

PROTOCOL

ACTION FOR HEALTH IN DIABETES

Look AHEAD

Clinical Trial

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1. EXECUTIVE SUMMARY

1.1 Background

Overweight and obesity are major health problems in the United States, affecting more than 50% of adults, with 22.5% classified as obese (body mass index ≥ 30 kg/m²). The long-term consequences of being overweight include increased mortality and increased morbidity from a variety of associated disease states. Nowhere is the long-term risk of obesity more manifest than in its effect on type 2 diabetes. The current epidemic of diabetes in the United States is largely attributable to the increased incidence of obesity. Similarly, cardiovascular disease is associated with obesity, mediated in part by the two- to four-fold increased risk for cardiovascular disease associated with type 2 diabetes. The direct and indirect costs attributed to obesity approach \$100 billion per year.

Although short-term weight loss has been demonstrated to ameliorate obesity-related metabolic abnormalities and cardiovascular disease risk factors, few, if any, studies have examined the long-term consequences of intentional weight loss in overweight or obese populations. Until recently, effective and reliable means for long-term weight loss in the setting of multi-center clinical trials were not available; however, several large randomized multi-center trials have demonstrated significant decreases in weight and increases in activity level for as long as three years. The weight loss results of these studies have made feasible a long-term study: Action for Health in Diabetes (Look AHEAD). Look AHEAD will focus on one of the diseases most affected by overweight and obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease.

1.2 Objective

The primary objective of Look AHEAD is to examine, in overweight volunteers with type 2 diabetes the long-term effects of an intensive lifestyle intervention program designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity. This program is compared to a control condition involving a program of diabetes support and education. The primary basis for the comparison is the incidence of serious cardiovascular events. Other outcomes, including cardiovascular disease risk factors, diabetes related metabolic factors and complications, and the cost-effectiveness of the intensive intervention are also studied.

1.3 Study Population

Approximately 5,000 volunteers with type 2 diabetes who are 45-75 years of age and overweight or obese (body mass index ≥ 25 kg/m²) will be recruited. Potential volunteers who are unlikely to be able to carry out the components of the weight loss intervention will be excluded.

1.4 Study Interventions

Eligible volunteers are randomly assigned to an intensive lifestyle intervention or to diabetes support and education. Treatment assignments are unmasked. The lifestyle intervention is implemented with individual supervision and group sessions and is aimed at achieving and maintaining at least a 7% decrease in weight from baseline and 175 minutes per week in physical activity. It is implemented during a four-year period with the most intensive application during the first year, less frequent attention during the next three years, and a minimum of twice yearly contacts during an extended follow-up period. To help participants achieve and maintain weight

loss, a variety of diet strategies (e.g. prepared meals and liquid formula), exercise strategies, and optional weight loss medications are utilized based on a preset algorithm and participant progress. Participants assigned to diabetes support and education are offered three sessions each year in diabetes management and social support. Study personnel advise volunteers' health care providers regarding the currently recommended metabolic and blood pressure goals and the therapies necessary to achieve those goals.

1.5 Outcomes

The primary outcome is the aggregate occurrence of major cardiovascular events including fatal and non-fatal myocardial infarctions and strokes, hospitalizations for angina, and cardiovascular deaths over a planned follow-up period of up to 13.5 years. Three composite secondary outcomes have also been defined: 1) cardiovascular deaths, myocardial infarctions (fatal or non-fatal), and strokes (fatal or non-fatal), 2) deaths (all causes), myocardial infarctions, strokes, and hospitalizations for angina; and 3) deaths (all causes), myocardial infarctions, strokes, hospitalizations for angina, coronary artery bypass graftings, percutaneous coronary angioplasty, hospitalizations for congestive heart failure, carotid endarterectomies, or peripheral vascular procedures such as bypass or angioplasty. Other study measures assist in establishing the feasibility of the weight loss intervention, characterize its effect on general health and additional diabetes and cardiovascular disease outcomes, examine mechanisms through which weight loss and physical activity may influence health, and assess the processes through which the intervention influences weight, body composition, diet, and physical activity.

1.6 Design and Power

The study is a two-armed randomized, controlled clinical trial. With 5,000 participants, the study has a >80% probability of detecting an 18% difference in major cardiovascular disease events between the two intervention groups.

1.7 Analyses

The primary study outcome -- time to incidence of a major cardiovascular disease event -- will be compared using proportional hazards regression. The primary analyses will include all participants in their originally assigned treatment groups regardless of adherence (intention-to-treat).

1.8 Transition from Randomized Controlled Clinical Trial to Observational Study

The DSMB determined, in August 2012, that the chance of detecting a difference in the primary outcome between treatment assignments was small and requested that the intensive lifestyle intervention be ended and Look AHEAD be converted to an observational study. This change took effect on September 14, 2012 with no further intensive lifestyle intervention sessions being offered at the sites.

2. BACKGROUND OF THE LOOK AHEAD CLINICAL TRIAL

2.1 Prevalence of Overweight/Obesity

Every year, overweight and obesity contribute to substantial morbidity and mortality¹⁻² and are responsible for billions of dollars in medical costs and lost productivity.³ Their prevalence has increased to the extent that a majority of adult Americans are now considered overweight or obese (body mass index ≥ 25 kg/m²).⁴ The prevalence of those classified as obese (body mass index ≥ 30 kg/m²) has increased from 16% to 22% in the past 15 years.⁴ Even more worrisome is the fact that the increase in prevalence is most pronounced among those at greatest risk for weight-related diseases. In addition, racial and ethnic minority populations are affected disproportionately by obesity. For example, 37% of African American women and 33% of Mexican American women have a body mass index ≥ 30 kg/m², compared to 22% of white women.⁵

The recent dramatic increase in obesity is believed to be mediated by environmental factors, including increased energy intake associated with larger portion sizes, increased consumption of high-fat, energy-dense foods, increased availability of low-cost, palatable foods,⁶ and decreased physical activity related to increasing mechanization at home, on the job, and during leisure time.⁷

2.2 Incidence and Prevalence of Type 2 Diabetes

With the increase in prevalence of obesity has come an alarming increase in the incidence and prevalence of type 2 diabetes. Data from the Third National Health and Nutrition Survey (NHANES III) suggest that type 2 diabetes affects more than 16 million adults in the United States, and almost one-third of these cases are undiagnosed.⁸

Based on American Diabetes Association criteria,⁹ the prevalence of diabetes (diagnosed plus undiagnosed) in the total population of people aged 40-74 years increased from 8.9% in the period 1976-1980 to 12.3% by 1988-1994, a relative increase of 38%.¹⁰ The prevalence of obesity had a similar increase during this time period. At present, 45% of individuals with known type 2 diabetes have a body mass index greater than 30 kg/m².¹¹

Studies in migrating populations and recently industrialized populations have shown that there is an increased incidence of diabetes as individuals become more overweight and adopt a more sedentary lifestyle and westernized diet.¹² In the United States, both obesity and low physical activity have been found to contribute independently to the risk of developing diabetes.¹³ Obesity and diabetes are strongly associated in all population groups, and especially in populations at high risk for diabetes such as the Pima Indians.¹⁴

2.3 Morbidity and Mortality

Obesity and the sedentary lifestyle that is an important contributor to obesity have marked consequences on morbidity and mortality. Obesity not only increases the risk of developing diabetes, but also complicates its management.¹⁵ Obesity increases insulin resistance and glucose intolerance, making diabetes in overweight individuals more difficult to treat pharmacologically. It also increases the likelihood of individuals with diabetes developing hypertension and cardiovascular disease.

Diabetes increases the risk of coronary heart disease by two- to four-fold and stroke by approximately two-fold.¹⁶ The powerful impact of diabetes on heart disease was seen in a seven-year study from Finland in which patients with diabetes who had not sustained a previous myocardial infarction had as high a risk of myocardial infarction as nondiabetic individuals who had previously had an myocardial infarction.¹⁷ Moreover, although there has been a decline in heart disease mortality in the general United States population (which has been attributed to improved treatment of heart disease and reductions in cardiovascular risk factors), the diabetic population has experienced a much smaller decline in mortality.¹⁸ In addition, there is now serious concern that the incidence of cardiovascular disease has not declined in the United States, and may have actually increased in some sub-populations.^{19,20}

Individuals with type 2 diabetes who are overweight are at particularly high risk of cardiovascular and all-cause mortality, as are individuals with diabetes with low levels of physical activity or poor fitness levels. Physical inactivity has been related prospectively to all cause mortality in men with diabetes,²¹ and to coronary heart disease and stroke in women with diabetes.²²

Obesity also is associated with a wide variety of other diseases, many of which seriously impair quality of life.² Obesity is a major risk factor for sleep apnea in both men and women, with the risk most clearly observed among individuals with a body mass index of 30 kg/m² or more. The risk of gallbladder disease, nonalcoholic steatohepatitis, disabling knee osteoarthritis, and gout is increased in overweight and obese individuals. High body weight also increases the risk of certain forms of cancer, specifically prostate, colon, endometrial, and postmenopausal breast cancer.

Physical activity may play an important role in mediating the relationship between obesity and ill-health. Because it is linked with higher rates of cardiovascular disease and all-cause mortality, physical inactivity is associated with decreased longevity. A sedentary lifestyle increases the risk of coronary heart disease, type 2 diabetes, some cancers, hypertension, osteoporosis, and loss of functional capacity and independence. Physical activity also is directly related to general well being and a number of psychosocial variables.²³⁻²⁶ Several studies have concluded that obese men who were fit appeared to be protected from early mortality.²⁷ However, because physical inactivity and obesity frequently are linked, and both appear to contribute to increased risk for many of the same diseases, it is difficult to separate their effects on health.

2.4 Current Public Health Recommendations

Because of the data linking obesity to health risk, public health authorities and many physicians recommend weight loss as a therapeutic strategy for those who are obese or who are overweight with comorbid conditions.⁵ The Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults state that “the initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline.”²⁸ Recommended weight-loss strategies include a low calorie diet to create a deficit of 500–1,000 kcal/day, behavior therapy, and increased physical activity. In addition, when appropriate, weight loss medications or bariatric surgery may be added to the treatment of participants who do not respond adequately to more conservative interventions. With respect to physical activity, there is now general agreement that a sedentary and unfit way of life leads to numerous health problems

and conditions. The reports from the Surgeon General, NIH, CDC, ACSM, and AHA also provide a consensus public health recommendation for physical activity: “adults should accumulate at least 30 minutes of moderate intensity physical activity over the course of most, preferably all, days of the week.”²³⁻²⁶ This consensus recommendation emphasizes “accumulation” of activity (multiple bouts of activity accumulated during the day), which is moderate in intensity (typically represented by walking at 3-4 mph).

2.5 Intentional Weight Loss

2.5.1 Efficacy and Costs of Weight Loss Efforts

It is clear that many adults in this country are attempting weight loss. Data from the Behavioral Risk Factor Surveillance System indicate that the prevalence of weight loss attempts among United States adults is 44% among women and 29% among men. Unfortunately, only 10% of women and 13% of men report using both the recommended strategies of eating fewer calories and exercising 150 minutes or more weekly.²⁹ Randomized controlled trials of structured weight loss interventions have typically shown that weight losses average 5-10% of initial weight, with maximum weight loss after 6-12 months of treatment followed by weight regain.³⁰ Similar results have been seen in non-research settings, with many individuals losing weight in the short term but regaining most or all of their lost weight within five years. Because of this difficulty in sustaining weight loss in the long term, multiple cycles of weight loss and regain are common. Attempts at weight reduction are costly. United States consumers spend more than \$33 billion yearly on weight loss products and services.³¹ There are also potential risks from weight loss, including the development of symptomatic cholelithiasis and the potential for bone loss. Therefore, it is important to document costs, as well as risks and benefits, of weight loss in those for whom it is recommended.

2.5.2 Short-term Effects of Intentional Weight Loss and Increased Physical Activity

When attempting to determine the health effects of weight loss, it is important to differentiate short-term (i.e., one year or less) from longer-term results. Much information is available about the former. However, there are few published studies assessing the impact of long-term intentional weight loss (defined as two or more years) on health.

There are a large number of randomized clinical trials evaluating short-term effects of weight loss in obese diabetic and nondiabetic populations.³²⁻³⁵ These studies have shown that behavioral interventions combining dietary modification and increased physical activity are most effective in achieving weight loss. Typically, participants enter these studies weighing approximately 100 kg and lose on average 5-10% of their body weight at the end of six months. In most of these studies, weight loss treatment is ended by six months, and participants are then followed for an additional period. By 18 months following study entry, participants maintain about a 5% weight loss, but by three to five years the mean weight has generally returned to baseline. There is some evidence that continuing contact may improve longer-term outcome.^{36,37}

Short-term weight loss studies have documented significant improvements in blood pressure, lipids, body fat distribution, insulin resistance, and glycemic control at six months, with some continued benefit after 12-18 months of follow-up.³⁸ Among individuals with diabetes, there is often an immediate and dramatic improvement in glycemic control, and diabetes medications frequently may be reduced or discontinued altogether. At one year, modest weight losses have been shown to produce sustained improvements in lipids, blood pressure, and glycemic control

among participants with type 2 diabetes.³⁹ The magnitude of improvement appears to be directly related to the amount of weight loss.³⁹

Physical activity is a significant component of weight loss programs. Programs combining diet and exercise produce larger long-term weight losses and greater improvements in cardiovascular risk factors than programs using diet alone.^{40,41} The benefit of adding exercise to a weight loss program is seen particularly in the maintenance of weight loss. The reduction of cardiovascular disease risk provided by physical activity may be independent of weight loss.^{37,42}

The FDA has recently approved two weight loss medications for long-term use (orlistat and sibutramine) in combination with lifestyle interventions. These medications have been tested in one- to two-year trials as adjuncts to lifestyle interventions.⁴³ Adjunctive use of weight loss medications has been shown to enhance weight loss modestly and to slow weight regain. Again, these weight losses have in many (but not all) cases been associated with improvement in risk factors.

2.5.3 Longer Term Studies of the Effects of Intentional Weight Loss

There have been only a few studies that have examined long-term (i.e., greater than two years) changes in risk factors and health outcomes resulting from intentional weight loss. Several of these are multi-center trials showing that modest weight loss (3-4 kg difference between treatment and control) at approximately three years⁴⁴⁻⁴⁷ has a long-term impact on blood pressure and/or the need for hypertension medication. Individuals who lose at least 4.5 kg initially (at six months) and maintain this weight loss over three years have the greatest reductions in blood pressure and decreased risk of hypertension.⁴⁸ Participants in weight loss programs also experience long-term improvements in quality of life even if the initial weight losses are regained.⁴⁹ These findings suggest that there may be benefits of participation in a lifestyle intervention even if significant weight loss is not maintained long-term. Surgical weight loss in those with extreme obesity has been shown to sustain reductions in diabetes risk.⁵⁰⁻⁵² However, one study found that post-surgical reductions in blood pressure were not sustained for eight years, despite a continued reduction in body weight.⁵⁰ Studies of bariatric surgical procedures, while valuable in their ability to examine the sustained effects of large weight losses, are not necessarily generalizable to the larger population of obese persons, for whom surgery may not be available or appropriate. A recent study suggests that weight loss brought about through lifestyle change may have a favorable impact on the development of diabetes.^{53,54} However, the impact of weight reduction on cardiovascular disease in persons with diabetes, or in the general population, has never been investigated.

2.5.4 Observational Studies

While clinical studies suggest salutary benefits of short-term weight loss, there have been several epidemiological studies that raise concern about possible adverse effects of weight loss. These studies have examined the effect of a history of weight loss on cardiovascular or all-cause mortality assessed over a subsequent long-term follow-up interval (three to twelve years). Studies with both diabetic and nondiabetic populations have observed that those who lost the most weight often had increased, not decreased, risk of subsequent cardiovascular and all-cause mortality.⁵⁵⁻⁵⁷ For example, in the Framingham Study a history of weight loss between ages 35 and 54 years increased the risk of mortality over a subsequent 10-year follow-up.⁵³ Similarly, a history of weight cycling (weight loss followed by regain) has been associated with a subsequent

increased risk of mortality.⁵⁸ A review of six observational studies of the effects of weight loss in type 2 diabetic individuals found no consistent effect: one of the six studies showed no association, two found weight loss was associated with decreased mortality, one with increased mortality, and in two the results differed by subgroup.⁵⁹ In many of these studies, involuntary weight loss could not be distinguished from voluntary weight loss.

There is also evidence from observational studies to suggest the opposite- that a period of weight loss may be associated with subsequent reduced risk of disease. As early as the 1950's, actuarial scientists in the life insurance industry observed that persons who had lost weight, and thus re-qualified for lower life insurance rates, experienced substantially lower mortality than their obese counterparts who did not lose weight.^{60,61}

More recently, in a twelve-year observational study focused specifically on intentional weight loss in patients with type 2 diabetes, a history of intentional weight loss was associated with a 25% reduction in total mortality; intentional weight loss of 20-29 pounds produced the largest reductions in mortality (33%).⁶² This study suggests that, in persons with diabetes, a period of intentional weight loss can have a positive effect on health many years later.

Periods of weight loss, even if followed by weight regain, may decrease the overall magnitude of weight gain that typically occurs with aging.⁶³ In the Nurses Health Study, women who gained weight from age 18 to age 30-55 were at greater risk of coronary heart disease and stroke over the next 14-16 years than those who had remained weight stable.^{64,65}

Few observational studies have examined the effect of weight loss on quality of life. However, in the Nurses Health Study, weight loss of 2.5 kg or more over four years of observation was associated with improved physical function and vitality.⁶⁶

2.6 Need for a Randomized Clinical Trial on Weight Loss and Health in Diabetes

Given the paucity of data on the impact of weight loss on morbidity and mortality, an increasing number of critics in both the lay press⁵² and professional literature^{67,68} have questioned whether obesity should be treated at all. They point to pharmacologic improvements in treatment of obesity's comorbid conditions, such as hypertension and dyslipidemia, that are effective without weight loss and the observational literature showing increases in mortality with weight loss.

Observational studies attempting to determine health effects of weight loss have limitations, such as the inability to separate intentional from unintentional weight loss (e.g., as a result of illness) or the inability to control adequately for preexisting illness and other confounding factors. The limitations of observational studies attempting to determine the effects of weight loss and/or physical activity on health can be addressed only through randomized intervention studies designed to measure changes in health outcomes that accompany intentional weight loss.⁵⁸

In 1997, a workshop was convened by the National Institutes of Health and Centers for Disease Control and Prevention to explore the desirability and feasibility of a randomized controlled trial to determine the long-term impact of weight loss on health outcomes such as disease incidence and mortality.⁶⁹ Workshop participants concluded that only a randomized controlled trial of intentional weight loss would provide needed guidance on the risks and benefits of weight loss that could inform rational clinical and public health policy. The participants suggested that such

a study focus on obese individuals who already had a comorbid medical illness, because of the clear public health recommendation for such individuals and because of their increased risk of adverse health-related outcomes.⁵⁷ Due to the increasing prevalence of type 2 diabetes in Americans and its attendant severe complications such as cardiovascular disease, and the clear association between type 2 diabetes and increased body weight, persons with diabetes were considered to be an appropriate population for this study.

2.7 Feasibility of a Study of Intentional Weight Loss in Individuals with Type 2 Diabetes

A study of the impact of weight loss on the reduction of cardiovascular disease must be able to provide interventions that maximize the possibility of sustained weight loss. This is particularly challenging in individuals with diabetes, since they appear to be less successful in weight loss and weight loss maintenance than nondiabetic individuals. Moreover, in the absence of weight loss intervention, nondiabetic individuals tend to gain weight over time, whereas individuals with diabetes may gain or lose weight following diagnosis. Thus it may be more difficult to produce long-term differences in weight changes for diabetic individuals assigned to weight loss intervention versus control conditions than it is to produce them with nondiabetic individuals.

While long-term weight loss is difficult, there is evidence that it can be achieved. New strategies are available that may increase the likelihood of success. Several large randomized controlled trials of weight loss interventions that include behavioral treatment, diet, and physical activity have been able to achieve and maintain modest weight losses for several years.⁴⁴⁻⁴⁶ Although long-term weight losses were modest (3-5% net difference between treatment and controls), these trials still showed positive benefits on hypertension, diabetes, and need for hypertensive medications.^{44,46}

Because of the importance of physical activity in enhancing weight loss and supporting weight maintenance, and the increasingly strong evidence that increased physical activity and fitness level can affect health independently of body mass index, it is important to have interventions available that can lead to sustained changes in physical activity. During the past decade several large and well-controlled randomized clinical trials of physical activity interventions have been conducted.⁷⁰⁻⁷⁴ Such studies have shown that moderate exercise such as walking can improve cardiovascular fitness. Unsupervised physical activity interventions and higher physical activity goals appear to be related to better long-term weight loss outcomes.

