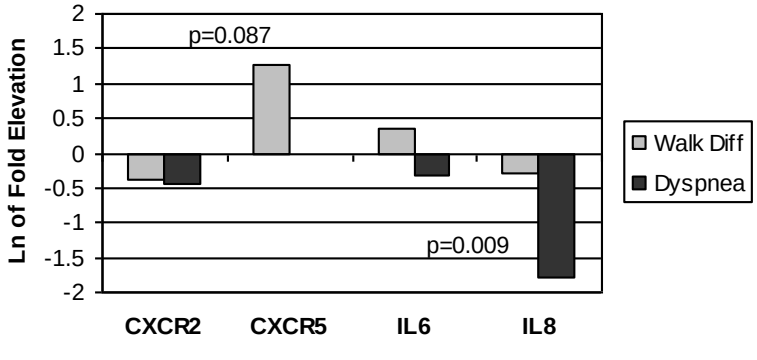
As part of our exploratory studies utilizing resources from the NIA initiative on "Exploratory Projects for Longitudinal Genetic Epidemiologic Studies on Aging, we have also been conducting analyses of genetic variation in candidate genes to determine whether this variation modulates the magnitude of physical performance responses to different physical activity interventions. Analyses are ongoing, but, preliminary data in three studies (described below) indicates that the ACE Insertion/Deletion polymorphism is likely to interact with physical activity to modify physical function.

The HABC study is a 7-yr cohort study of 3075 well-functioning men and women aged 70-79 years (51% male, 42% black, mean age=73.6 years). We found a significant interaction for the development of physical disability (defined as persistent difficulty in walking ¼ mile or climbing 10 steps) between the genotype (modeled as the number of I alleles) and physical activity status (<1,000 kcal/wk versus ≥1,000 kcal/wk) in both an

unadjusted model (p = 0.002) and a model adjusting for age, gender, race, site, education, smoking status, alcohol use, knee pain, diabetes, cardiovascular disease, low FEV_1, and hypertension (p= 0.011). Among the physically active, those having the II genotype developed functional limitation 45% faster (adjusted hazard ratio 1.45; $CI_{[95\%]}$: 1.07-1.97) than those of the ID or DD genotype.

We also conducted a recall of participants in the ADAPT trial described earlier and were able to obtain DNA from 211 (67% of the original sample). There were no associations between ACE I/D genotype and baseline measures of physical performance—nor were overall changes in these measures related to genotype. However, when analyses were stratified to those who performed physical activity (i.e., a combination of aerobic and resistive physical activity in this study), there was a trend for a significant effect (P=0.08) of ACE genotype on 6- and 18- month changes in knee strength with the DD genotypes showing greater gains in strength compared to the II. There was a significant interaction between ACE I/D genotype and physical activity treatment on change in knee strength (P=0.014). In addition, although not statistically significant (P=0.34), changes in 6 minute walking distance tended to be higher in the II vs. the DD genotypes in response to physical activity. *These data indicate that changes in physical performance with physical activity training in older individuals may be dependent on ACE I/D genotype.* However, because the HABC study is an observational study and because the ADAPT study included a diet intervention, plus only 2/3 of the ADAPT sample was available for analyses, this hypothesis needs to be tested in a randomized trial of physical activity in older individuals. Our power calculations indicate that completion of 50 II and 50 DD participants in a physical activity and 50 II and 50 DD in a control group is sufficient to detect genotype differences in changes in walking speed and strength in response to physical activity. Because the frequency of the least common I allele of the ACE I/D genotype is 25%, there should be sufficient statistical power in LIFE (50 II in each treatment group) to examine this hypothesis. Studies with large sample sizes (such as LIFE) are needed to begin to identify whether this genotype and/or other potential genetic

Figure C.2 PBMC mRNA expression and Physical Function (n=19)



markers may be used to identify older individuals who are most likely to benefit from a physical activity intervention. *A priori* collection of DNA from participants in LIFE will insure that these analyses will eventually be conducted.

Also in Health ABC we used archived samples of peripheral blood mononuclear cells with mRNA message stabilized using RNAlater™. Messenger RNA expression levels of CXCR2, CXCR5, IL6 and IL-8 were determined in 19 Health ABC participants using samples collected in Year 6. None of the 19 analyzed mRNA samples was identified as partially degraded. We related these values to two important aspects of physical function: self-reported difficulty walking 0.25 miles and dyspnea. We compared the five participants with self-reported difficulty 6 months prior to the specimen collection to the 14 with no difficulty. CXCR5 levels were 3.5 times higher among the functionally limited (p= 0.08, Wilcoxon 2-tailed test). We also observed that that IL-8 mRNA levels were significantly lower in the eight participants reporting dyspnea (p = 0.009, Wilcoxon, 2-tailed test). These data show the potential for important findings relevant to the LIFE intervention with very small sample sizes.

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