Evidence is also accumulating to indicate the importance of continued treatment contact. In studies with six months of weight loss treatment and no maintenance contact, there is gradual but consistent weight regain after termination of therapy. In contrast, studies with multi-component behavior-based weight loss interventions conducted in weekly or biweekly sessions over an extended period (e.g. 9-18 months) have maintained initial weight losses (typically 10-12% reduction of initial body weight) as long as intervention contact was maintained. Weight regain (typically a 33% regain during the first six months) occurred after therapist contact was terminated.^{34,75-81} Of particular note, one recent study using a behavioral weight loss intervention, accompanied by a portion controlled diet, found 8-10% weight losses throughout four years of intervention and follow-up with monthly contact.^{47,82} Similarly, maintaining contact with participants appears to promote long-term adherence to exercise.

There is also evidence that adjunctive use of weight loss medication can enhance weight loss and slow the rate of regain, although information on more than two years of treatment is lacking.^{83,84} Benefits of combining lifestyle programs with weight loss medication have been shown for both diabetic and nondiabetic populations.

Thus it is now possible to test the hypothesis that participation in an intensive multi-component weight loss intervention will reduce the risk of cardiovascular disease and improve other clinically important health outcomes.

3. OVERVIEW OF TRIAL DESIGN

The Look AHEAD randomized controlled clinical trial will examine the impact on several health outcomes of a lifestyle intervention program designed to produce weight loss. The primary study objective is to determine whether participation in a lifestyle intervention is effective in reducing the incidence of serious cardiovascular disease events in overweight adults with type 2 diabetes. Other important study objectives are to assess the impact of weight loss and fitness changes on a range of disease processes and outcomes and to evaluate the cost-effectiveness of the weight loss intervention.

The study cohort will include 5,000 overweight (body mass index of at least 25 kg/m²) individuals with type 2 diabetes (as established by self-report with verification or treatment). Individuals with or without a prior history of cardiovascular disease will be recruited. Section 4 presents the complete eligibility criteria for the trial.

Participants will be stratified according to center, and randomly assigned to either Lifestyle Intervention or a control intervention, Diabetes Support and Education. The Lifestyle Intervention is designed to produce and maintain weight loss and increased fitness through a lifestyle program augmented, if indicated, by subsequent use of weight loss medication. This intervention includes individual and group sessions with weekly meetings for six months followed by decreasing frequency of contact over the remainder of the trial. The Diabetes Support and Education group will receive sessions of nutrition and physical activity education and social support. Participants in both arms will receive comparable education in issues related to diabetes management. Section 5 provides a general description of interventions.

Participants in Look AHEAD will receive their general medical care from a health care provider who is separate from the Look AHEAD staff. The participants' own physicians will manage their diabetes and provide general health care during the trial. Section 6 provides a description of medical management for trial participants.

Participants will be recruited over 2.5 years. They will be followed annually through 2014, resulting in a maximum of 13.5 years of participant follow-up. To the extent that it is feasible, staff collecting assessment data will be distinct from those administering the intervention. Event adjudicators will be masked to the participants' intervention assignment. Outcome measures include those that might be positively affected by weight loss (e.g. cardiovascular events) and those that might be negatively affected (e.g. bone mineral density). The study will also assess some of the potential mechanisms by which weight loss may influence cardiovascular events and mortality (e.g. through improved control of cardiovascular risk factors). Section 8 summarizes the outcome measures collected by the trial.

Five thousand participants will provide a minimum of 80% power to detect an 18% relative decrease in the rate of the primary outcome in participants assigned to the Lifestyle Intervention.

3.1 Rationale for Major Design Decisions

3.1.1 Selection of Primary Outcome Measure

Cardiovascular morbidity and mortality were selected as the primary outcome measure for the following reasons. Although it is well known that weight loss improves cardiovascular risk

factors, at least in the short term, it is not known whether weight loss reduces cardiovascular disease morbidity and mortality. Given that cardiovascular disease is the major cause of morbidity and mortality in type 2 diabetes, this issue is of major public health importance. A positive effect of weight loss on cardiovascular events would provide a simple, powerful public health message.

Progression of atherosclerosis as assessed by B-mode ultrasound measures of carotid intima-media thickness was considered as a surrogate outcome measure but rejected. Although there are considerable cross-sectional data linking carotid intima-media thickness with cardiovascular events, only limited data are available at this time showing that progression of carotid intima-media thickness is related to progression of cardiovascular disease. Moreover, while some of the benefits of weight loss are likely to be mediated through atherosclerosis, weight loss may also benefit cardiovascular disease through pathways other than atherosclerosis.

Weight loss and physical activity are known to reduce many cardiovascular disease risk factors, at least in the short term. In this way, weight loss and increased physical activity may facilitate medical control of these factors. In addition, these interventions may reduce the incidence of cardiovascular disease more effectively and economically, and with fewer adverse effects, than by reliance primarily on medication. Weight loss and physical activity interventions also may reduce cardiovascular risk through mechanisms other than established cardiovascular risk factors and mechanisms.

3.1.2 Selection of Interventions

Since Look AHEAD is an efficacy study designed to evaluate the health outcome of lifestyle intervention, a decision was made to compare a control condition of diabetes support and education with a maximal weight loss program (rather than comparing several different approaches to weight loss). Prior research suggests that there is a dose-response relationship between the magnitude of weight loss and the observed change in cardiovascular risk factors, including lipids, blood pressure and glycemic control. It is also clear that long-term maintenance of weight loss increases the chance of producing long-term changes in these risk factors. Therefore the Look AHEAD Lifestyle Intervention incorporates the strategies expected to maximize long-term weight loss success, including the combination of diet, exercise, and behavior modification, ongoing contact with a combination of group and individual sessions, and use of weight loss medications as appropriate. Surgical approaches to obesity were excluded from the intervention strategies since these approaches are receiving intensive investigation in the Swedish Obesity Study.⁵⁰

Although the goal of the lifestyle intervention is to maintain weight loss long-term, it is recognized that many individuals who attempt to lose weight will ultimately regain it or experience weight cycles. Prior research suggests that participation in a lifestyle intervention, even with minimal sustained weight loss, improves hypertension control and decreases the risk of developing diabetes. To maximize the potential health benefits of the lifestyle intervention, a low fat diet (<30% of kcal from fat with <10% saturated fat) and increased physical activity are key components of the intervention. Exercise is considered a key component of the intervention, not only to maximize the long-term maintenance of weight loss, but also because physical activity and fitness, independent of body weight have been shown to be strongly associated with cardiovascular disease risk in both diabetic and non-diabetic populations.

All clinics will offer a comparable lifestyle intervention using treatment materials developed by the Look AHEAD Lifestyle Intervention Committee. This intervention will include both group and individual sessions with the latter specifically designed to adapt the intervention to the needs of the individual participant. All intervention material will be designed to be culturally appropriate for individuals of diverse backgrounds and education. Because most of the intervention is delivered in groups and uses commercially available foods and home-based physical activity, the intervention, if efficacious, could in the future be delivered outside the research setting.

3.1.3 Selection of Study Population

The study will be conducted in overweight individuals with type 2 diabetes. Diabetes is an increasingly prevalent health problem in the United States, and it has significant impact on cardiovascular morbidity and mortality. Patients with diabetes are typically advised to lose weight as the first step of treatment. Approximately 20-30% of the Look AHEAD sample will have a history of cardiovascular disease. The decision to include individuals with a history of cardiovascular disease was based on several considerations: the higher event rate in these individuals, the desire to be able to generalize to the type 2 diabetic population (which, based on NHANES III data, includes 29% individuals with heart disease or stroke⁸⁵), and the fact that during screening many individuals without a known history of cardiovascular disease will be found to have evidence of cardiovascular disease. Moreover, it appears that lifestyle intervention can be effective in individuals with a history of heart disease. The Trial of Nonpharmacologic Interventions in the Elderly⁸⁶ found that weight losses between individuals with and without a history of cardiovascular disease were similar. Dietary intervention studies have successfully reduced mortality in individuals with a history of cardiovascular disease, as have cardiac rehabilitation programs.^{87,88}

3.1.4 Medical Management by Participants Own Health Care Provider

The Look AHEAD trial is neither designed nor staffed to provide comprehensive medical care to all participants, nor is this necessary to address the principal study objective of the trial. Look AHEAD participants will receive their diabetes and general health care from providers outside of the study. This approach allows the study to assess the benefits of weight loss compared to the medical care received in the general community. This approach also may maximize the willingness of physicians to refer patients to the study (i.e., they will not have to worry about losing their patients).

As will be described, Look AHEAD will try to facilitate effective medical management through participant education curricula, through providing clinical data on diabetes control and cardiovascular risk factors, through communication to physicians on current consensus recommendations for management of diabetes, lipids, and hypertension, and through communication concerning safety issues that arise in relation to interventions.

3.1.5 Economic Evaluation

Traditionally, medical interventions have been judged solely on whether or not they were clinically effective. During the past 15 years, the increasing costs of medical care have led health care decision makers to broaden the criteria they use to evaluate new therapies to include

questions of value for the cost. The most common measure of such value is the cost-effectiveness ratio.⁸⁹

The primary clinical hypothesis of Look AHEAD is that the multifactorial intervention that is implemented in the trial will reduce morbidity and mortality. However, it is anticipated that these benefits will be accompanied by increased costs. Thus, there is a need to determine whether the anticipated improvements in health are worth their cost. The economic evaluation in Look AHEAD is designed to address this issue.

The primary economic question is: “Is the intensive lifestyle intervention being tested in Look AHEAD cost-effective?” In order to estimate cost-effectiveness, Look AHEAD will estimate various components of cost and of effectiveness. The primary effectiveness measures in Look AHEAD are “hard” cardiovascular outcomes, and the economic evaluation will estimate net cost per outcome averted (e.g., heart attack, stroke, hospitalization). In addition, Look AHEAD will also use a standard of economic evaluation that reflects both the length of a person’s survival and the quality of that survival. One common method used to calculate such an outcome is to apply the participant’s estimate of her/his quality of life during the trial to the number of years of life lived. Simply put, one year of life in optimal health is assigned a value of 1; death is given a value of 0. The value of a year in less than perfect health is given a value between 0 and 1.⁹⁰ The result is a measure of quality adjusted life years (QALYs), which will be used as an additional measure of effectiveness.

Differences between the intervention group and control group will be calculated separately for costs, and for effectiveness. The ratio of these differences (i.e., the cost-effectiveness and cost-utility ratios) is then calculated. One can judge the relative value of the intervention by comparing the magnitude of this ratio with either the ratios of other commonly accepted interventions or with a predetermined standard (e.g. a ceiling ratio of \$60,000 per quality-adjusted life year saved).

3.2 Clinical Trial Objectives

The major objectives of the Look AHEAD clinical trial are as follows.

3.2.1 Primary Trial Hypothesis

The primary hypothesis is that the incidence rate of the first post-randomization occurrence of a composite outcome, including

- i. cardiovascular death (including fatal myocardial infarction or stroke),
- ii. non-fatal myocardial infarction,
- iii. non-fatal stroke, or
- iv. hospitalization for angina

over a planned follow-up period of up to 13.5 years will be reduced among participants assigned to the Lifestyle Intervention compared to those assigned to the control group (Diabetes Support and Education). This composite outcome is defined in greater detail in Appendix C. Section 9.1 provides details on the statistical procedures that will be used to test this hypothesis. Interim stopping rules for overall trial efficacy will be based on the accrued rate of this primary outcome (Section 7.2).

3.2.1.1 Rationale for Change in Definition of Primary Endpoint

The Look AHEAD trial was designed to have sufficient statistical power to detect an 18% reduction in the rate of major cardiovascular events among participants assigned to Intensive Lifestyle Intervention compared to Diabetes Support and Education over 10.5 years of follow-up. Originally, it was projected to provide 90% power based on an expected event rate of 3.125% per year in the Diabetes Support and Education group. A lower-than-expected rate in the first 24 months of follow-up prompted a revision of this expectation: to 80% power based on an event rate of 2.0% per year. Five years into the trial, however, it appeared that the actual event rate in the Diabetes Support and Education group was about 0.7% per year and that the trial lacked the statistical power necessary to detect the originally hypothesized effect.

To address this problem, the Steering Committee created an Endpoint Working Group, composed of Look AHEAD investigators with expertise in trials, representatives from NIH, and two senior consultants not otherwise affiliated with Look AHEAD, to investigate the possibility of modifying the study protocol in response to the unexpectedly low observed event rate. Many options were considered. Simply extending study follow-up appeared impractical, since many additional years would be required to compensate for an event rate 66% below that required for 80% power. Therefore, the Endpoint Working Group deliberated extensively about expanding the definition of the primary endpoint, in light of growing evidence of the many ill effects of obesity and widely recognized secular trends in the treated natural history of atherosclerotic cardiovascular disease. It recommended that the primary endpoint should be expanded to include hospitalized angina and the duration of the trial should be increased by two years. Together, these changes were projected to provide greater than 80% power for the trial. These recommendations were adopted by the Steering Committee and have led to revisions in the protocol document. The members of the Endpoints Working Group were masked to data on differences between intervention groups throughout the course of determining the revised endpoints. The Data and Safety Monitoring Board was not involved in choosing the revised endpoints, although they did approve the process by which the Endpoints Working Group developed the revised endpoints.

3.2.2 Secondary Trial Hypotheses

Three secondary trial hypotheses are defined based on the incidence rate of the first post-randomization occurrence of three composite outcomes:

Composite 1:

- i) cardiovascular death (including fatal myocardial infarction or stroke),
- ii) non-fatal myocardial infarction, or
- iii) non-fatal stroke;

Composite 2:

- i) death (all cause),
- ii) non-fatal myocardial infarction,
- iii) non-fatal stroke, or
- iv) hospitalization for angina;

Composite 3:

- i) death (all cause),
- ii) non-fatal myocardial infarction,

- iii) non fatal stroke,
- iv) hospitalization for angina,
- v) coronary artery bypass grafting and/or percutaneous coronary angioplasty,
- vi) hospitalization for congestive heart failure,
- vii) carotid endarterectomy, or
- viii) peripheral vascular disease (bypass procedure or angioplasty)

Each will be tested to see if, over a planned follow-up period of up to 13.5 years, their incidence will be reduced among participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.

3.2.3 Other Objectives

Data will be collected to help understand the mechanisms by which weight loss may influence cardiovascular disease, diabetes, and other health outcomes. These data will be used to assess differences between study arms, interpret inter-relationships among intermediate measures, and understand how factors influence incidence rates of disease and health events. Look AHEAD will assess the feasibility of the prescription of weight loss interventions and its broad public health impact. Key objectives are listed below.

Cardiovascular disease risk Look AHEAD will use measures of blood pressure, hypertension control, incident hypertension, lipids, incident hyperlipidemia, inflammatory markers, hemostasis factors, and fitness to assess the relative impact of the Lifestyle Intervention on components of cardiovascular disease risk.

Costs and cost effectiveness Look AHEAD will estimate cost, cost effectiveness, health state preferences (or “utilities”), and cost-utility ratios associated with its interventions. It will determine the net cost of the Lifestyle Intervention relative to Diabetes Support and Education.

Diabetes control and complications Look AHEAD will use measures of nephropathy (including albuminuria), amputation, and glycemic control (both metabolic measures and drug use) to characterize the relative impact of Lifestyle Intervention on diabetes control and complications.

General health Look AHEAD will contrast Lifestyle Intervention with Diabetes Support and Education with respect to a number of health conditions that may also influence the overall prescription of weight loss: incident obesity-related cancer, gall bladder disease, fractures, bone mineral density, self report of knee osteoarthritis symptoms and disability, sleep apnea, and urinary incontinence.

Hospitalizations Look AHEAD will characterize the relative impact of Lifestyle Intervention on the average number of hospitalizations experienced by participants.

Intervention and process factors Look AHEAD will use measures of physical activity, dietary intake, body weight, fitness, and body composition to examine delivery of the Lifestyle Intervention and characterize relationships between these process factors and health outcomes.

Quality of life and psychological outcomes Look AHEAD will examine the relative impact of the Lifestyle Intervention on quality of life and psychological outcomes, including physical and social functioning, pain, eating disorders and depression.

3.3 Phases of the Trial

3.3.1 Recruitment Phase

Participants will be recruited over a 2.5 year period. At the end of screening, all participants will attend an educational session on the management of diabetes.

3.3.2 Phase I

The first year after randomization will be Phase I of the study. Participants randomized to the Lifestyle Intervention will be seen four times per month (three group sessions and one individualized session) for six months and then twice per month for six months, with an opportunity for more frequent follow-up. The goal will be to induce a 7-10% weight loss and to increase exercise to 175 minutes per week. Participants assigned to Diabetes Support and Education will be offered three educational/support sessions. Post-randomization assessments for events will occur at Month 6 by phone and at Month 12 during a clinic visit. Most baseline measures will be repeated at Year 1 (see Table 8.2).

3.3.3 Phase II

Years 2-4 after randomization will be Phase II of the intervention. Participants randomized to Lifestyle Intervention will be seen at least one time per month in person with at least one other contact each month (in person or by phone, e-mail, voice-mail, or mail). The goal of Phase II is to maintain a weight loss of 7-10% and an activity level of greater than 175 minutes per week. Participants assigned to Diabetes Support and Education will be offered three educational/support group sessions each year throughout this phase. Assessment will occur by phone every six months and at annual clinic visits. Only a minimal set of measures will be taken during clinic visits at Year 2 and 3, but almost all Baseline measures and Year 1 measures will be repeated at Year 4 (see Table 8.6).

3.3.4 Phase III

Years 5 and beyond will be Phase III of the trial, with the primary purpose being to follow participants for the monitoring of cardiovascular events. Since participants are recruited over 2.5 years, this phase of the trial will be variable length, ranging up to 13.5 years. Participants in the Lifestyle Intervention will be offered monthly on-site individual contact with a counselor. Open groups will be offered one time per month. Sites will offer one refresher group and one national campaign per year. Participants assigned to Diabetes Support and Education will be seen once yearly throughout this phase, with the added options of continuing to attend one annual session throughout Phase III and repeat the 3 educational sessions for as long as these are being conducted for participants still in Phase II. Assessments will be conducted at six-month intervals by phone and at twelve-month intervals at the clinic. The primary focus of these assessments will be to collect data on cardiovascular events.

3.3.5 Phase IV

Based on a decision by the DSMB, the Intensive Lifestyle Intervention was stopped on September 14, 2012, because the likelihood of detecting a difference in the primary outcome between the two intervention groups was small. Participants were mailed a letter dated October 9, 2012, explaining the termination of the ILI and describing continued follow-up. Participants in the ILI were invited to meetings to discuss the transition from the intervention to a general education intervention. The transition was completed in January 2013.

Phase IV is similar to Phase III with the one difference being that the ILI and DSE participants receive the same general education intervention. Follow-up for outcomes and clinical exams continue as described for Phase III.

3.3.6 Coordinating Center Follow-up of UCLA Participants

The Coordinating Center will schedule one last call/attempt to reach the UCLA participants who did not transfer to USC. Participants will be notified that this will be the last attempted call and encouraged to re-engage in the study. Participants wishing to re-engage will be facilitated; those who do not re-engage will be offered a mailing of a close-out packet of study information when the study closes. Participant contact information will be updated. The Coordinating Center will enter a Lost to Follow-Up and Inactive Participant Tracking form for all UCLA non-transfers. A Participant Status Form will be entered to indicate that a close-out call was completed and if participant wishes to receive a close-out packet. The vital status of these participants will be tracked until the study ends by using the Internet, Social Security Death Index, or similar death search engines. If the death of a participant is identified, next of kin will be contacted and a death certificate will be obtained to provide information for outcome adjudication.

3.4 Sample Size Justification

The original target sample size for the Look AHEAD clinical trial is 5,000 participants who will be followed for a maximum of 11.5 years. This target was expected to provide a minimum of 90% power at the (two-sided) 0.05 significance level to detect an 18% relative decrease in the rate of primary outcomes among participants assigned to Lifestyle Intervention. The rate of primary outcomes among participants assigned to Diabetes Support and Education was expected to be approximately 3.125% per year (see Appendix B for discussion of event rate projection). Supporting calculations were based on the assumption that recruitment will be uniform over 2.5 years and that 2% of the participants will be lost annually with respect to endpoint ascertainment in each arm. Table 3.4 contains the power for testing the primary study hypothesis across a range of event rates and lengths of follow-up, based on standard formulae.⁹¹

Table 3.4 Power to detect a relative 18% decrease in the annual rate of primary outcomes for varying annual event rates among participants assigned to Diabetes Support and Education

Annual Event Rate: Diabetes Support and Education	Maximum Length of Follow-up (Years)					
	9.5	10.0	10.5	11.0	11.5	12.0
2.750 %	0.83	0.84	0.86	0.87	0.89	0.90
3.000 %	0.85	0.87	0.88	0.90	0.91	0.92
3.125 %	0.87	0.88	0.90	0.91	0.92	0.93

3.250 %	0.88	0.89	0.91	0.92	0.93	0.93
3.500 %	0.90	0.91	0.92	0.93	0.94	0.95

3.4.1 Revised power computation

With the extension of the study to a maximum of 13.5 years of follow-up, modification of the primary endpoint, and actual randomizations and observed dropout rate, the study power is expected to be 80% at the (two-sided) 0.05 significance level to detect a 18% relative decrease in the rate of primary outcomes among participants assigned to Lifestyle Intervention if the event rate in the Diabetes Support and Education group is 2% per year (see Appendix H for details on the monitoring plan).

4. STUDY POPULATION

The eligibility and ineligibility criteria for Look AHEAD identify participants who have moderate or high risk for occurrence or recurrence of cardiovascular disease events, who are likely to adhere to the intervention, for whom the intervention is safe, and who are likely to benefit from weight loss.

The coordinating center will monitor the distribution of the recruited cohort with respect to age, gender, insulin use, prior cardiovascular disease, and other factors expected to influence the incidence rate of the trial's composite primary outcome. Based on this monitoring activity, targeted recruitment strategies may be developed to ensure that the study cohort is consistent with the event rates necessary to provide adequate power for meeting study objectives.

Source of medical care Look AHEAD participants will receive their general medical care from health care providers outside of the Look AHEAD staff. Participants who do not have a source of usual medical care or who currently receive their care from Look AHEAD physicians will be helped to identify an alternative source of medical care.

4.1 Eligibility Criteria

Gender Men and women are eligible. Look AHEAD will endeavor to recruit approximately equal numbers of men and women.

Type 2 diabetes mellitus Diabetes mellitus will be determined by self-report with verification (medical records, current treatment, verification from personal health care provider, or test results meeting the 1997 American Diabetes Association criteria of fasting glucose > 126 mg/dl, symptoms of hyperglycemia with casual plasma glucose > 200 mg/dl or two-hour plasma glucose > 200 mg/dl after a 75 gram oral glucose load). In an effort to identify individuals with type 2 diabetes (the population that would be most responsive to weight loss), individuals who have a clinical history strongly suggestive of Type 1 diabetes will be excluded. Individuals taking oral hypoglycemic medication or insulin and those who are treated with diet and exercise are eligible. No more than 30% of the study population will be using insulin at entry into the study.

Body mass index Overweight individuals, with body mass index of 25 kg/m^2 or greater (27 kg/m^2 if currently taking insulin) are eligible. Weight loss is recommended for overweight individuals with one or more cardiovascular risk factors, including diabetes mellitus. There is no upper eligibility criterion for body mass index, however an upper limit on weight has been set (Section 4.2.1).

Age Individuals aged 45-75 years old are eligible. Individuals older than 75 years of age are excluded due to their increased risk of competing mortality and potential safety concerns related to weight loss.

Ethnicity All ethnic groups are eligible for the study. Look AHEAD has the goal of recruiting 33% of the study cohort from ethnic minority groups including African Americans, Hispanic Americans, American Indians, and Asian Americans. Data from NHANES III indicate that

approximately 23% of individuals meeting the eligibility criteria for Look AHEAD will be from ethnic minorities.⁸⁹

Blood pressure Look AHEAD will enroll individuals whose blood pressure is under at least moderate control: treated or untreated resting systolic/diastolic blood pressure less than 160/100 mmHg. Individuals whose blood pressure exceeds these levels during screening will be told to seek treatment. Such individuals may be rescreened after three months to re-assess blood pressure eligibility.

Glycemic control Look AHEAD will enroll individuals whose HbA1c is less than 11% or equal to 11%. Individuals whose HbA1c exceeds this level may require more urgent care and will be told to seek treatment. Such individuals may be re-screened after three months to re-assess HbA1c eligibility.

Lipid control Individuals with a fasting triglycerides concentration less than 600 mg/dl are eligible. Individuals whose fasting triglycerides concentration exceeds this level may be re-screened after three months to re-assess triglycerides eligibility.

History of cardiovascular disease Look AHEAD will recruit individuals both with and without a history of cardiovascular disease. Data from NHANES III indicate that approximately 29% of individuals meeting the eligibility criteria defined by the trial will have a history of cardiovascular disease.⁸⁵ Cardiovascular event rates in diabetic individuals with heart disease are expected to be approximately twice those of diabetic individuals without a history of heart disease.

Eligible participants include those with a history of uncomplicated myocardial infarction, coronary artery bypass surgery, percutaneous coronary angiography, atherectomy or stent placement, chronic stable angina pectoris, no resting or exercise induced complex arrhythmias, and stable NYHA Class I or Class II congestive heart failure if they are beyond three months. Participants with a history of carotid or peripheral artery atherectomy, angioplasty, or bypass surgery are also eligible for inclusion if they meet functional criteria for inclusion.

All participants will undergo a supervised maximum exercise stress test using the established study protocol. The exercise stress test will be conducted while the participant is continued on any prescribed medication for cardiovascular disease. Abnormalities will result in exclusion or in further evaluation. Individuals who develop exercise induced angina pectoris or significant ST segment depression of 1.5 mm or greater at low to moderate workloads (less than 7 METs) may be included if they have been evaluated by a cardiologist and considered safe for participation in the Lifestyle Intervention protocol.

Willingness to participate Participants must be willing to be randomized to either Diabetes Support and Education or the Lifestyle Intervention and to follow the protocol to which they have been assigned. Individuals who are unwilling to consider using weight loss medications are eligible for the study, however they must be willing to modify their diet and their activity and to attempt to lose 7% of their body weight if they are assigned to the Lifestyle Intervention.

4.2 Exclusion Criteria

The following criteria are used to exclude individuals for whom weight loss might not be safe, those who may have difficulty adhering to the lifestyle intervention, or those with medical conditions that might interfere with the intervention goals.

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 communicate with local study staff
- Current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
- Hospitalization for depression in past six months
- Self-report of alcohol or substance abuse within the past twelve months, current consumption of more than 14 alcoholic drinks per week, and/or current acute treatment or rehabilitation program for these problems (Long-term participation in Alcoholics Anonymous is not an exclusion.)
- Plans to relocate to an area not served by Look AHEAD or travel plans that do not permit full participation in the study
- Lack of support from primary health care provider or family members
- Failure to complete the run-in for dietary intake and exercise (see Section 4.6)
- In past three months, weight loss exceeding 10 lbs (Such individuals may have difficulty losing additional weight.)
- Current use of medications for weight loss
- Self-reported inability to walk two blocks
- History of bariatric surgery, small bowel resection, or extensive bowel resection
- Chronic treatment with systemic corticosteroids (Weight gain associated with steroids may interfere with the intervention goals. Use of hormone replacement therapy or oral contraceptives will not lead to exclusion.)
- Another member of the household is a participant or staff member in Look AHEAD
- Weight greater than 350 pounds unless equipment is available to conduct maximal exercise test for heavier individuals
- 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

- Currently pregnant or nursing (These individuals can be re-contacted for screening after delivery or when finished nursing.)
- Cancer requiring treatment in the past five 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)
- HIV positive (self-report), due to effects on weight and body composition of HIV and medications used to treat HIV
- Active tuberculosis (self-report)
- Cardiovascular disease (heart attack or procedure within the past three months or participation in a cardiac rehabilitation program within last three months, stroke or

history/treatment for transient ischemic attacks in the past three months, or documented history of pulmonary embolus in past six months)

- Participants also will be excluded if they meet any of the following criteria:
 - unstable angina pectoris or angina pectoris at rest
 - a history of cardiac arrest
 - complex ventricular arrhythmia at rest or with exercise (e.g., ventricular tachycardia)
 - uncontrolled atrial fibrillation (heart rate of 100 beats per minute or more)
 - NYHA Class III or IV congestive heart failure
 - acute myocarditis, pericarditis or hypertrophic cardiomyopathy
 - clinically significant aortic stenosis
 - left bundle branch block or cardiac pacemaker unless evaluated and cleared for participation by a cardiologist
 - cardiac defibrillator
 - heart transplant
 - history of aortic aneurysm of at least 7 cm in diameter or aortic aneurysm repair
 - resting heart rate less than 45 beats per minute or greater than 100 beats per minute
- Any abnormality during the maximum exercise stress test that indicates that it would be unsafe to participate in the Lifestyle Intervention (This includes angina pectoris or significant ST segment depression at low levels of exercise, unless evaluated and cleared for participation by a cardiologist; exercise induced ventricular arrhythmias; abnormal hemodynamics, such as flat or decreasing systolic blood pressure with increasing workload; and an abnormal response to exercise which, in the opinion of the exercise physiologist or physician, would make it unsafe for the individual to participant.)
- Those at moderate to high risk for cardiac complications during exercise and/or who are unable to self-regulate activity or understand the recommended activity level (The phrase moderate to high risk is defined according to AHA/ACSM criteria. Information for this determination is available from the medical history and the ECG performed during maximal exercise stress testing.)
- Renal disease: urine dipstick protein of 4+ (equivalent to approximately > 1 g/day), serum creatinine exceeding 1.4 mg/dl (women) or 1.5 mg/dl (men), or currently receiving dialysis
- Chronic obstructive pulmonary disease that would limit ability to follow the protocol (investigator judgment)
- Self-reported chronic hepatitis B or C or cirrhosis
- Inflammatory bowel disease requiring treatment in past year
- Cushing's syndrome (clinic diagnosis or self-report)
- Acromegaly (clinical diagnosis or self-report)
- Amputation of lower limbs as result of non-traumatic causes
- Any major organ transplant (does not include cornea or hair transplants)
- Conditions not specifically mentioned above may serve as criteria for exclusion at the discretion of the clinical site

4.3 Recruitment

The goal for the overall study will be 5,000 participants, or approximately 313 in each of the 16 clinical centers, to be recruited over 2.5 years with 33% deriving from ethnic/racial minorities. Each clinical center will develop a site-specific recruitment plan to accommodate the variability

across centers in catchment area characteristics, media market outlets, and access to diabetic patients. Each site-specific recruitment plan will reflect a variety of approaches directed both at population-based recruitment and at recruitment from identified diabetic patient groups. A central media group will develop a variety of materials (e.g., brochures, media kits, video ads for television outlets, five-minute video-tapes and slide sets for community events, newspaper ads, billboards, medical care setting displays, posters), typically for local-site production as needed.

4.4 Informed Consent

Before individuals may participate in any screening procedures, informed consent must be obtained. Clinics will be 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 will be 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 D. In the event a significant protocol change occurs, the informed consent should be adjusted appropriately and sites will submit the revised documents to their IRB for approval.

Local IRB's will determine whether it is necessary to re-consent participants.

4.4.1 Institutional Regulatory Requirements

Annually, sites will submit to the Coordinating Center stamped IRB approval letters and current copies of all consent forms. These records will be maintained by the Coordinating Center as a central archive. Upon request, the consent forms may be released for internal IRB review.

4.5 Screening Process

The purpose of the staged screening process is to identify and verify eligible participants through a series of visits achieving the objectives of an informed consent process, complete baseline measurements and procedures, and randomize participants into the Look AHEAD study. Some flexibility and alternatives in scheduling are expected, however, all eligibility and baseline data must be reviewed prior to scheduling randomization. Specific details may be found in the Manual of Operations.

Look AHEAD will include several screening steps before randomization of the participants.

- A preliminary screen will be completed to determine eligibility either by phone or at the clinical site as a separate visits or in combination with the Informational Orientation Visit (IOV) to eliminate a substantial proportion of ineligible volunteers
- Informational Orientation Visit (Potential participants will be provided with information about the study, their questions will be answered, and they will receive a consent form to review with clinic staff.)
- Clinic visit (SV1) for laboratory tests, anthropometric measures, questionnaires, start of run-in
- Clinic visit (SV2) for completion of run-in, behavioral screen, treadmill test, physician visit

Flexibility and alternative approaches in scheduling these steps are expected, due to varying local circumstances, but all screening procedures will take place before randomization. Additional screening visits may be required at some clinics due to scheduling issues or location of facilities.

4.6 Study Run-In

All participants will complete a two-week run-in period prior to randomization. They will be asked to record information about diet and physical activity daily during this period. Successful completion of self-monitoring will be required for eligibility.

4.7 Randomization Visit

Eligible participants will be randomized to one of the two arms of the study, Diabetes Support and Education or Lifestyle Intervention, according to a randomization scheme that will be controlled by the coordinating center. Randomization will be stratified by clinical center.

4.8 Retention and Efforts to Maintain Contact with Inactive Participants

4.8.1 Retention Promotion Efforts

Retention will be promoted by:

- 1) examining and attempting to remove barriers (e.g., by addressing parking and other transportation issues, adjusting clinic hours, and providing or reimbursing for child and elder care);
- 2) incorporating a variety of methods to promote contact with all participants and provide social support for all participants, including those in Diabetes Support and Education;
- 3) providing all staff and investigators who have contact with Look AHEAD 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.

4.8.2 Efforts to Maintain Contact with Inactive Participants

Look AHEAD will make every effort to maintain contact with inactive participants. The goal will be to maintain 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 will be given to attending annual assessment visits; even participants who are unwilling to continue attending intervention sessions will be strongly encouraged to attend the assessment visits.

4.9 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 reports are submitted to the clinical centers and the Look AHEAD 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 Look AHEAD clinic, a graded response of assistance that is based on clinic-specific retention issues is provided.

4.10 Participant Honorarium

Randomized participants will be provided a modest honorarium to defray costs associated with attending clinic visits and to recognize their time and effort. The honorarium is given for attendance at annual assessments, regardless of level of participation in intervention activities.

5. INTERVENTIONS

5.1 Interventions

Eligible participants are randomized to the two arms of the study: a control group referred to as “Diabetes Support and Education” or to Lifestyle Intervention.

5.2 Aspects of the Intervention Common to Both Study Arms

All participants attend a one-hour diabetes education class at the end of the screening process. This session provides basic education about diabetes, with particular emphasis on aspects of diabetes care related to the trial such as management of hypoglycemia, cardiovascular disease symptoms, and foot care. All participants at risk of hypoglycemia are encouraged to use blood glucose self-monitoring equipment and strips. The importance of eating a healthy diet and being physically active for both weight loss and improvement of glycemic control are stressed. All individuals who smoke are encouraged to stop smoking and are provided with self-help materials and/or referral to local programs, as appropriate. Participants in both interventions and their physicians are given results from study examinations after each annual examination (as described in Section 6). All participants will continue to receive their medical care and medical management of their diabetes from their usual source of medical care, not from the Look AHEAD study staff.

5.3 Diabetes Support and Education

The control group for Look AHEAD is known as Diabetes Support and Education. The goal is to offer a valuable educational experience to these participants and to respond to their interest in education and support, thereby helping to retain them in the trial.

5.3.1 Contact Mode and Frequency

Participants assigned to Diabetes Support and Education are invited to attend three group educational / social support sessions each year for 4.0 to 6.5 years after study randomization begins. One educational or social support session annually will continue to be offered beginning with year 5 until the end of the trial. Attendance is strongly encouraged but not required at these sessions. These participants also attend regularly scheduled clinic visits for annual assessment and participate in telephone calls for data collection and safety monitoring.

5.3.2 Content of Educational Sessions

The educational sessions offered for Diabetes Support and Education include one session each year on diet/nutrition and one session related to exercise. These sessions are informational and do not teach behavioral self-regulation skills. The content of these sessions are developed by the Diabetes Support and Education committee to standardize the intervention across clinics. Different nutrition and exercise topics are covered each year. Sessions are conducted by an individual with a background in diabetes education, exercise, or nutrition.

5.3.3 Content of Support Sessions

Support sessions are also offered annually to participants assigned to Diabetes Support and Education. These provide an opportunity for participants to discuss issues related to living with diabetes. These sessions will involve open discussion, facilitated by a member of the Look AHEAD staff.

5.4 Lifestyle Intervention

The active intervention condition for Look AHEAD is known as Lifestyle Intervention. This intervention combines diet modification and increased physical activity with a goal of sustained weight loss. Information related to safety of weight loss intervention in individuals with diabetes (e.g. hypoglycemia and foot care) is presented. The lifestyle intervention is modeled on group behavioral programs developed for the treatment of obese patients with type 2 diabetes^{34,92,93} and includes treatment components from the Diabetes Prevention Program.

The intervention utilizes strategies that have been shown to be most effective for long-term weight loss and weight loss maintenance. These include a portion-controlled diet (i.e., a diet which provides portions of food with a fixed calorie and macronutrient content) during the initial phase of weight loss, a multi-component approach to intervention (including behavioral techniques, diet modification, physical activity, and social support), and ongoing regular contact throughout the follow-up period. Weight loss medication and advanced behavioral strategies are offered in later months of the weight loss program for participants having difficulty achieving or maintaining weight loss.

All centers in Look AHEAD are utilizing the same lifestyle intervention. A treatment manual developed by Look AHEAD and approved by the Steering Committee will contain lessons and materials for the participants and an accompanying guide for the counselors. All centers will use these materials, which have been designed to be appropriate for individuals of different backgrounds and education. In addition all counseling staff will be trained by the Lifestyle Intervention Committee and monitored to ensure that they deliver the intervention as designed. These procedures will help ensure standardization of the intervention across centers.

The intervention has been designed to allow individual flexibility of treatment strategies. This is primarily accomplished by the use of individual sessions in combination with group meetings. Individual participants select the specific foods they wish to consume, the types of physical activities in which they would like to engage, and whether or not to use weight loss medications. Participants not adhering to the intervention will be helped to identify the barriers they are experiencing and to utilize the strategies that they feel will be most helpful to them in overcoming these barriers. Table 5.4.1 summarizes the Lifestyle Intervention.

5.4.1 Contact Mode and Frequency

Participants assigned to the Lifestyle Intervention will receive education in diabetes management that will parallel sessions provided those assigned to Diabetes Support and Education. The Lifestyle Intervention involves a combination of regularly scheduled group and individual sessions. The Lifestyle Intervention is divided into three phases.

Phase I (Months 1-12) During Months 1-6, participants are seen in clinic weekly with three group meetings and one individual counseling session per month. The individual sessions allow tailoring of the group-based intervention to individual needs.⁹⁴ Flexibility is provided in the proposed protocol so that participants who miss a visit can receive additional individual sessions. Participants are scheduled for a total of 24 visits during the first 26 weeks (six months). During Months 7-12, participants are seen in clinic at least twice a month. Group sessions are provided every-other-week, with participants encouraged to attend at least one group meeting per month. They also continue their monthly one-on-one meetings with individual counselors.

Phase II (Months 13-48) A minimum of two contacts per month are expected during this phase. One contact is on-site and the other by phone, mail, e-mail, or voice mail. More frequent contact is permissible if desired by the participant. A clinic, at its discretion, may offer an ongoing “open” group that is led by an individual counselor and meets regularly throughout the trial to offer group support. Refresher groups will be offered three times a year. These convene once a week for up to six weeks and will be designed to reverse weight gain or promote weight maintenance.

Phase III (Months 49+) From Month 49 through January 2013 participants will be offered monthly on-site individual contact with a counselor. Open groups will be offered one time per month. Sites will offer one refresher group and one national campaign per year.

Phase IV Beginning January 2013, all participants in the intensive lifestyle intervention and diabetes support and education were converted to a general education intervention based on a recommendation by the DSMB that the intervention be stopped due to futility with respect to the primary outcome.

Table 5.4.1 Look AHEAD Lifestyle Intervention Arm

GROUP OBJECTIVE	Mean loss \geq 7% of initial weight
OBJECTIVES FOR PARTICIPANT BEHAVIOR	Intake of 1200-1800 kcal/day, depending on baseline weight; gradual progression to 175 minutes of physical activity per week
CONTENT	
Knowledge	Proper diabetes management, caloric control, sound nutrition, methods to increase activity, exercise precautions
Motivation	Self-efficacy, outcome expectations, importance of lifestyle modification
Self-Regulatory Skills	Self-monitoring, goal-setting, self-reinforcement, social support, cognitive restructuring, relapse prevention
Experience	Facilitative group process and support combined with individual counseling
Environmental	Practical assistance in overcoming barriers to adherence
CONTACT SCHEDULE	
<i>Phase I</i> Months 1-6	Three group meetings per month; One individual counseling session per month
Months 7-12	Two group meetings per month offered, with participants expected to attend at least one; one individual counseling session per month
<i>Phase II</i> Months 13-48	Minimum of one on-site, individual counseling session per month; minimum of one contact per month by telephone, postcard, voice-mail, or e-mail; optional “open” group meetings provided at site’s discretion; three refresher courses offered each year
<i>Phase III</i> Months 49 to January 2013	Monthly on-site individual contact with a counselor. Open groups offered one time per month. One refresher group and one national campaign offered per year.
<i>Phase IV</i> <u>January 2013 and beyond</u>	<u>Educational sessions one to two times per year with DSE.</u>
MONITORING AND ADHERENCE	Individual counselors will collect data on attendance, weight and self-monitoring of diet and exercise; data will be entered into a computer-based tracking system; feedback will be given to participants

5.4.2 Weight Loss Counselors

The Lifestyle Intervention is delivered by a team of lifestyle counselors. The intervention team at each site ideally includes individuals with a combined expertise in nutrition, exercise physiology, behavior modification (psychology/social work) and diabetes education. Experience providing weight reduction therapy and leading groups is an important qualification of all lifestyle counselors.

5.4.3 Weight Loss Groups

It is anticipated that two new groups with approximately ten members per group will be started every four months. Groups are offered at different times of day and evening to accommodate different schedules. Participants complete the Phase I of the program with their assigned group (closed-group format).

5.4.4 Weight Loss Goals

The Look AHEAD Lifestyle Intervention is designed to induce a minimum weight loss of 7% of initial body weight during the first year. Each clinical center is expected to achieve a mean weight loss $\geq 7\%$ across all of their participants. Centers that do not achieve at least a 5% mean weight loss will receive extra assistance to help them increase their weight loss outcomes. Group behavioral weight loss interventions similar to the Look AHEAD Lifestyle Intervention produce mean weight losses of 7%-10% of initial weight over 20-26 weeks in patients with type 2 diabetes.^{34,92,93,95}

Individual participants in Look AHEAD are encouraged to lose 10% (or more) of their initial body weight, with the expectation that “aiming high” will ensure that a greater percentage of participants achieve the minimum 7% weight loss.

5.4.5 Diet

Restriction of caloric intake is the primary method of achieving weight loss. In order to aim for a weight loss of 10% of initial weight, the calorie goals are 1200-1500 kcal/day for individuals weighing 250 lbs (114 kg) or less at baseline and 1500-1800 kcal/day for individuals who weigh more than 250 lbs. These goals can be reduced to 1000-1200 kcal/day and 1200-1500 kcal/day, respectively, if participants do not lose weight satisfactorily. These calorie levels should promote a weight loss of approximately one to two lbs/week.⁵

The composition of the diet is structured to enhance glycemic control and to minimize cardiovascular risk factors. The recommended diet is based on guidelines of the ADA and National Cholesterol Education program^{96,97} and includes a maximum of 30% of total calories from total fat, a maximum of 10% of total calories from saturated fat, and a minimum of 15% of total calories from protein.

During the first four weeks of the intervention, participants are encouraged to follow a portion-controlled diet, given findings that this approach produces significantly larger weight losses than having participants consume a self-selected diet of conventional foods.^{34,82,98} Portion-controlled diets provide patients servings of food with a fixed calorie and macronutrient content. Participants choose from two prototype diets. The first includes the use of a commercially available liquid meal replacement that will replace two meals and snacks each day. This regimen is combined with an evening meal of either a frozen entrée or conventional table foods to provide a total of 1200-1800 kcal/day depending on the individual's baseline weight. The second option,

for those who do not accept or tolerate the liquid/prepared meal prototypes, involves the consumption of a very structured meal plan, with the same calorie range, using foods that participants prepare themselves.⁹⁹ Individual monthly sessions with the counselor provide an opportunity to tailor these diet options to the participant's preferences, lifestyle, and health.⁸⁸

Individuals who are successful and desire to continue on this diet are allowed to do so, with a monthly review at the individual session to re-assess progress. Long-term replacement (with a liquid supplement) of one meal and one snack a day also will be an option, given the favorable long-term (51 months) results reported by Flechtner-Mors, et al.⁴⁷ Meal replacements and structured meal plans will also be options in a "tool-box," that can be used to reverse weight regain (Section 5.5).

5.4.6 Physical Activity

Physical activity is a cornerstone of the proposed intervention, because it contributes to long-term weight loss maintenance,¹⁰⁰ improves cardiorespiratory and muscular fitness, and reduces risk factors for cardiovascular and metabolic disease.^{25,101} In addition, controlled trials employing physical activity as a key part of weight loss intervention have observed significant reductions in the incidence of diabetes^{54,102} and hypertension.⁴⁶

The physical activity program of Look AHEAD relies heavily on unsupervised exercise, with gradual progression toward a goal of 175 minutes of moderate intensity physical activity per week by the end of the first six months. Exercise bouts of ten minutes and longer are counted toward this goal. Exercise is recommended to occur five days per week. In general, occupational activity will not be counted towards the physical activity goal.

Moderate-intensity walking is encouraged as the primary type of physical activity. To enhance participation, the intervention will allow for individual choices in types of moderate physical activities and the tailoring of exercise programs based on each participant's physical fitness test and safety issues.

Unsupervised exercise is encouraged for most sessions, as it has been shown to be as effective in weight loss and risk factor modification as supervised exercise.^{103,104} However, sites will have the option of providing one supervised exercise session per week to stimulate social support for exercise.

5.4.7 Behavioral Strategies

The Lifestyle Intervention will include training in cognitive behavioral strategies to help produce and maintain changes in dietary intake and physical activity. All participants will self-monitor their intake (recording calories and fat grams) throughout the first six months and periodically thereafter. Key behavioral strategies such as stimulus control techniques, problem solving, and relapse prevention will be taught during the first six months. Individual sessions will focus primarily on goal setting, problem solving, and motivational interviewing.

5.5 Behavioral and Medication Toolbox

The intervention plan calls for six months of treatment with lifestyle strategies alone, with no weight loss medications. Participants who fail to lose at least 1% of body weight per month

during the first six months or who fail to attend treatment sessions regularly and fail to complete diet and activity diaries are identified and given special assistance by their lifestyle counselor. Efforts are made to identify the barriers for the individual participant and to develop strategies to reduce these barriers.

After six months of lifestyle strategies alone, a toolbox of weight loss medications and advanced behavioral strategies may also be employed. Weight loss medications and advanced behavioral strategies to be included in the toolbox are selected by the Look AHEAD Pharmacologic and Lifestyle Committees and approved by the Steering Committee.

The general principles governing the use of weight loss drugs in Look AHEAD are as follows:

- Drugs are used only as an adjunct to an intensive program of exercise and dietary modification.
- Only drugs that have received FDA approval for use in weight loss are included in the toolbox.
- The use of drugs is guided by the individual Look AHEAD participant's past medical history and preferences.
- Participants who do not wish to use weight loss medications are not required to do so.
- Strict standards for drug safety are set. While any drug may have some side effects, drugs are discontinued for any important or lasting adverse events.
- Objective standards for judging drug efficacy at the individual level are set, and drugs are discontinued if such standards are not met.

The only drug originally approved for the toolbox was orlistat, however the Steering Committee later voted to discontinue its use based on finding limited effectiveness. It is assumed that over time additional weight loss medications that meet the above criteria will be added to the toolbox as approved by the Steering Committee.

Advanced behavioral strategies also are considered for use with specific participants after six months of intervention. Examples of advanced behavioral strategies include provision of exercise equipment, enrolling participants in a supervised exercise program, providing food coupons or food, or enrolling participants in a cooking class. Selection of a particular strategy is based on the barriers experienced by the participant.

5.5.1 Triggers for Initiating Toolbox

No weight loss medications or advanced behavioral strategies are started within the first six months of intervention, during which time diet, exercise, and less intensive behavioral strategies are used to induce weight loss. After this six-month interval, drug therapy or more intensive (advanced) behavioral toolbox strategies are initiated in either of the following circumstances:

- Sub-optimal weight loss over the first six months of intervention
- Significant weight regain or difficulty with weight loss maintenance

Specific algorithms governing use of medications in these two situations are approved by Steering Committee and defined in the Manual of Operations. The basic principle is that clinics strongly suggest use of medication or advanced behavioral strategies for individuals with clearly

sub-optimal weight loss or marked regain; in other situations, use of medication is based on the participant's request.

5.5.2 Procedures for Initiating Toolbox

Procedures for initiating drugs and advanced behavioral toolbox strategies as adjuncts to the Look AHEAD lifestyle intervention are as follow. First, each participant with indications for adjunctive therapy (described above) undergoes a standard clinical evaluation, including a medical history and physical examination to detect possible contraindications to the use of specific drugs. Second, participants view a videotape with information on Look AHEAD weight loss drugs. The videotape presents information concerning expected benefits, possible adverse effects, and recommended precautions. Following the videotape, participants also are questioned about their preferences for drugs and/or their interest in using an advanced behavioral toolbox strategy. Third, clinic professionals, including physicians, nurses, dietitians, case managers, and behaviorists discuss the circumstances of each participant, and recommend a course of action. In most cases, such recommendations are strongly influenced by general Look AHEAD guidelines and a set of pan-clinic algorithms designed to help clinic professionals prioritize the use of drugs and advanced behavioral toolbox strategies.

Participants who are about to start treatment with a weight loss drug are asked to sign a consent form specifically related to the use of that medication, unless they have already consented as part of the informed consent procedure at entry into Look AHEAD. The consent form indicates the risks and benefits of the specific medication and the procedures being implemented in the trial to minimize the risks, including the schedule of medical monitoring while on the medication.

5.5.3 Procedures for Monitoring and Stopping Toolbox Strategies

If a weight loss medication is initiated, appropriate medical monitoring by Look AHEAD staff is implemented. This may involve weekly, biweekly, or monthly visits for review of side effects, extra monitoring of blood pressure, etc. The specific follow-up protocol differs for each medication and is described in the Look AHEAD Manual of Operations. Medication is stopped if there is evidence of allergy or other idiosyncratic response to medication or a significant adverse event (e.g., blood pressure elevation). Likewise, medication is stopped if the participant is not adhering or does not achieve the expected benefit in terms of weight loss or weight loss maintenance. Similar approaches are used for monitoring the effectiveness of the advanced behavioral strategies. If adverse effects occur (e.g. injury from too much exercise) or the expected weight loss/weight maintenance benefits are not achieved, the advanced behavioral strategy is discontinued.

5.5.4 Adherence and Monitoring

A computerized tracking system is used to monitor participants' adherence to various components of the Lifestyle Intervention. Areas tracked include weight, attendance at individual and group treatment sessions, and self-monitoring of diet and physical activity. Data also are collected on use of weight loss medication and advanced behavioral strategies. Clinics having difficulty achieving and/or maintaining the 7% weight loss goal are given guidance by the Lifestyle Intervention Committee or its designees. Additional site visits may be implemented to assist these clinics.

6. PARTICIPANT MANAGEMENT

6.1 Medical Care

In addition to type 2 diabetes, many study participants will have hypertension, dyslipidemia, and other conditions that require medical management. Given the relatively long duration of the Look AHEAD trial, many participants will develop health problems that require acute or chronic medical management. The Look AHEAD trial is neither designed nor staffed to provide comprehensive medical care to all participants, nor is this necessary to address the principal study objective of the trial. Accordingly, it will be necessary for all participants to have an established source of medical care independent of Look AHEAD staff. If a participant does not have a health care provider at the start of the trial, or loses the health care provider during the trial, Look AHEAD staff will assist in finding an appropriate health care provider. The Look AHEAD staff can assist the participant by referral to health care facilities, including physicians and clinics at the medical center of the Look AHEAD site. However, the site's investigator who is responsible for intervention decisions or outcome assessments of Look AHEAD participants should not also serve as the health care practitioner for the Look AHEAD participants.

6.1.1 Goals of Medical Care

It is the position of Look AHEAD that all participants, regardless of randomization to Lifestyle Intervention or Diabetes Support and Education, should receive comprehensive management of type 2 diabetes mellitus and of other cardiovascular risk factors, notably, hypertension and plasma lipids. The medical care should be in accord with current standards of care developed by the American Diabetes Association, JNC-VI, NCEP, and other consensus recommendations for primary care.

Type 2 Diabetes Mellitus The recommended goal for glycemic control for Look AHEAD participants is to achieve and maintain an HbA1c value less than 7%.

Hypertension The recommended goal for blood pressure for Look AHEAD participants is to achieve and maintain a blood pressure of less than 130/80 mmHg.

Lipids The recommended goal for management of lipoproteins for Look AHEAD participants is to achieve and maintain LDL-cholesterol less than 100 mg/dl. There are secondary goals for HDL-cholesterol (> 45 mg/dl) and triglycerides (< 200 mg/dl) that are in accord with ADA goals and the emerging NCEP consensus that will be released in May, 2001.

6.1.2 Providing Patient Education and Medical Information to Participants

Although Look AHEAD is not providing medical management to the participants, there are several steps that are being taken to assist participants and their health care providers in the effort to achieve these therapeutic targets. At entry to Look AHEAD, all participants are provided with a program of patient education on diabetes mellitus and other cardiovascular risk factors. A description of Look AHEAD, information on the therapeutic targets for diabetes, blood pressure and lipids, and a synopsis of current consensus recommendations for achieving these targets are sent to each participant's health care provider.

Data related to HbA1c, blood pressure, lipid values, ECG, urine albumin, estimated GFR, and serum creatinine values that are obtained during scheduled study visits are provided to participants and their primary care providers within one-two weeks in a form that clearly indicates abnormal values and ranges. Standards of care or generally accepted guidelines for interpretation and/or interventions related to these parameters also will be provided.

6.1.3 Participants Who Reach Alert Values for Blood Pressure

There are a number of reasons why Look AHEAD participants may not achieve or maintain the target levels for blood pressure. While the primary responsibility for medical therapy will rest with the participant and her/his primary care provider, if blood pressure is greater than 170/100 mmHg, the physician or other staff member will speak with the participant and his/her physician.

In the event of a medical emergency occurring at the clinical site for Look AHEAD, the study staff will undertake, under the direction of the Principal Investigator or designated staff, all necessary supportive medical care.

6.2 Participant Safety

The study will monitor 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 in participants enrolled in the Lifestyle Intervention, including safety in the use of any weight loss medications. Also, if a volunteer has a medical or surgical illness, the safety of continuing or resuming participation in interventions will be ascertained by the medical staff at the local center in cooperation with the participant's primary care physician.

6.2.1 Hypoglycemia Related to Exercise and Lifestyle Interventions

For patients who may be susceptible to hypoglycemia because they are using insulin or oral hypoglycemic medications that increase insulin secretion, weight loss interventions have the potential to increase the risk of hypoglycemia, especially during the time when diet and/or physical activity interventions are implemented.

Participants will be educated about symptoms of hypoglycemia, instructed to self-monitor glucose levels, and urged to contact the clinic if they have symptoms or blood glucose values suggestive of hypoglycemia. Look AHEAD clinic staff may reduce medications according to a standard algorithm based on glucose levels and symptoms. Changes in diabetic regimens will be communicated to the participant's primary care physician. Overall management of diabetes medications will remain under the control of the participant's primary care physician.

6.2.2 Cardiovascular Events

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

6.2.3 Hyperglycemia

The glycemic goals for all participants will follow the recommendations of the American Diabetes Association.¹⁰⁵

6.2.4 Symptomatic Hypotension

Weight loss may reduce blood pressure. Look AHEAD clinic staff will contact the personal care provider of any participants receiving medication for blood pressure control who develop symptomatic hypotension to discuss adjustment or discontinuation of these medications. If a personal care provider cannot be contacted in a timely manner, Look AHEAD physicians may elect to adjust these medications and the personal care provider will be notified by phone and follow-up letter.

6.2.5 Diabetic Neuropathy/Foot Ulcers

Participants at risk for foot ulceration secondary to peripheral neuropathy, peripheral vascular disease, or for other reasons are advised to limit weight bearing exercises. Participants in the Lifestyle Intervention are helped to identify other types of non-weight-bearing physical activities, such as swimming or bicycling.

6.2.6 Adverse Events

Adverse events, pre-existing conditions, and serious adverse events are defined by the Food and Drug Administration and other governing bodies. In the context of trials testing drugs, serious adverse events are defined by the FDA as: 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 Look AHEAD is treatment in the emergency room for severe hypoglycemia.

In the Look AHEAD safety monitoring system, participants who report adverse events to any staff person at any time will be referred to unmasked medical staff responsible for identifying, recording, and managing these events. Safety-related events will be 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 will not at any time communicate information regarding these events to study assessment personnel. Look AHEAD will maintain an outcome database that is completely separate and distinct from the safety monitoring system. This is necessary because many of the Look AHEAD staff members will 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 Look AHEAD participants will be 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 will contain solely those adverse events that are reported through these regularly scheduled event interviews conducted by designated outcome assessment staff who are masked to intervention assignment.

Collection of serious adverse events was changed following the conversion of the trial to an observational study (Phase IV). After (January 2013), only adverse events related to the clinic visits or general education intervention (e.g., injury due to a fall in the clinic; loss of confidential data) will be reported and tracked.

7. PLANS FOR FEASIBILITY EVALUATION AND STOPPING RULES

The progress of Look AHEAD and the study's potential of attaining its goals will be regularly evaluated by the Data and Safety Monitoring Board (DSMB -- Section 10.9). This committee will review and provide feedback to the NIDDK on the overall performance of the study group, including its success with respect to goals for recruitment, retention, and data quality. Several key criteria that the DSMB will use to inform its recommendations on the continuation of the Look AHEAD trial are summarized in this section.

7.1 Feasibility Evaluation

The feasibility of the trial will be formally assessed by the DSMB early in the study to ensure that the trial interventions are being successfully delivered. Data on the first 25% of participants recruited into Look AHEAD will be examined when these participants have all reached Year 1 and again when they have reached Year 2. Three criteria will be used to judge the success of the intervention.

1. To demonstrate success of the intervention at achieving a difference between study arms at one year, there must be at least a 5 percentage points difference in the average percentage point change in weight from Baseline to Year 1 between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.
2. Since the Look AHEAD goal is to achieve absolute weight loss (rather than diminished weight gain), a second feasibility criterion at Year 1 is also defined. The average absolute percent weight loss from Baseline among the first 25% of Lifestyle Intervention participants not using insulin at Baseline must be at least 5% at Year 1. Because insulin use may influence weight changes, the average percent weight loss from Baseline in insulin-using participants in the Lifestyle Intervention will also be estimated, however the sample size is not sufficient to estimate this percentage precisely. Weight loss in this cohort is targeted to be at least 3% at Year 1.
3. To assess the ability of the Lifestyle Intervention to produce longer-term effects, feasibility criteria based on two-year changes also are defined. These acknowledge the potential that changes in fitness, as well as changes in weight, may have an impact on cardiovascular disease in the long term. The longer-term feasibility of the trial will be assessed based on the following criterion. At Year 2, for the first 25% of participants there must be at least a 5% difference in the average percent change in weight or fitness from Baseline between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education. The fitness measure at Year 2 will be collected only in the subset of 25% of the study participants who are the first to reach their two-year post-randomization anniversary.

The DSMB will consider these feasibility criteria in the context of early trends in glucose control, atherogenic risk factors, and, as the study proceeds, cardiovascular event rates.

7.2 Stopping Rules For Efficacy and Futility

Incidence rates of the primary and secondary composite outcomes will be monitored throughout the trial and used for interim analyses of efficacy and futility. Group sequential methods for events rates will be used to control the Type I error to be 0.05 across these repeated analyses.¹⁰⁶⁻¹⁰⁸ Critical values for interim testing will be defined based on an O'Brien-Fleming type bound¹⁰⁹ and will use a spending functions to allow flexibility in the number and timing of interim analyses.¹¹⁰ With this approach, interim tests early in the trial are conservative and the reduction in the overall power of the trial caused by interim testing is small. Conditional power calculations will be used to assess the futility of continuation in the presence of a negative treatment effect.¹¹¹

The intervention was stopped for futility by the DSMB on September 14, 2012, at which point the trial was converted to an observational study.

7.3 Stopping Based On Safety Concerns

At each meeting, the DSMB will review data on adverse events and other safety issues to make an overall recommendation to the NIH concerning the safety of continuing Look AHEAD. Consistent with NIH policy, each Look AHEAD Principal Investigator will receive a report summarizing the DSMB review of the adverse event data. Principal Investigators are responsible for providing this report to the IRB at their institution.

8. DATA TO BE COLLECTED

This section reviews the types of data that will be collected by the clinical centers, central laboratory and reading centers; stored in the central study database; and analyzed to meet the scientific goals of the study. The Manual of Procedures provides details concerning the collection, management and analysis of specimens associated with each measure.

8.1 Overview of Data Collection Schedule

Baseline data will be collected during the series of screening visits and prior to beginning the interventions. Months 1-12 are designated as Phase I. Most Baseline measures will be reassessed at the end of this phase (Month 12) to determine the effect of the intensive intervention. Months 13-48 are designated as Phase II. Most Baseline measures also will be reassessed at the end of this phase (Month 48) to examine the long-term impact of the Lifestyle Intervention. Months 49 on are designated as Phase III. Follow-up visits past Year 4 on are intended primarily for collection of data on CVD events and those measures that potentially mediate the effect of the intervention on CVD events (weight, blood pressure, lipids, and HbA1c). Four sites will collect DEXAs at Year 8.

8.2 Schedule of Data Collection Visits

Follow-up data will be collected through regularly scheduled examinations and telephone interviews as outlined in Table 8.2. Clinic visits will occur annually (Months 12, 24, 36, etc. post-randomization until close-out in 2014). At Months 3 and 9 questionnaires will be mailed to all participants randomized prior to January 1, 2003. Structured telephone interviews will also occur at Month 6 and midway between each annual visit (i.e., at Months 18, 20, 42, etc. until close-out in 2014). These clinic visits, telephone interviews or self-administered outcomes forms will obtain interim medical history with a special emphasis on cardiovascular disease events, other illnesses, operations, hospital admissions, and alterations in prescriptions. Some will assess aspects of quality of life and health utilities. Each scheduled visit will include a discussion of adherence issues.

8.2.1 Home Visits or Out-of-Clinic Visits

Home visits or out-of-clinic visits may be completed for participants who are “lost-to-follow-up” to collect data and to provide an opportunity to encourage them to attend clinic for outcome measurements. A home visit or out-of-clinic visit may be done at the participant’s home, institution, health care facility, or other location as deemed acceptable by clinic staff and agreeable with participant. Home visits or out-of-clinic visits are expected to be rare and may not be used regularly to take place of clinic visits.

Table 8.2 Measures and Frequency

Measure	Screening and Baseline	Year				Extended Follow-up
		1	2	3	4	
Fasting blood collection						
HbA1c	X	X	X	X	X	Every other year
Fasting glucose	X	X	X	X	X	
Serum creatinine	X	X	X	X	X	Every other year
Cholesterol, LDL, HDL, triglycerides	X	X	X	X	X	Every other year
DNA storage	X					
Serum and plasma storage	X	X	X	X	X	Every other year
Inflammatory Markers (analyses TBD)	X	X			X	*Analyses Yr12 or close-out
Urine albumin, creatinine, eGFR	X	X	X	X	X	Every other year**
Seated blood pressure and pulse	X	X	X	X	X	Annual
Ankle-brachial index	X	X	X	X	X	
Waist circumference	X	X	X	X	X	Annual
Weight	X	X	X	X	X	Annual
Height	X				X	Year 8, Year 12 or close-out
ECG	X		X		X	Every Other Year
Cardiovascular fitness test	X	X	25%		X	
Substudies						
Body composition (DEXA) (N=1,200)	X	X			X	Year 8
Accelerometry (N=2,400)	X	X			X	
Citrated plasma collection	X	X			X	

* Analyses TBD at Yr12 or closeout (originally PAI-I, Fibrinogen and CRP).

**Urine samples will be collected at one additional visit in the out years, frozen and stored at the central lab.

8.3 Masking of Data Collection

To the extent feasible, staff collecting outcome data will be masked to the participants' intervention assignment. Data collection staff will not be involved in conducting the Lifestyle Intervention or the Diabetes Support and Education sessions. This separation is in an effort to promote objectivity of data collection and to minimize the opportunity for bias, which is considered particularly important for interview questionnaires and probing for events where the potential for differential ascertainment exists.

All primary and secondary outcomes will be adjudicated by investigators who are masked to treatment assignment. The adjudication will be done according to standard definitions.

8.4 Primary Outcome Measure

The primary outcome is a combination of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for angina. The Events Adjudication Committee will review pertinent medical records to confirm outcomes. Death certificates and other pertinent information will be obtained for all deaths. Internet-based resources will be used to increase the

completeness of records. The definition of the primary outcome measure is described in detail in Appendix C.

8.5 Secondary Outcome Measures

Pertinent medical records will be obtained for the following array of events and procedures: death, myocardial infarction, stroke, hospitalization for angina, coronary artery bypass grafting, percutaneous coronary angiography, hospitalization for congestive heart failure, carotid endarterectomy, and peripheral vascular bypass or angioplasty. The Look AHEAD Events Adjudication Committee will review the pertinent medical records and death certificates to confirm these events and procedures (See Appendix C).

8.6 Other Outcomes

Additional data collected by Look AHEAD are described below. Some of these measures are collected on all participants. Others are collected on only a portion of the participants, based on sample-size considerations. Outcomes fall into two categories, physical measures, and self-reported measures.

8.6.1 Physical Measures

Accelerometry At Baseline, Year 1, and Year 4, 2400 participants will wear accelerometers for one-week periods to monitor physical activity. These participants will also complete the Paffenbarger questionnaire for the same one-week period¹¹² and repeat the questionnaire at Year 8 and Year 12 or close-out. Centers participating in this substudy will be selected based on criteria proposed by the Core Measures Committee relating to experience, overall costs, and inclusion of a range of populations.

Albuminuria Albumin and creatinine will be measured in a spot urine sample at Baseline and annually through Year 4 by the Look AHEAD Central Laboratory and every other year thereafter. The incidence and progression of microalbuminuria or greater levels of excretion will be assessed using an albumin to creatinine ratio. Serum creatinine will also be measured at these times and GFR will be estimated. In addition to the analyses above, urine will be collected at one additional visit during the out years. These samples will be frozen and then stored at the Look AHEAD Central Lab for future research.

Body composition Dual x-ray absorptiometry (DEXA) will be performed on approximately 1,200 participants at Baseline, Year 1, Year 4, and Year 8, to assess body composition and bone mineral density (hip, spine, and total). Scans will be reviewed by Look AHEAD Reading Center to ensure uniform quality. Centers participating in this substudy will be selected based on criteria proposed by the Core Measures Committee relating to experience and availability of appropriate equipment, overall costs, and inclusion of a range of populations.

Cardiorespiratory fitness Fitness will be assessed at Baseline with a maximal treadmill test and at Year 1 and Year 4 with a submaximal treadmill test. The first 25% of the participants will also have a submaximal treadmill test at Year 2, as part of the feasibility evaluation for the study. The test will be repeated at Year 4. The Baseline symptom-limited maximum stress test represents current standards of care for exercise prescriptions and is critical for developing

standard criteria for subsequent submaximal tests. Estimated maximal MET capacity will serve as a primary measure for assessing change. Heart rate, blood pressure and perceived exertion will be determined during the exercise test, but gas exchange will not be measured.

Diabetes control Look AHEAD will include measurement of hemoglobin A1c and fasting glucose at Baseline and Years 1, 2, 3, and 4. Hemoglobin A1c will also be measured every two years during extended follow-up to assess diabetes control. These assays will be performed by the Look AHEAD Central Laboratory. In addition, Look AHEAD will track use of insulin and other medications used to control diabetes.

Dyslipidemia Lipid/lipoprotein concentrations (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) will be measured at the Look AHEAD Central Laboratory at Baseline, Year 1, Year 2, Year 3, and Year 4 and every two years during extended follow-up. Current medication use will be collected at each clinic visit. Look AHEAD will use these data to track the incidence and prevalence of dyslipidemia.

Electrocardiograms Electrocardiograms will be obtained at Baseline, Year 2, Year 4, Year 6, Year 8, Year 10, Year 12, and close-out according to a standard protocol. Technicians will receive central training. Tracings will be transmitted to the Look AHEAD ECG Reading Center for centralized reading and data processing.

Citrated plasma Citrated plasma will be collected at Baseline, Year 1, and Year 4 and shipped to the Look AHEAD Central Laboratory for analyses designed to explore mechanisms at the end of the trial. At design, it was anticipated that the study would observe improvements in markers of atherosclerotic disease in the intensive intervention group relative to the diabetes support and education comparison group. When the study was designed, it was envisioned that these mechanistic substudies would consist of analyses of a subsample of approximately 1700 participants for the analytes c-reactive protein, fibrinogen, and PAI-1. The Look AHEAD Steering Committee will determine the uses of these specimens toward the end of follow-up in order to utilize the most current scientific information and quickly implement substudies when unmasked data are available.

Hypertension and blood pressure measures Through annual blood pressure measurements and self-reported current medication use, Look AHEAD will track the incidence and prevalence of hypertension. Ankle/arm blood pressure will be measured at Baseline, Year 1, Year 2, Year 3, and Year 4 as a measure of peripheral artery disease.

Stored samples and DNA Serum and plasma will be collected at Baseline, Year 1, Year 2, Year 3, Year 4, Year 6, Year 8, Year 10, and Year 12, for central archival. DNA samples will be collected at Baseline (and subsequent years, if Baseline samples are inadequate) and stored for later use in genetic analyses.

Weight, height, and waist circumference Body weight will be measured annually throughout the entire study on all participants, using calibrated scales. Participants will be weighed in light indoor clothing. Waist circumference will be measured annually throughout the entire study. Height will be measured at Baseline and Years 4, 8 and 12.

8.6.2 Self-Reported Measures

Costs The use of medical resources (i.e. number and type of hospitalizations, ambulatory visits, medications, procedures) will be assessed from participant's self-report. The cost per type of hospitalization, outpatient encounter, etc. will be estimated using available US data and aggregated to estimate total direct medical costs for each intervention arm. The costs of the intervention will be estimated by periodic reports of clinic time spent by staff on the intervention. In addition to direct medical costs, selected indirect costs will be estimated by self-report.

Events Events will be assessed at 6-month intervals by telephone and at the clinic visits by an interviewer masked to the participants' intervention condition. Medical records for all hospitalizations will then be obtained. All events will be adjudicated by a central committee, which is masked to participants' intervention assignments.

Health behaviors Participants will report on their weight control practices, eating habits, and use of tobacco and alcohol and frequency of self-monitoring blood glucose at each biannual assessment through Year 4 and then Year 8 and Year 12 or close-out. Beginning with Year 8 and then annually, participants will report their weekly average use of aspirin, multi-vitamins, calcium and vitamin D and report the number of falls they experienced in the past year. Physical activity will be monitored in a subset of approximately 2400 participants through the use of the Paffenbarger Questionnaire at Baseline, Year 1, and Year 4. This subset of participants will also wear an accelerometer for this period (see above). Dietary intake will be assessed in the first 157 participants enrolled in each clinic at Baseline, Year 1, and Year 4. Note: The Paffenbarger Questionnaire will also be administered to the entire study cohort at Year 8 and Year 12 or close-out.

Health outcomes Look AHEAD will record (through self report), diagnoses and/or treatment of the following medical conditions: knee osteoarthritis,¹¹³ gall bladder disease, reproductive history, obesity-related cancers, and urinary incontinence. Lower extremity amputation will be ascertained by self-report, including location of amputation and cause. Participants also will complete a symptom checklist and report all prescription medications.

Psychosocial measures A battery of psychosocial measures will be assessed including standardized assessments such as the Beck Depression Inventory¹¹⁴ and an eating disorders questionnaire.¹¹⁵

Quality adjusted life years (QALYS) Two common approaches are routinely used to calculate QALYs. One reflects participants' preferences for their health, while the second reflects society's preferences. Both are included in Look AHEAD:

1. **EuroQol Feeling Thermometer** This is a visual analog scale that assesses participant-based preferences for their current health status.^{116,117} It will be measured at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months thereafter through close-out on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date.

2. **Health Utilities Index** This series of questions has been indexed to population norms for health states and allows the estimation of comparable population-based preference weights for quality adjusted life years (QALYs).¹¹⁸⁻¹²⁰ It will be measured at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months through Year 4, and then annually through close-out on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date.

Total QALYs are then calculated as the sum of the product of the number of years of life and the preference weights in each of those years, for both the study participant's and society's perspectives.

Quality of life The Short Form 36 (SF-36) version will be used to measure general health related quality of life.¹²⁶ It can be used to calculate domain scores plus two summary scores: physical summary (four domains, 21 items), and mental health summary (four domains, 14 items). The SF-36 will be collected at Baseline, Month 3, Month 6, Month 9, Month 12, and every six months through Year 4, and then annually through close-out on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date.

Sociodemographics Information on employment, household composition, and education is collected annually through Year 4 by self-report.

Weight history, personal medical history, family medical history At Baseline only, participants report their weights at various ages, history of weight cycling, and family and personal history of disease.

Technology Use At Year 10, participants will complete a self-administered form regarding their technology habits and usage.

Table 8.6 Questionnaires and Frequency										
Measure	Baseline	Months								Extended Follow-up
		6	12	18	24	30	36	42	48	
Costs										
Outpatient visit questionnaire	X	x	x	X	x	X	x	x	x	Every 6 mo Year 8 only
Participant resource use	X		x		x		x		x	
Events										
CVD events and health outcomes		x	x	X	x	X	x	x	x	X
Health Behaviors										
Eating patterns	X		x		x		x		x	Yr8, Yr12 or close-out
Dietary assessment (N=157 per clinic)	X		x						x	
Paffenbarger (Baseline, Yr1, Yr4 (N=2400 subset), Yr8 and Yr12/closeout (N=entire Look AHEAD cohort)	X		x						x	*Yr8, Yr12 or close-out
Tobacco and alcohol use	X		x		x		x		x	Yr8, Yr12 or close-out
Weight control practices	X		x		x		x		x	Yr8, Yr12 or close-out
Health Outcomes										
Knee osteoarthritis	X		x						x	Annually
Reproductive history	X		x		x		x		x	
Urinary incontinence	X		x		x		x		x	Annually
Symptoms checklist	X		x		x		x		x	Annually
Prescription medication use	X		x		x		x		x	Annually
Psychosocial Measures										
Beck Depression Inventory	X		x		x		x		x	Year 8 only
Eating disorders	X		x		x		x		x	Year 8 only
Quality Adjusted Life Years										
EuroQuol Feeling Thermometer	X	**	x	X	x	X	x	x	x	Every 6 mo
Health Utilities Index	X	**	x	X	x	X	x	x	x	Annually
Quality of Life										
Health quality of life (SF-36)	X	**	x	X	x	X	x	x	x	Annually
Sociodemographics										
	X		x		x		x		x	Yr8, Yr12 or close-out
Weight, Personal Medical, and Family Medical History										
	X									Annually
Technology Use										Yr10

*Yr8 and Yr12 or close-out, questionnaire to be administered to all participants

** Indicates administration at Month 3, Month 6, and Month 9 on participants randomized prior to January 1, 2003; it will be measured at these times except Month 3 and Month 9 for participants randomized on or after this date

8.7 Ancillary Studies

An ancillary study makes use of Look AHEAD participants, but collects data that are not part of the routine Look AHEAD database. A major objective of ancillary studies is to provide further information concerning the effects of the study interventions. Ancillary studies are distinguished from substudies in that they are not funded by Look AHEAD and may focus on issues peripheral to the goals of Look AHEAD. In addition to the routine follow-up protocol of the total study cohorts, the participants involved in the ancillary studies may have additional baseline and/or follow-up procedures. The ancillary studies must not interfere with the basic objectives and follow-up of the major trial, nor may they change the interventions. Informed consent for the ancillary studies may differ from that of the general Look AHEAD study since other procedures and alternatives may be involved. Each ancillary study has a separate protocol that must be approved by the Look AHEAD Substudies and Ancillary Studies Committee and the Steering Committee, as well as the institutional review board of the participating institution(s). The Look AHEAD Substudies and Ancillary Studies Committee has developed a guideline governing ancillary studies (Appendix G).

8.8 Data Management

All clinical sites use the World Wide Web to enter Look AHEAD data collected on hard copy forms completed on each participant. Each site has a password-protected area within the Look AHEAD web site through which data are entered. Documentation of the data entry system is maintained at the coordinating center. Site-specific reports relating to participant demographics, recruitment goals, and follow-up rates are available via the web site.

Participant randomization is accomplished via the World Wide Web data management system. The program requires data entry of certain eligibility criteria and determines whether the criteria are met before providing the randomization code. Randomization is balanced within center.

Data from central resource centers are transmitted to the coordinating center using electronic media. Tailored data management protocols are developed for each resource center.

The study's internet-based data entry system protects confidentiality and data security. Using acrostics rather than subject names provides additional data security. Text containing identifying information is not included in data files.

All medical information and study charts will remain confidential to the extent the law allows. The results from the study may be published, but will have no identifiers, and the results will be given for groups of people, not individuals. All information collected from participants will be kept on a computer data base at WFUHS and will be identified by participant ID number and acrostic only. Computer files containing names, addresses or other identifiers will be limited to authorized personnel at the site who have access to the computer data base using a password protected program. To further protect privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose research information that may identify any participant in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

8.9 Quality Control

Oversight of quality control rests with the appropriate Look AHEAD committee. Quality control procedures are devised by these committees to monitor recruitment and retention, clinic operations, screening, randomization, data collection, follow-up, clinical and biochemical measurements, forms completion and data entry procedures, and the implementation of the intervention.

Each committee with an oversight role routinely monitors its area of interest, utilizing data reports provided by the coordinating center, and working actively to improve the performance of clinical centers, if problems arise. Regular site visits will be scheduled for all clinical centers, regardless of performance, to ensure that developing problems are detected early, that activities are consistent across centers, and that successful implementation strategies are shared.

Laboratory quality control procedures include the use of externally submitted blind duplicates, regular review of all internal and external quality control data for the laboratory, and periodic monitoring visits. Quality control procedures for central reading centers are based on readings of duplicate material and/or blinded re-readings of all or a subset of the same material. Clinic staff receive central training, re-training, and certification in the study protocol.

9. DATA ANALYSIS

This section describes some of the major statistical approaches and analyses that will be performed during Look AHEAD. Additional details are provided in Appendix H.

9.1 Primary and Secondary Hypotheses

The primary study hypothesis of Look AHEAD will be tested based on a two-tailed significance level of 0.05. In this analysis, the "intention to treat" approach will be used in which participants are grouped according to randomization assignment. Additional, secondary analyses may be performed that account for crossover from the assigned intervention group and loss to endpoint ascertainment.

The main comparisons of intervention groups with respect to the distribution of time until the first post-randomization occurrence of a primary outcome (Section 3.1) will be based on survival analyses.¹²²⁻¹²⁵ This approach is useful in that it allows for varying lengths of follow-up among participants and for comparisons to be made over the entire course of the follow-up period. To compare intervention arms, we will use a Mantel-Haenszel test with unit weighting, stratified by clinical center and history of prior cardiovascular disease. This test is equivalent to a log-rank test and, if the proportional hazards assumption is warranted, to a Cox proportional hazards model.¹²⁶ Since the primary outcome measure is the first occurrence of fatal or non-fatal myocardial infarction or stroke, all other causes of death will be treated as competing risks. This means that Kaplan-Meier estimates of "disease-specific survival" will not have any straightforward interpretation.¹²⁶ Alternative methods will be used to describe the distribution of time-to-primary outcome for persons randomized to receive the Lifestyle Intervention and those assigned to receive Diabetes Support and Education. Estimates for the proper cumulative incidence function and the associated confidence intervals, will be constructed.¹²⁶ To compare intervention arms in secondary analyses involving additional covariates, we will use the Cox proportional hazards model,¹²⁴ if the underlying assumptions appear warranted. Markers indicating clinical centers and baseline prevalent cardiovascular disease will be used as covariates. Log/log plots of survival will be used to examine the assumption of proportional hazards.

Failure time is measured from the time of randomization. Some minor biases may occur due to this choice, for example if there is a differential drop-out rate between randomization and the start of interventions. The period of time between randomization and the first intervention session is kept as short as possible by not performing the randomization until groups of potential eligible participants accrue.

The composite outcomes defining the three secondary hypotheses will also be assessed at significance level 0.05 using similar approaches.

9.2 General Statistical Approach

The objectives in Look AHEAD require a broad range of analytical techniques. In reporting Look AHEAD results, we will clearly distinguish between the primary hypothesis and secondary objectives and will discuss results from these different outcome measures appropriately. In this

context, we are comfortable with performing significance tests of secondary objectives at 0.05 levels of significance.

Many objectives for Look AHEAD involve comparisons of distributions of times to events. Incidence distributions will be compared using survival analyses. The general approach to these data will follow that for the testing the primary study hypothesis, as described above. Other important questions concern the impact of intervention assignment on clinical measures, laboratory measures, symptoms and events, health-related quality of life, adherence measures, and cost will be assessed. Many of these measures will be collected longitudinally. Both relational and distributional descriptions will be made. Patterns of continuous variables across time, by intervention arm and for various subgroups will be explored by repeated measures methods.¹²⁷⁻¹²⁹ Patterns of categorical variables across time will be addressed via generalized estimation equations.¹³⁰⁻¹³² Predictors of outcome and compliance will be identified. Participant adherence data (e.g. self-reported physical activity and attendance at intervention sessions) will be modeled across time and contrasted among interventions. In secondary analyses, adherence data will be used as predictor variables in modeling intervention efficacy.

Look AHEAD will assess, for subgroups of participants, the relative effect of intervention assignment on the incidence of primary and secondary endpoints. Point estimates for the relative hazard of endpoints will be developed for each subgroup and formal tests for the equivalence of these estimates will be conducted. Factors defining the subgroups were selected based on the expectation that they may be important for determining whether weight loss interventions are prescribed for individuals, influencing either the relative success of the intervention in producing and sustaining weight loss or the relationship between weight loss and cardiovascular disease. The formal subgroups to be assessed are listed in the analysis plan (Appendix H).

Survival analyses will be used to investigate the relationships between the cardiovascular disease events and secondary outcome measures such as physical activity, fitness, and various laboratory measures. Weight change will be included in some models as a covariate in order to test hypotheses concerning the effects of these secondary outcomes on the cardiovascular disease events independent of weight loss.

Missing data are inevitable and statistical methods must take this into account in order to draw valid conclusions. Information collected during the study related to reasons that values are missing will be helpful in examining assumptions about missing data, e.g., whether data are missing completely at random, missing at random, or non-ignorably missing.¹³³ Maximum likelihood approaches will be adopted if data are missing at random. Broad-based statistical methodology for addressing non-ignorable missing data is emerging;¹³⁴⁻¹³⁶ it is expected that new methods will be available as the trial progresses. In general, all available data will be used in estimation and inference. Selection models, pattern mixture models, and shared parameter random effects models will be fit, and sensitivity analyses will be performed to check the robustness of study conclusions.

9.3 Economic Evaluation

The primary economic hypotheses are: 1) that the ratio of discounted costs per QALY saved (as measured from the participants' perspective by the use of the feeling thermometer from the

EuroQol instrument) is significantly less than an acceptable ceiling ratio in general use at end of study (determined prior to analysis) and 2) that the ratio of discounted costs per QALY (as measured from the general public's perspective by the use of the Health Utilities Index) is significantly less than an acceptable ceiling ratio in general use at end of study (determined prior to analysis). These will be confirmed if the net health benefits of those in the active intervention arm (calculated using a current and acceptable ceiling ratio at end of study) are greater than those in the Diabetes Support and Education arm ($p < 0.05$).

Costs will be measured as the sum of the costs of the intervention, hospitalization, outpatient medical care, and medications. They will be calculated by multiplying measures of resource use times estimates of unit costs for each of the resources. QALYs will be calculated by summing the area under each individual's QALY curve (constructed by plotting the feeling thermometer and Health Utilities Index scores for each interview during follow-up).

The estimates of mean differences in costs and outcomes – which will be used to create net health benefits and the cost per QALY ratios -- will be derived from multivariable regression analyses. For the evaluation of the difference in costs, the dependent variable in the regression will either be costs or the natural log of costs (determination of the form of the dependent variable will be based on statistical tests of its distribution). If the dependent variable used in the analysis is the log of costs, a smearing retransformation^{137,138} will be used to estimate the absolute difference in costs between the treatment groups. Independent variables will include the treatment group (the coefficient for which will provide a measure of the difference in cost associated with the intervention) as well as the clinical center and other covariates that are found to be correlated with the outcome that is being analyzed. Whether or not the covariates are differentially distributed across the treatment groups will not be a factor considered in their selection. If there are substantial differences in the potential length of follow-up of participants in the trial, the Lin interval method will be adopted to account for such differences.¹⁴³

Net health benefits are calculated by multiplying the difference in effects by the currently acceptable ceiling ratio and netting out the difference in costs. Ninety-five percent confidence intervals will be calculated using a bootstrap procedure.

In addition to evaluating net health benefits / cost-effectiveness, Look AHEAD will also test whether the incremental costs and the incremental QALYs (calculated using both the participants' and society's preferences) associated with the Lifestyle Intervention are greater than \$0. The statistical tests of these additional hypotheses will be derived from the results of the multiple regression analysis of costs and QALYs that were performed to construct net health benefits and the cost-effectiveness ratio.

A test of whether the incremental hospitalizations associated with the behavioral intervention will be less than zero will also be performed using multiple regression analysis. Considerations like those discussed above will be made to determine the form of the dependent variable and to determine the independent variables that will be included in the model.

Multiple regression analyses will be used to test whether participants assigned to the Lifestyle Intervention have higher summary scores on the SF-36 (Version 2) and significantly higher

physical function, energy/fatigue, role-emotional, and pain domain scores than participants assigned to Diabetes Support and Education.

10. TRIAL ORGANIZATION

10.1 Clinical Centers

Each clinical center consists of an interdisciplinary team of clinical investigators who provide the areas of expertise necessary for the successful completion of the Look AHEAD protocol.

Clinical center responsibilities include:

1. Recruiting participants for the trial,
2. Confirming eligibility of all participants,
3. Implementing the interventions in a systematic and standardized fashion consistent with the study protocol,
4. Collection high quality data according to the study protocol,
5. Making provisions to ensure the safety of trial participants,
6. Collaborating in design and monitoring of the study, including regular attendance at Steering Committee meetings, and
7. Collaborating in the analysis and dissemination of study results.

10.2 Coordinating Center

The coordinating center has primary responsibility for monitoring quality and analyzing data generated by the clinical centers. Additional responsibilities of the coordinating center include:

1. Preparing (with the aid of the Steering Committee and NIH staff) the protocol, forms, manuals, and intervention materials;
2. Developing the experimental statistical design of the trial;
3. Working with the investigators in the development and pre-testing of forms and procedures, and assuming responsibility for the reproduction and distribution of forms, hardware, and software associated with the distributed data entry system;
4. Collaborating in designing and monitoring the implementation of the trial interventions;
5. Training interventionists, data coordinators and other clinical center personnel, and monitoring clinic performance;
6. Coordinating central resources;
7. Managing quality control aspects associated with the collection and management of data;
8. Summarizing clinical center performance at regular intervals for the Steering Committee;
9. Providing detailed reports regarding participant recruitment, data collection, and interim results to the Data and Safety Monitoring Board; and
10. Preparing, in collaboration with the clinical investigators, various manuscripts of trial results.

10.3 Federal Sponsors

Look AHEAD is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The NIDDK Project Office is responsible for the administration and monitoring of the study. Representatives of this office participate in all phases of planning, scientific design, implementation, evaluation and communication relating to Look AHEAD, as well as in the general organization and fiscal management of the trial. The NIDDK Coordinator serves as Executive Secretary to the Data and

Safety Monitoring Board, and provides direct liaison to the NIDDK Director concerning issues relating to data and safety monitoring in Look AHEAD.

The NIDDK reserves the right to terminate or curtail the study (or an individual award) in the event of:

1. a major breach in the protocol or substantial changes in the agreed-upon protocol with which the Institute does not agree;
2. human subject ethical issues that may dictate a premature termination;
3. failure to achieve and sustain a clinically meaningful difference in weight loss between the control and the lifestyle intervention; or
4. substantial shortfall in recruitment and/or retention of subjects.

Other Federal sponsors of Look AHEAD include the National Heart, Lung and Blood Institute, the National Institute of Nursing Research, and the Centers for Disease Control and Prevention. Members of these agencies actively participate as scientists on subcommittees and in Steering Committee deliberations. In addition, Look AHEAD welcomes the support of the National Center for Minority Health and Health Disparities and the Office of Research on Women's Health, which have provided funding to advance research on health disparities and women's health.

Look AHEAD also encourages future collaborations with other potential Federal sponsors, either in direct support of added core measures or through sponsorship of ancillary studies. Scientists from other sponsoring agencies will be invited to participate as appropriate in Look AHEAD committees.

10.4 Other Sponsors and Contributors

The Look AHEAD study group recognizes the important roles that non-federal contributions and partial sponsorship may play in the supporting the development and conduct of the trial. The study group has adopted a policy statement that controls interactions between Look AHEAD investigators and industry sponsors/contributors (Appendix F).

10.5 Steering Committee

The Steering Committee is the governing body that provides the leadership for Look AHEAD and establishes scientific and administrative policy for the study. It holds the primary responsibility for developing the trial design and common clinical protocols, recommending appropriate procedures to manage the conduct and monitoring of study operations, and reporting the study results. The Steering Committee is comprised of the Principal Investigators of each clinical center, the Principal Investigator of the coordinating center, and the NIDDK Project Coordinator. Each member of the Steering Committee will have one vote. All major scientific decisions will be determined by majority vote of the Steering Committee.

The Steering Committee for Look AHEAD has a Chair and a Co-Chair, chosen from among the Steering Committee members (but not the Project Coordinator or coordinating center director), or alternatively, from among experts in the field of obesity clinical research who are not participating directly in the study. Committees appointed by the Executive Committee, comprised of investigators and staff from the clinical centers and coordinating center, will be

involved in design of the protocol and manual of operations and in ongoing functions of the trial (e.g. review of ancillary studies and preparation of publications). Committees may also seek the input of consultants and include representatives of central resources. In addition, representatives from sponsoring organizations may be invited to attend committees. Not every clinical center will be represented on each committee.

10.6 Executive Committee

An Executive Committee comprised of the Study Chair and Co-Chair, the Principal Investigator of the Coordinating Center, and the NIDDK Project Coordinator is convened to effect management decisions required between Steering Committee meetings, as needed, for efficient progress of the trial. The Executive Committee reports its actions to the Steering Committee on a regular basis. Meetings of the Executive Committee will generally be held by conference call according to a regular schedule. This Committee also develops timelines for the accomplishment of tasks, selects committee members and chairs, presents information to the Data and Safety Monitoring Board, and develops Steering Committee meeting agendas.

10.7 Other Standing Committees

The Look AHEAD Executive Committee will constitute committees of investigators and staff throughout the trial, as needed. Committee membership will be predicated on nomination from principal investigators and approval from the Executive Committee.

10.8 Central Resources

The Look AHEAD study group will develop central laboratories, reading centers, recruitment cores, and repositories as needed for conduct of the study. Investigators and staff from these centers may participate in training and quality control activities, but will not participate in policy issues or trial governance. Thus, while these individuals may be invited to attend committee meetings, they will hold no rights to voting. Individuals from central resource centers may be invited to participate in the publication of Look AHEAD data under the publications policy for the study.

10.9 Data and Safety Monitoring Board

An independent Data Safety and Monitoring Board (DSMB) will be appointed by the NIDDK Director to review periodically the progress of the Look AHEAD trial. It will be comprised of experts in relevant medical, psychological, statistical, operational, and bioethical fields who are not otherwise involved in the study. The Data Safety and Monitoring Board will oversee participant safety, evaluate performance, monitor data quality, and provide operational and policy advice to the NIDDK regarding the status and continuation of the overall study, study components, and study sites. The NIDDK Program Official and the Director of the Division of Digestive Diseases and Nutrition (or representative) may participate as ex-officio, non-voting members of the Board. The Data Safety and Monitoring Board will review progress and report to the NIDDK at least once per year.

11. STUDY TIMELINE

Look AHEAD will be conducted over a fifteen-year period from October 1, 1999 to July 31, 2015. There are five operational phases for the trial:

<u>Trial Activities</u>	<u>Calendar Time</u>
Protocol Development and Review	10/29/99 - 02/06/01
MOP Development, Central Staff Training	02/07/01 - 05/31/01
Recruitment and Enrollment	06/01/01 – 04/30/04
Follow-up	06/01/01 – 08/31/14
Close-out and Analysis	09/01/14 – 07/31/15

Note that feasibility of continuing the study will be assessed at two times:

- When the first 25% of the cohort has reached one year after randomization - estimated 04/01/02
- When the first 25% of the cohort has reached two years after randomization - estimated 04/10/03.

The criteria for this feasibility assessment are addressed in Section 7.

12. PARTICIPATING SITES

12.1 Clinical Sites

Clinic Code		Clinic Code	
01	Johns Hopkins University School of Medicine Baltimore, Maryland	11	University of Minnesota Minneapolis, Minnesota
02	Pennington Biomedical Research Center Baton Rouge, Louisiana	12	St. Luke's-Roosevelt Hospital Center New York, New York
03	University of Alabama at Birmingham Birmingham, Alabama	13	University of Pennsylvania Philadelphia, Pennsylvania
04	Massachusetts General Hospital Boston, Massachusetts	14	University of Pittsburgh Pittsburgh, Pennsylvania
05	Joslin Diabetes Center Boston, MA	15	Brown University Providence, Rhode Island
06	University of Colorado Health Sciences Center Denver, Colorado	16	University of Texas Health Science Center San Antonio, Texas
07	Baylor College of Medicine Houston, Texas	17	VA Puget Sound Health Care System and University of Washington
08	Los Angeles School of Medicine Los Angeles, California (transferred to USC effective April 1, 2005)	18	Southwestern American Indian Center Arizona
09	The University of Tennessee-Memphis Memphis, Tennessee	19	Northern Navajo Medical Center Shiprock, NM
10	The University of Tennessee Memphis East Clinic Memphis, Tennessee	21	University of Southern California Los Angeles, California

12.2 Coordinating Center

Wake Forest School of Medicine
Winston-Salem, North Carolina

12.3 Federal Sponsors

National Institute of Diabetes and Digestive and Kidney Diseases
National Heart, Lung and Blood Institute
National Institute of Nursing Research
National Center for Minority Health and Health Disparities
Office of Research on Women's Health
Centers for Disease Control and Prevention

12.4 Central Resource Centers

Central Laboratory	Northwest Lipid Research Laboratories University of Washington Seattle, Washington
ECG Reading Center	EPICARE Wake Forest University School of Medicine Winston-Salem, North Carolina
DEXA Reading Center	Prevention Sciences Group University of California at San Francisco San Francisco, California
Diet Assessment Center	University of South Carolina School of Public Health Department of Epidemiology and Biostatistics Columbia, SC

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APPENDIX A: DEFINITION OF TERMS AND ABBREVIATION

ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CK	Creatinine kinase
CT	Computed tomography
CVD	Cardiovascular disease
DEXA	Dual x-ray absorptiometry
DSMB	Data and Safety Monitoring Board
DPP	Diabetes Prevention Program
ECG	Electrocardiogram
FDA	Food and Drug Administration
FHS	Framingham Heart Study
GFR	Glomerular filtration rate
HDL	High density lipoprotein cholesterol
HOPE	Heart Outcomes Prevention Evaluation Study
IRAS	Insulin Resistance and Atherosclerosis Study
IRB	Institutional Review Board
JNC-VI	Joint National Consensus
LDL	Low density lipoprotein cholesterol
Look AHEAD	Action for Health in Diabetes
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCEP	National Cholesterol Education Program
NIH	National Institutes of Health
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Health Association
RVG	Radionuclide ventriculogram
TIA	Transient ischemic attack
WHI	Women's Health Initiative

APPENDIX B: DETAILS OF SAMPLE SIZE PROJECTIONS

B.1 Summary

As described in Section 3.4, the power for the primary trial hypothesis was estimated to be 90% for an 18% effect, if we assume an overall event rate of 3.125% under the null hypothesis, a maximum of 11.5 years of follow-up, uniform recruitment over 2.5 years, a rate for loss to endpoint ascertainment of 2% per year, and a two-sided 0.05 level test. Table 3.4 shows the sensitivity of this estimate to changes in the overall event rate and length of follow-up for the primary outcome in the Diabetes Support and Education group.

Event rates for primary and secondary prevention patients were computed from data collected by the Atherosclerosis Risk in Communities (ARIC) study¹⁴⁰ and the Cardiovascular Health Study (CHS).¹⁴¹ If we assume that the population from which Look AHEAD participants is drawn consists of 75% primary prevention patients and weight the ARIC and CHS data equally, the overall population event rate is estimated to be 3.72%. This event rate is adjusted by applying: a five percent increase to account for silent myocardial infarctions, which were not part of the ARIC/CHS analysis, and a 20% reduction in event rate due to healthy volunteer effect. The adjusted rate is then

$$3.72\% \times (1 + 0.05) \times (1 - 0.2) = 3.125\%.$$

The power is robust to slight changes in the mix of primary and secondary prevention patients. Sensitivity analyses were performed to determine how the mixture of primary/secondary prevention participants recruited into Look AHEAD would affect the power for testing primary hypothesis. In Table B.1, the underlying assumed annual event rates and associated power are provided for assumptions that the Look AHEAD cohort is comprised of 25%, 30% or 35% participants with a history of cardiovascular disease events.

Table B.1 Impact of Including 25%, 30%, and 35% Participants with Prior History of Cardiovascular Disease Events on Anticipated Annual Event Rates and Power

% Secondary	Annual event rates	Adjusted	Power
25%	3.72%	3.125%	92%
30%	3.95%	3.31%	93%
35%	4.17%	3.50%	94%

The power is also robust to slight changes in how the ARIC and CHS data are combined. Sensitivity analyses were performed to investigate how the mixture of population event rates obtained from ARIC and CHS would affect the power. Baseline age of participants in ARIC, CHS, and Look AHEAD range from 45-65, at least 65, and at least 45, respectively. Because event rates increase in elder, the impact on power due to difference in age is examined using the following sets of weight for the estimation of population event rate.

Table B.2 Robustness of Projected Study Power For Different Weighting of ARIC and CHS Event Rates

Weights		Annual event rates	Adjusted	Power
ARIC	CHS			
60%	40%	3.41	2.86%	90%
50%	50%	3.72	3.125%	92%
40%	60%	4.03	3.38%	93%

Additional calculations were done to assess the impact of increasing the loss-to-endpoint-ascertainment from 2 to 5%, and to assess the power for detecting an 18% effect in the subgroup of primary prevention participants only. Increasing the loss-to-endpoint-ascertainment rate from 2 to 5% results in a drop in the power from 92% to 88%. If participants with no history of cardiovascular disease make up 75% of all participants, and there is an 18% effect in this subgroup, the power for detecting this effect will be 83%. Thus even if there is no effect among the participants with a history of cardiovascular disease, the study is powered to detect an effect in a subgroup analysis excluding them.

B.2 Methods and Assumptions

Table B.3 presents event rates for primary outcomes obtained from ARIC and CHS for primary and secondary prevention participants. Selection criteria are Type 2 diabetics with age at least 45 years. Participants were excluded who weighed greater than 350 pounds or who had blood pressure greater than 160/100 mmHg, triglycerides greater than 600 mg/dl, fasting plasma glucose greater than 216 mg/dl, or serum creatinine greater than 1.5 mg/dl (males) or greater than 1.4 mg/dl (females). ARIC and CHS participants with fasting plasma glucose greater than 216 mg/dl were excluded to account for the Look AHEAD criteria that individuals with HbA1c greater than 11% be excluded, based on the equation:¹⁴⁶

$$\text{FPG} = 17 * \text{HbA1c} + 29.1$$

Table B.3 Event Rates from ARIC and CHS

	Rate Per Year	Mean Age	Mean BMI	Ages 45-50 years	Ages 50-70 years	Ages 70+ years
ARIC						
Primary	0.94%	55.5	31.0	24.7%	75.3%	0.0%
Secondary	5.84%	57.4	31.2	15.5%	84.5%	0.0%
CHS						
Primary	4.24%	72.4	28.9	0.0%	35.3%	64.7%
Secondary	8.40%	72.9	27.6	0.0%	31.4%	68.6%

Additional independent data exploring event rates was obtained from the San Antonio Heart Study.^{143,144} Incidence of cardiovascular disease events among 50-65 year old participants with type 2 diabetes who were not receiving insulin was 2.92% annually. With inclusion of participants with at least one other cardiovascular risk factor, the annual event rate increases to 9.44%. These data are consistent with the combined ARIC/CHS event rates, and suggest that the event rate for participants in the 50-65 year age range will be high enough to assure sufficient

power. Furthermore, in all our computations, we assume constant hazard rate over the 11.5 year follow-up period. Since we expect event rates will increase as age increases, our approach is conservative.

APPENDIX C: DEFINITION OF THE PRIMARY AND SECONDARY OUTCOME MEASURES

C.1 Primary Outcome Measure

The primary outcome measure of the Look AHEAD clinical trial is the combined incidence of cardiovascular deaths (including fatal myocardial infarctions and strokes, and other cardiovascular causes), non-fatal myocardial infarctions, non-fatal strokes, and hospitalization for angina according to the definitions below. Further details on event documentation are contained in the Look AHEAD Manual of Operations.

C.1.1 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 by Look AHEAD criteria; 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.

C.1.2 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 test¹⁴⁴
 - b) elevation of serum CK MB to twice the upper limit of normal for the laboratory that performed the test¹⁴⁵
 - c) total serum CK at least twice the upper limit of normal for the laboratory that performed the test¹⁴⁵
 - 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.¹⁴⁴

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 ≥ 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 ≥ 0.3 mV (or pseudonormalization ≥ 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 Look AHEAD but will be recorded for the database.

C.1.3 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.¹⁴⁶ 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

1. an area of increased density indicative of intracranial hemorrhage identified by CT or MRI; or
2. the demonstration of an intracerebral hemorrhage at autopsy or surgery or in the absence of a technically adequate CT or MRI; or
3. 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 are 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.

C.1.4 Hospitalization for Angina

Hospitalized angina is defined as a “Yes” to the question below, *plus* an indication of either item 1 or 2, *plus* at least one of items 3-7.

Angina pectoris (including unstable angina) requiring and/or occurring during hospitalization? Chest pain, tightness, or shortness of breath produced by myocardial ischemia that does not result in infarction (usually caused by coronary insufficiency.)

Items:

1. Physician diagnosis of angina and receiving medical treatment for angina on this admission (e.g., nitrate, beta-blocker, or calcium-channel blocker).
2. Physician diagnosis of angina and receiving medical treatment for angina on this admission plus current medical record documenting a history of coronary heart disease by previous catheterization or revascularization procedure.
3. CABG surgery or other revascularization procedure on this admission.
4. 70% or greater obstruction of any coronary artery on angiography on this admission.
5. Horizontal or down-sloping ST-segment depression or abnormal ST elevation ≥ 1 mm on exercise or pharmacological stress testing with pain on this admission or immediately preceding and leading to this admission.
6. Scintigraphic or echocardiographic stress test positive for ischemia on this admission or immediately preceding and leading to this admission.
7. Resting ECG shows horizontal or down-sloping ST depression or abnormal ST elevation ≥ 1 mm with pain that is not present on ECG without pain on this admission.

C.2 Secondary Outcome Measures

The three Look AHEAD secondary outcome measures are clusters of events based on the components of the primary outcome measure and the following.

C.2.1 Total Mortality

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

C.2.2 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.

C.2.3 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. Look AHEAD will identify only in-patient diagnoses of heart failure. The adapted criteria for CHF are:

1. CHF diagnosed by physician and receiving medical treatment for CHF (for instance, diuretics, digitalis, vasodilators, beta-blockers or ACE inhibitors) while hospitalized
2. Pulmonary edema \ congestion by chest x-ray
3. Dilated ventricle or poor left ventricular function (eg, 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: PND 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 Look AHEAD 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, Look AHEAD will be able to reconstruct the Framingham definition of heart failure.

C.2.4 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

C.2.5 Peripheral Vascular Disease

In Look AHEAD, 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
3. Surgical or vascular procedure for abdominal aortic aneurysm

**APPENDIX D
MODEL CONSENT FORMS**

**APPENDIX D.1 MODEL CONSENT
GENERAL**

***THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.***

**APPENDIX D.2 MODEL CONSENT
GENERAL PHASE III**

***THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.***

APPENDIX D.2b MODEL CONSENT
GENERAL PHASE IV

THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.

**APPENDIX D.3 MODEL CONSENT
ACCELEROMETRY**

***THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.***

**APPENDIX D.4 MODEL CONSENT
ORLISTAT**

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MODEL CONSENTS.***

**APPENDIX D.5 MODEL CONSENT
DNA**

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MODEL CONSENTS.***

**APPENDIX D.6 MODEL CONSENT
STORAGE of DNA SAMPLE in NIDDK CENTRAL REPOSITORY**

***THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.***

**APPENDIX D.7 MODEL CONSENT
SUPPLEMENTAL GENERAL CONSENT FOR USE OF STORED BLOOD
SPECIMENS
NON-LOOK AHEAD RESEARCHERS**

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MODEL CONSENTS.***

**APPENDIX D.8 MODEL CONSENT
STORAGE OF BLOOD SPECIMENS IN NIDDK CENTRAL REPOSITORY**

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MODEL CONSENTS.***

**APPENDIX D.9 MODEL CONSENT
STORAGE OF URINE SAMPLES IN NIDDK CENTRAL REPOSITORY**

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MODEL CONSENTS.***

**APPENDIX D.10 MODEL CONSENT
USE AND STORAGE OF URINE SAMPLES**

***THIS DOCUMENT IS LOCATED IN THE LOOK AHEAD WEB SITE SECTION TITLED
MODEL CONSENTS.***

**APPENDIX D.11 MODEL CONSENT
GWAS
SHARING OF GENETICS RESULTS WITH NIH DATA BANK**

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MODEL CONSENTS.***

APPENDIX E: Look AHEAD DUALITY OF INTEREST POLICY

Revision 1 dated December 1, 2008

Approved by the Look AHEAD Steering Committee May, 2000

Background:

Successful transfer of technological advances from a biomedical research setting to clinical practice almost inevitably requires the interface of academic investigators and industrial interests. Billions of federal dollars support the academic biomedical research community with numerous statutes and programs demonstrating federal interest in the promotion of interactions among government, academia and industry. The Stevenson-Wydler Technology Innovation Act of 1980 (Public Law (P.L.) 96-480) encourages technology transfer, particularly through industrial-academic collaborations. The Patent and Trademark Act Amendments of 1980 (P.L. 96-517) allow universities and other funding recipients to apply for patents developed with federal funding and expressly promote collaboration between commercial concerns and nonprofit organizations. The Economic Recovery Tax Act of 1981 (P.L.97-34) is aimed at fostering research and development by small companies and associated university partners. The Federal Technology Transfer of 1986 (P.L. 99-502), which amended P.L. 96-480, and Executive Order 12592 provide similar patent and licensing authority to federal laboratories, and encourage them to participate in cooperative research and development agreements with the private sector and nonprofit organizations, including universities.

In practical terms it is impossible to fully separate the interests of the industrial, academic and governmental communities, nor is it desirable to do so. The professional meetings and scientific forums attended by every academic scientist often are partly sponsored by industry. Continuing professional education is largely underwritten by industry. Some scientists benefit from industrial sponsored research grants, payments for their expert advice as consultants or honoraria for lectures. Scientists may hold equity interests in pharmaceutical and other biomedical industries, either from mutual fund holdings or direct holdings. Royalties and licensing arrangements may result in reimbursements to a scientist for intellectual property rights.

In an environment where scientists may benefit directly or indirectly from commercial ties, the potential to influence scientific objectivity exists. Clinical trials are especially vulnerable to such influences, whether perceived or real. In these circumstances, a *potential* conflict of interest occurs when there is a divergence between an individual's private interests and his or her professional obligations to the research project, such that an independent observer might reasonably question whether the individual's professional actions or decisions, including the design, conduct or reporting of the research are influenced or determined by considerations of personal gain, financial or otherwise. Allegations of conflicts of interest threaten the integrity of the scientific community. Policies that promote disclosure of potential conflicts of interest and propose means to manage those conflicts aim to protect the credibility and integrity of research investigators so public trust and confidence in the research results is preserved.

Purpose:

The Look AHEAD Steering Committee has developed the following duality of interest policy to promote the fair, open, and unfettered discussion of study protocol issues and to ensure that the scientific design, conduct or reporting of the study is not biased by commercial

influences. Policies developed in other multicenter clinical trials [Healy, et al., 1989; Topol, et al., 1992] were reviewed and influenced these policy decisions.

Components:

The Look AHEAD Duality of Interest Policy comprises three components:

1. written full disclosure and means of reducing conflict,
2. verbal disclosure during the course of meetings,
3. publication of the Policy.

1. Written full disclosure and means of reducing conflict:

Principal Investigators and members of selected committees must fully disclose all commercial ties that provided remuneration (as defined below) during the previous year that may be related to products or services considered for use in the Look AHEAD clinical trial. Disclosure is to occur annually on a calendar year basis. This disclosure applies to remuneration received by principal investigators or committee members, their spouses and/or dependent children. Such industrial ties include, but are not restricted to, any pharmaceutical, behavior modification, and/or technology company. The investigator should use her/his judgment in deciding which to report, but should disclose ties to any commercial firms that make products for which there is a weight loss claim. The categories below provide guidelines for investigators in making decisions on what types of activities to declare. A disclosure form has been developed should to report the following types of commercial interests:

1. equity holdings (excluding mutual funds or blind trusts),
2. research contracts or grants,
3. intellectual property rights (patents, royalties, etc.),
4. fees for speeches, lectures, and/or presentations (if received directly from industry or a company acting on behalf of an industrial sponsor),
5. consulting fees,
6. other honoraria (either direct or donated),
7. travel or meeting expenses (if received directly from industry), and
8. other forms of compensation (salaries, pensions, equipment, property).

At the beginning of each study year, all members of selected Look AHEAD committees will affirm their intent to abide by this policy for the upcoming year by filling out a Look AHEAD disclosure form and transmitting it to the Look AHEAD coordinating center or using a web-based submission. The Look AHEAD Executive Committee will have oversight of this process for all individuals with the exception of themselves, for whom the process of oversight will devolve to the Look AHEAD Policy and Protocol Committee.

Failure to submit the annual documentation to the coordinating center will preclude participation in Look AHEAD committees. The Look AHEAD Executive Committee will review these updated and signed forms. The updated and signed duality of interest forms submitted by the Look AHEAD Executive Committee members will be reviewed by the Look AHEAD Committee Overseeing Protocol with members of the Executive Committee being recused. If potential conflicts of interest are deemed to exist, recommendations will be made for mechanisms to limit the potential impact of such conflicts. Such recommendations may include

removal of committee chairmanship and voting rights on issues where a potential conflict of interest may exist.

Completed duality of interest forms will be collected through the publication date of the primary study results manuscript of the Look AHEAD trial and thus will extend to cover the period of time one year past this date. These will be stored in a secure manner at the coordinating center and will be destroyed after the close of the study on a date determined by the Look AHEAD Steering Committee. Look AHEAD staff that are required to complete the Duality of Interest form may do so electronically by accessing the form and submitting it via the study web site beginning 2008.

Members of the Look AHEAD study group who are not principal investigators and are not members of committees are encouraged, but not bound, to follow these guidelines.

2. Verbal disclosure during the course of meetings:

As scientific issues that relate to use of specific commercial products are discussed and voted on in Look AHEAD committee meetings, the chairs of these committees will ask all members to consider if they have any important potential conflicts of interest on the subject to be discussed. If they or the committees responsible for oversight (Executive or Policy and Protocol Committees) consider there to be a potential conflict of interest, they are expected to declare such to the committee. Attendees are expected to absent themselves from participation in any of these activities if they or the committees responsible for oversight judge that conflicting interests preclude them from making an impartial decision.

3. Publication of the Policy:

The Look AHEAD Research Group will publish this duality of interest policy on its website.

References:

- Healy B, Campeau L, Gray R, et al. Conflict of interest guidelines for a multicenter clinical trial of treatment after coronary-artery bypass-graft surgery. *N Engl J Med* 1989; 320:949-951.
- Topol EJ, Armstrong P, Van de Werf F, et al. Confronting issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion. *J Am Coll Cardiol* 1992; 19:1123-1128.

APPENDIX F: INDUSTRY POLICY

Look AHEAD Industry Policy

Approved by the Look AHEAD Steering Committee, September, 2000

Background:

Clinical studies under the auspices of the National Institutes of Health are typically conducted by extramural investigators for part or all of the Research Plan. Clinical studies also provide an opportunity for industrial participation. When industry chooses to participate and provides resources, be they in cash or kind, there is the potential for financial gain through this partnership. By recognizing the potential for financial gain, mechanisms must exist to protect the study from undue influence by industry, premature release of data or the making of incorrect claims related to industry's participation in the study.

Purpose:

The Look AHEAD Steering Committee has developed the following policy to promote fair negotiation with industry regarding its participation in the study.

Policy:

In discussions with industry, the following will apply:

1. Control of the clinical study and use of products within the study must lie entirely with the National Institutes of Health and the investigators of the study;
2. The opportunity to contribute to Look AHEAD will be broadly communicated to all potential industry contributors;
3. Contacts with industry will be coordinated by the Executive Committee. Specifically, discussions with industry will be initiated by the Chairs of the Steering Committee or their designees. Following this initial contact, continued discussions and the implementation of an agreement will be done according to the policies of the National Institutes of Health;
4. Confidentiality of data must be maintained during the course of Look AHEAD. Thus, access to interim data by industry will not be possible. Data will be shared at the end of the study when they become available to the scientific community and the general public or before the end of the study if they have been released into the public domain; and
5. Neither the choice of a product in Look AHEAD nor the results of Look AHEAD should be represented as an endorsement of a product.

APPENDIX G
Look AHEAD ANCILLARY STUDIES PROTOCOL

4/16/2007 Revision
(Revised to amend web site URL only)

Look AHEAD
Action for Health in Diabetes
Ancillary Study Policy

Definition

In Look AHEAD, an ancillary study is defined as one that derives support from sources other than the cooperative agreement grant funds awarded by NIH for support of the main trial.

An ancillary study's objectives are not duplicative of and do not interfere with the Look AHEAD study but use Look AHEAD participants, samples, or data collected by Look AHEAD.

Look AHEAD represents a large and uniquely well characterized population sample of obese individuals with type 2 diabetes. To make the best possible use of this extraordinary resource, Look AHEAD encourages investigators to develop ancillary studies in conjunction with the trial and to involve other investigators, within and outside of Look AHEAD, in this process. An ancillary study may involve data collection from one or more Look AHEAD Centers for one or more cohorts.

Role of Sub studies and Ancillary Studies (SAS) Committee

The Steering Committee must approve all ancillary studies to ensure that they do not impose an unacceptable burden to staff or participants or conflict with the aims of Look AHEAD. Data collection may not proceed without the approval of the SAS Committee. The Steering Committee designates the SAS Committee to conduct a preliminary review of all proposed ancillary studies.

If any SAS member proposes an ancillary study, collaborates with an investigator who proposes an ancillary study, or is affiliated with the institution of an investigator who proposes an ancillary study, he or she will be recused from considering that ancillary study proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest.

Ancillary Study Review

The Sub studies and Ancillary Studies (SAS) Committee will conduct preliminary review and provide recommendations to the Steering Committee for approval of ancillary studies concepts through the process described in this chapter. Proposals will be assessed to evaluate whether they would interfere with other parts of the protocol, would hamper continued recruitment or participation in Look AHEAD, or would be inconsistent with the Look AHEAD aim of facilitating a broad range of research.

If an ancillary study proposal meets the test of non interference with Look AHEAD, it may still compete with other proposed ancillary studies for limited additional participant or staff time

and/or biological resources (e.g., blood). To maximize efficiency, the SAS may recommend that several similar and potentially competing proposals be combined.

Highest priority will be given to studies which:

- have the highest scientific merit,
- do not interfere with or duplicate the main Look AHEAD objectives,
- produce the least burden on Look AHEAD participants and the least demand on Look AHEAD resources such as blood samples
- require the unique characteristics of the Look AHEAD cohort, and
- contribute to the aim of examining a broad range of research questions.

If a change occurs in the design or concept of the ancillary study after it has been approved, the SAS committee should be notified. The Steering Committee will be asked to approve the alterations, based on the recommendation of the SAS Committee.

The Data and Safety Monitoring Board (DSMB) may also be asked to judge the demands the proposed study places on participants and the priority in relation to Look AHEAD objectives.

Outside Funding Required for Ancillary Studies

Investigators proposing ancillary studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01s), grants from academic institutions, or private sources (e.g., drug companies, non-profit health organizations).

In assessing the acceptability of an ancillary study proposal, the Steering Committee will be concerned with both the explicit and the hidden costs to Look AHEAD entailed by the proposal (e.g., costs to the Coordinating Center for coordinating the additional data collection, costs to Clinical Centers for notification of alert values). The ancillary study's PI should provide evidence that adequate support for carrying out these functions is available at his/her institution; if not, the coordinating center will conduct the activities required using resources that must be included in the ancillary study budget.

Scientific Review of Ancillary Studies.

For proposals submitted to the NIH, either in response to an RFA or as investigator-initiated R01 applications, scientific review is through the regular NIH peer review system. For other proposals, if no other acceptable peer review has taken place, the scientific merit of a proposal will be reviewed by the SAS, supplemented with additional experts as necessary.

IRB Approval

All ancillary studies must receive necessary approvals from IRBs at the individual institutions involved. Documentation of IRB approval is required to be submitted to the Look AHEAD

Coordinating Center before an ancillary study can be initiated in conjunction with Look AHEAD.

Confidentiality

Confidentiality of individually identifiable data about Look AHEAD participants must be assured. LOOK AHEAD provides no assurances that ancillary studies will be able to identify and contact participants in the future, particularly after Look AHEAD ends.

Industry-sponsored Ancillary Studies

Proposals for industry-sponsored ancillary studies are evaluated in accordance with the procedures described above. In addition, it is the responsibility of the PI to obtain agreement with the industry sponsor through an appropriate contractual mechanism that all data relevant to the Look AHEAD ancillary study will be shared with the Coordinating Center and the Steering Committee. Conduct of industry-sponsored ancillary studies also must comply with all existing Look AHEAD and NIH policies and guidelines.

Procedure for Proposing an Ancillary Study in Conjunction with Look AHEAD

Each ancillary study must include a Look AHEAD Principal Investigator or Co-investigator on the proposal and must have the approval of the Principal Investigator at each Look AHEAD site proposed. The Principal Investigator of the ancillary study is responsible for submitting the study proposal to the SAS Committee, monitoring the study to ensure continuing compatibility with Look AHEAD, and serving as a liaison to the Look AHEAD Steering Committee, including attendance as requested at SAS and Steering Committee meetings. The appended form, "Preliminary Proposal for Look AHEAD Ancillary Study" must be submitted to the Look AHEAD Coordinating Center to propose an ancillary study. This form is also available on the Look AHEAD website: www.lookaheadtrial.org. The form may be submitted online or by mail or FAX. To assess the proposal, the SAS and Steering Committees need to know what additional information will be collected at any of the Look AHEAD clinic visits, the expected burden to participants, and the amount of time needed to complete the measurement. If Look AHEAD core data, staff, and/or analyses are needed for the ancillary study, this information should be provided. The SAS and the Steering Committee will consider the following questions, which should be addressed in completing the form:

1. What, if any, measurements (questionnaires, biologic samples, physical measures) are needed and when will they be collected?
2. What is the additional burden to staff and participants from the proposed measurements?
3. Which Look AHEAD centers have agreed to participate? Have the collaborating investigators approved the proposal? Is collaboration with investigators from additional? Look AHEAD sites desired or planned?
4. What is the sample to be studied in terms of the number and characteristics of the participants? Justify the sample size.
5. How will the ancillary study be funded? Would any additional unreimbursed work or

personnel time be expected of Look AHEAD?

6. Where will the data analyses be conducted? What is the estimated burden to the Coordinating Center?
7. How will the confidentiality and other aspects of protection of human subjects be maintained?

The Preliminary Proposal for Look AHEAD Ancillary Studies form should be filled out before submitting an application for funding to a funded entity. Coordinating Center staff are available to assist the investigator in the preparation and processing of the form. The Preliminary Proposal form describing the concept will generally be discussed by the SAS Committee on a conference call will 2-4 weeks after receipt. Sufficient time should be allowed for this process. The investigator may be asked to make him/herself available at the time of the call to address questions that may arise. The SAS Committee will provide a letter to the investigator shortly after the call, indicating whether the proposal is potentially acceptable.

A copy of the final funded proposal should be submitted to the Sub studies and Ancillary Studies Committee.

Data Issues

The release of any Look AHEAD data from the Coordinating Center to an ancillary study investigator is subject to the rules regarding release of data defined in the Look AHEAD Publications Policy.

Data collected by the ancillary study must be provided electronically to the Look AHEAD Coordinating Center for integration into the main database. In return, ancillary study investigators receive an analysis file containing their data and approved data from the main study. The ancillary study PI is given the first opportunity to analyze, present, and publish data collected for the specific aims of the ancillary study.

After a reasonable time (in general, 18 months after the ancillary study PI has received the cleaned data), the ancillary study data are made available for additional uses by Look AHEAD investigators, in collaboration with the ancillary study investigators. It is the responsibility of the ancillary study PI to state in writing in advance to the Steering Committee any special circumstances that would mitigate against these guidelines for data sharing. Reasonable and justified requests for limiting Steering Committee access to the data will be considered.

Publications and Presentations

Proposals must be submitted for all publications, presentations and abstracts from an ancillary study for review and approval by the Publications Committee prior to submission or presentation, in accordance with the general rules for publications and presentations.

Each manuscript and abstract is generally expected to include a Look AHEAD investigator as co-author, except under circumstances that should be stated and justified as part of the original submission to the SAS Committee.

APPENDIX H: Look AHEAD STATISTICAL ANALYSIS PLAN

This document summarizes material from the Look AHEAD protocol and describes additional analytical details that have been approved by the Steering Committee and the Look AHEAD Data and Safety Monitoring Board.

1. PLANS FOR FEASIBILITY EVALUATION AND STOPPING RULES

The progress of Look AHEAD and the study's potential of attaining its goals will be regularly evaluated by the Data and Safety Monitoring Board. This committee will review and provide feedback to the NIDDK on the overall performance of the study group, including its success with respect to goals for recruitment, retention, and data quality. Several key criteria that the DSMB will use to inform its recommendations on the continuation of the Look AHEAD trial are summarized in this section.

1.1 Feasibility Evaluation

The feasibility of the trial will be formally assessed by the DSMB early in the study to ensure that the trial interventions are being successfully delivered. Data on the first 25% of participants recruited into Look AHEAD will be examined when these participants have all reached Year 1 and again when they have reached Year 2. Three criteria will be used to judge the success of the intervention.

- To demonstrate success of the intervention at achieving a difference between study arms at one year, there must be at least a 5 percentage points difference in the average percentage point change in weight from Baseline to Year 1 between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education.
- Since the Look AHEAD goal is to achieve absolute weight loss (rather than diminished weight gain), a second feasibility criterion at Year 1 is also defined. The average absolute percent weight loss from Baseline among the first 25% of Lifestyle Intervention participants not using insulin at Baseline must be at least 5% at Year 1. Because insulin use may influence weight changes, the average percent weight loss from Baseline in insulin-using participants in the Lifestyle Intervention will also be estimated, however the sample size is not sufficient to estimate this percentage precisely. Weight loss in this cohort is targeted to be at least 3% at Year 1.
- To assess the ability of the Lifestyle Intervention to produce longer-term effects, feasibility criteria based on two-year changes also are defined. These acknowledge the potential that changes in fitness, as well as changes in weight, may have an impact on cardiovascular disease in the long term. The longer-term feasibility of the trial will be assessed based on the following criterion. At Year 2, for the first 25% of participants there must be at least a 5% difference in the average percent change in weight or fitness from Baseline between participants assigned to the Lifestyle Intervention compared to those assigned to Diabetes Support and Education. The fitness measure at Year 2 will be collected only in the subset of 25% of the study participants who are the first to reach their two-year post-randomization anniversary.

The DSMB will consider these feasibility criteria in the context of early trends in glucose control, atherogenic risk factors, and, as the study proceeds, cardiovascular event rates.

1.2 Stopping Rules For Efficacy and Futility

Incidence rates of the primary and secondary composite outcomes will be monitored throughout the trial and used for interim analyses of efficacy and futility. Group sequential methods for events rates will be used to control the Type I error to be 0.05 across these repeated analyses.¹⁻³ Critical values for interim testing will be defined based on an O'Brien-Fleming type bound⁴ and will use a spending functions to allow flexibility in the number and timing of interim analyses.⁵ With this approach, interim tests early in the trial are conservative and the reduction in the overall power of the trial caused by interim testing is small. Conditional power calculations will be used to assess the futility of continuation in the presence of a negative treatment effect.⁶

1.3 Stopping Based On Safety Concerns

At each meeting, the DSMB will review data on adverse events and other safety issues to make an overall recommendation to the NIH concerning the safety of continuing Look AHEAD. Consistent with NIH policy, each Look AHEAD Principal Investigator will receive a report summarizing the DSMB review of the adverse event data. Principal Investigators are responsible for providing this report to the IRB at their institution.

2. DATA ANALYSIS

This section describes some of the major statistical approaches and analyses that will be performed during Look AHEAD.

2.1 Primary and Secondary Hypotheses

The primary study hypothesis of Look AHEAD will be tested based on a two-tailed significance level of 0.05. In this analysis, the "intention to treat" approach will be used in which participants are grouped according to randomization assignment. Additional, secondary analyses may be performed that account for crossover from the assigned intervention group and loss to endpoint ascertainment.

The main comparisons of intervention groups with respect to the distribution of time until the first post-randomization occurrence of a primary outcome will be based on survival analyses.⁷⁻¹⁰ This approach is useful in that it allows for varying lengths of follow-up among participants and for comparisons to be made over the entire course of the follow-up period. To compare intervention arms, we will use a Mantel-Haenszel test with unit weighting, stratified by clinical center and history of prior cardiovascular disease. This test is equivalent to a log-rank test and, if the proportional hazards assumption is warranted, to a Cox proportional hazards model.¹¹ Since the primary outcome measure is the first occurrence of hospitalized angina, fatal or non-fatal myocardial infarction or stroke, or other cardiovascular death, all other causes of death will be treated as competing risks. This means that Kaplan-Meier estimates of "disease-specific survival" will not have any straightforward interpretation.¹¹ Alternative methods will be used to describe the distribution of time-to-primary outcome for persons randomized to receive the Lifestyle Intervention and those assigned to receive Diabetes Support and Education. Estimates

for the proper cumulative incidence function and the associated confidence intervals, will be constructed.¹¹ To compare intervention arms in secondary analyses involving additional covariates, we will use the Cox proportional hazards model,⁹ if the underlying assumptions appear warranted. Markers indicating clinical centers and baseline prevalent cardiovascular disease will be used as covariates. Log/log plots of survival will be used to examine the assumption of proportional hazards.

Failure time is measured from the time of randomization. Some minor biases may occur due to this choice, for example if there is a differential drop-out rate between randomization and the start of interventions. The period of time between randomization and the first intervention session is kept as short as possible by not performing the randomization until groups of potential eligible participants accrue.

Because the three composite outcomes defining the secondary hypotheses are pre-specified and highly correlated, each will be assessed at significance level 0.05 using similar approaches.

2.2 General Statistical Approach

The objectives in Look AHEAD require a broad range of analytical techniques. In reporting Look AHEAD results, we will clearly distinguish between the primary hypothesis and secondary objectives and will discuss results from these different outcome measures appropriately. In this context, we are comfortable with performing significance tests of secondary objectives at 0.05 levels of significance.

Many objectives for Look AHEAD involve comparisons of distributions of times to events. Incidence distributions will be compared using survival analyses. The general approach to these data will follow that for the testing the primary study hypothesis, as described above. Components of the primary and secondary composite outcomes will be analyzed individually to explore the consistency of effects. Other important questions concern the impact of intervention assignment on clinical measures, laboratory measures, symptoms and events, health-related quality of life, adherence measures, and cost will be assessed. Many of these measures will be collected longitudinally. Both relational and distributional descriptions will be made. Patterns of continuous variables across time, by intervention arm and for various subgroups will be explored by repeated measures methods.¹²⁻¹⁴ Patterns of categorical variables across time will be addressed via generalized estimation equations.¹⁵⁻¹⁷ Predictors of outcome and compliance will be identified. Participant adherence data (e.g. self-reported physical activity and attendance at intervention sessions) will be modeled across time and contrasted among interventions. In secondary analyses, adherence data will be used as a predictor variable in modeling intervention efficacy.

Survival analyses will be used to investigate the relationships between the cardiovascular disease events and secondary outcome measures such as physical activity, fitness, and various laboratory measures. Weight change will be included in some models as a covariate in order to test hypotheses concerning the effects of these secondary outcomes on the cardiovascular disease events independent of weight loss.

Missing data are inevitable and statistical methods must take this into account in order to draw valid conclusions. Information collected during the study related to reasons that values are missing will be helpful in examining assumptions about missing data, e.g., whether data are missing completely at random, missing at random, or non-ignorably missing.¹⁸ Maximum likelihood approaches will be adopted if data are missing at random. Broad-based statistical methodology for addressing non-ignorable missing data is emerging;¹⁹⁻²¹ it is expected that

new methods will be available as the trial progresses. In general, all available data will be used in estimation and inference. Selection models, pattern mixture models, and shared parameter random effects models will be fit, and sensitivity analyses will be performed to check the robustness of study conclusions.

2.3 Economic Evaluation

The primary economic hypotheses are:

- that the ratio of discounted costs per quality-adjusted life year (QALY) saved (as measured from the participants' perspective by the use of the feeling thermometer from the EuroQol instrument) is significantly less than an acceptable ceiling ratio in general use at end of study (determined prior to analysis) and
- that the ratio of discounted costs per QALY (as measured from the general public's perspective by the use of the Health Utilities Index) is significantly less than an acceptable ceiling ratio in general use at end of study (determined prior to analysis).

These will be confirmed if the net health benefits of those in the active Lifestyle Intervention arm (calculated using a current and acceptable ceiling ratio at end of study) are greater than those in the Diabetes Support and Education arm ($p < 0.05$).

Costs will be measured as the sum of the costs of the intervention, hospitalization, outpatient medical care, and medications. They will be calculated by multiplying measures of resource use and estimates of unit costs for each of the resources. QALYs will be calculated by summing the area under each individual's QALY curve (constructed by plotting the feeling thermometer and Health Utilities Index scores for each interview during follow-up).

The estimates of mean differences in costs and outcomes – which will be used to create net health benefits and the cost per QALY ratios -- will be derived from multivariable regression analyses. For the evaluation of the difference in costs, the dependent variable in the regression will either be costs or the natural log of costs (determination of the form of the dependent variable will be based on statistical tests of its distribution). If the dependent variable used in the analysis is the log of costs, a smearing retransformation^{22,23} will be used to estimate the absolute difference in costs between the treatment groups. Independent variables will include the treatment group (the coefficient for which will provide a measure of the difference in cost associated with the intervention) as well as the clinical center and other covariates that are found to be correlated with the outcome that is being analyzed. Whether or not the covariates are differentially distributed across the treatment groups will not be a factor considered in their selection. If there are substantial differences in the potential length of follow-up of participants in the trial, the Lin interval method will be adopted to account for such differences.²⁴

Net health benefits are calculated by multiplying the difference in effects by the currently acceptable ceiling ratio and netting out the difference in costs. Ninety-five percent confidence intervals will be calculated using a bootstrap procedure.

In addition to evaluating net health benefits / cost-effectiveness, Look AHEAD will also test whether the incremental costs and the incremental QALYs (calculated using both the participants' and society's preferences) associated with the Lifestyle Intervention are greater than \$0. The statistical tests of these additional hypotheses will be derived from the results of the multiple regression analysis of costs and QALYs that were performed to construct net health benefits and the cost-effectiveness ratio.

A test of whether the incremental hospitalizations associated with the behavioral intervention will be less than zero will also be performed using multiple regression analysis. Considerations

like those discussed above will be made to determine the form of the dependent variable and to determine the independent variables that will be included in the model.

Multiple regression analyses will be used to test whether participants assigned to the Lifestyle Intervention have higher summary scores on the SF-36 (Version 2) and significantly higher physical function, energy/fatigue, role-emotional, and pain domain scores than will participants assigned to Diabetes Support and Education.

3. SEQUENTIAL MONITORING PLAN FOR LOOK AHEAD

3.1 General Outline of the Group Sequential Monitoring

Event rates for the primary outcome will be monitored throughout the trial and used for interim analyses of efficacy and futility. Group sequential methods for event rates will be used to control the Type I error to be 0.05 across these repeated analyses. Critical values for interim testing will be defined using two-sided O'Brien-Fleming-type bounds defined by a spending function to allow flexibility in the number and timing of interim analyses. Accumulating person-years will be used as the time scale for the spending function. Conditional power calculations based on the B-value approach will be used to assess the futility of continuation in the presence of a negative treatment effect. Boundary values that exceed ± 8 will be truncated. Conditional power calculations based on the B-value approach will be used to assess the futility of continuation.

The test statistic used to compare event rates in the two study arms will be the same as that proposed for the study's primary analysis, i.e. the comparison of Lifestyle Intervention versus Diabetes Support and Education in a Mantel-Haenszel test with unit weighting, stratified by clinical center and history of prior cardiovascular disease. Under the assumption that recruitment is uniform over 2.5 years and the dropout rate is 2% per year, the maximum number of person-years the study is projected to accumulate is approximately 40,625. (This number does not take into account the expected event rate over the course of the study, so it is an upper bound for the actual likely accumulation of person-years. Also, See 3.2, which addresses a change in study protocol.) Using this maximum will make the sequential tests conservative during the trial, and bounds for the final analysis can be adjusted so that the overall type 1 error is still 0.05. The table below presents an example of person-year accumulation, boundary values, the cumulative type 1 error, and the cumulative probability of exceeding a bound under the alternative hypothesis used in study's power analysis.

Table 3.1 An illustration of the proposed sequential monitoring plan

Number of analysis	Study year	Proportion of person-years elapsed	Lower bound	Upper bound	Cumulative type 1 error	Cumulative probability of crossing boundary
1	0.5	0.01	-8.00	8.00	0.000	0.000
2	1.5	0.05	-8.00	8.00	0.000	0.000
3	2.5	0.15	-8.00	8.00	0.000	0.000
4	3.5	0.26	-4.26	4.26	0.000	0.004
5	4.5	0.36	-3.54	3.54	0.000	0.058
6	5.5	0.47	-3.10	3.10	0.002	0.193
7	6.5	0.57	-2.80	2.80	0.006	0.369
8	7.5	0.66	-2.58	2.58	0.012	0.534
9	8.5	0.75	-2.42	2.42	0.019	0.669
10	9.5	0.84	-2.29	2.29	0.029	0.768
11	10.5	0.92	-2.18	2.18	0.039	0.840
12	11.5	1.00	-2.10	2.10	0.050	0.889

These boundaries should be used as guidelines along with other considerations when the Data and Safety Monitoring Board deliberates continuation of the study.

It is expected that the assessments of futility will not be conducted in the earliest stages of the study, but will be performed whenever requested by the Data and Safety Monitoring Board. Conditional power will be computed under three assumptions:

- continuation of whatever effect is observed at the time,
- the null hypothesis of no difference between the study arms, and
- the alternative hypothesis of an 18% reduction of event rate in the Lifestyle Intervention arm compared to the Diabetes Support and Education arm.

In addition to sequential monitoring for early rejection of the null hypothesis and computation of conditional power, early assessment of the study's feasibility will be done as described in the protocol.

3.2 Modifications to the Group Sequential Monitoring Plan to Account for the Augmented Primary Endpoint and Extension

The Look AHEAD interim monitoring plan was designed around the expected total number of person-years of follow-up that would be observed over 11.5 years, and the timing of analyses has been computed based on the proportion of observed person-years available at each DSMB meeting. The protocol has been modified to allow for two additional years of follow-up. If the trial is extended by two years, this original time scale will be distorted: a larger number of total person-years will be observed, and the timing of past interim analyses with respect to the new expected total will be changed. This will be accommodated by using an ad-hoc bound for the one analysis at which the change is first incorporated, and then resuming normal monitoring at the next and all remaining meetings.

The current interim monitoring plan for Look AHEAD computes group sequential bounds based on an O'Brien-Fleming type spending function and a time scale defined by the number of observed person-years divided by 40625. If the study is extended by two years, the expected

maximum number of person-years will be 47690, and the information time of the six interim analyses performed through May 2008 will be smaller than what was used to compute the bounds for those analyses. Table 1 below shows the times, bounds, nominal and cumulative alpha computed through May 2008. The type 1 error that will be “spent” through May 2008 is 0.00502, leaving 0.04498 for the duration of the study.

Table 1. Interim analyses through May 2008.

Information Time with Extension	Original Information Time	Person -Years	Lower Bound	Upper Bound	Nominal type 1 error for upper bound	Cumulative type 1 error (Alpha)
0.00	0.00	0	-8.0000	8.0000	0.00000	0.00000
0.22	0.26	10720	-4.2420	4.2420	0.00001	0.00002
0.27	0.32	12994	-3.8060	3.8060	0.00007	0.00015
0.32	0.38	15353	-3.4780	3.4780	0.00025	0.00055
0.37	0.44	17855	-3.2218	3.2218	0.00064	0.00145
0.43	0.50	20339	-3.0149	3.0149	0.00129	0.00305
0.47	0.55	22259	-2.8782	2.8782	0.00200	0.00502

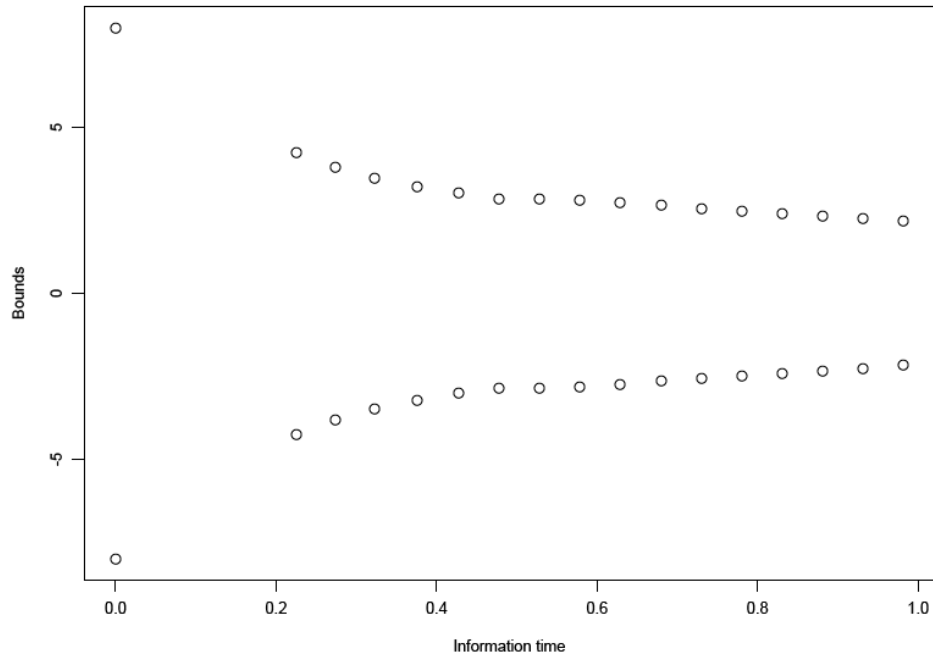
In anticipation of the trial extension, the remaining type 1 error will be redistributed over future interim analyses. This is done using an O’Brien-Fleming type spending function. Future bounds will be computed under the assumption that no previous interim analyses have been performed, using the proportion of 47690 person-years observed at each analysis, and spending a total type 1 error of 0.04498 ($= 0.05 - 0.00502$) by the end of the study. This approach ignores the change of time scale.

The difficulty in ignoring the changed time scale is that the nominal type 1 error at the first post-extension interim analysis (planned for March, 2009) decreases slightly, so that the bound increases slightly, relative to the May 2008 interim analysis. This is awkward since bounds typically stay the same or decrease as a study progresses. This analysis plan is represented in Table 2; Figure 1 shows these bounds graphically. There is a small bump in the bounds near 0.5 on the time scale. This would have negligible impact on any decision to terminate or continue the study, but could be considered a flaw in the monitoring plan. This can be avoided by using an ad hoc bound at the March, 2009 meeting. The bound can be 2.8782, which is the same as the bound for May 2008. Although this is ad hoc, it is reasonable, it allows an adequate test for the March, 2009 meeting, and bounds never increase (Table 2, Figure 1).

Table 2. Ad hoc bound for March 2009.

Information Time with Extension	Original Information Time	Person -Years	Lower Bound	Upper Bound	Nominal type 1 error for upper bound	Cumulative type 1 error (Alpha)
0.00	0.00	0	-8.0000	8.0000	0.00000	0.00000
0.22	0.26	10720	-4.2420	4.2420	0.00001	0.00002
0.27	0.32	12994	-3.8060	3.8060	0.00007	0.00015
0.32	0.38	15353	-3.4780	3.4780	0.00025	0.00055
0.37	0.44	17855	-3.2218	3.2218	0.00064	0.00145
0.43	0.50	20339	-3.0149	3.0149	0.00129	0.00305
0.47	0.55	22259	-2.8782	2.8782	0.00200	0.00502
0.53	0.62	22750	-2.8782	2.8782	0.00200	0.00654
0.58		27554	-2.7966	2.7966	0.00258	+0.00516
0.63		29959	-2.7361	2.7361	0.00311	+0.00767
0.68		32364	-2.6408	2.6408	0.00414	+0.01077
0.73		34769	-2.5502	2.5502	0.00538	+0.01446
0.78		37174	-2.4671	2.4671	0.00681	+0.01872
0.83		39579	-2.3911	2.3911	0.00840	+0.02353
0.88		41984	-2.3215	2.3215	0.01013	+0.02885
0.93		44389	-2.2575	2.2575	0.01199	+0.03464
1.00		47690	-2.1611	2.1611	0.01534	+0.04346

Figure 1. Graph of bounds if an ad hoc bound is used for March 2009.



4. SUBGROUP ANALYSES

Look AHEAD will assess, among the following subgroups of participants, the effect of the intervention within and uniformity of relative hazard of the primary and secondary endpoints between participants assigned to Lifestyle Intervention versus Diabetes Support and Education. Estimates of intervention assignment will be computed within each subgroup. Point estimates for the relative hazard of endpoints will be developed for each subgroup and formal tests for the equivalence of these estimates will be conducted. Factors defining these subgroups were selected based on the expectation that they may be important for determining whether weight loss interventions are prescribed for individuals, influencing either the relative success of the intervention in producing and sustaining weight loss, or the relationship between weight loss and cardiovascular disease. The formal subgroups to be assessed in these analyses are:

- sex,
- ethnicity (grouped as African-American, Asian, Hispanic-Latino, Native American, and white), and
- prior cardiovascular disease at baseline.

Subgroup analyses will be covariate-adjusted for the other subgroup factors.

In tertiary analyses, investigators will examine factors that may interact with intervention effectiveness: a longer list of factors. These analyses would not be used to "rescue" a negative result on the primary hypothesis.

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