VERSION 2.4

Weight Loss Maintenance Trial

PROTOCOL

February 23, 2010

Table of Contents

FIGURES

TABLES

PROTOCOL

1. Overview

Overweight/obesity is the second leading cause of preventable death in the US, and is growing in prevalence at an alarming rate. Control of overweight/obesity is increasingly recognized as a high national priority because of its contribution to cardiovascular disease (CVD) risk factors and ultimately to CVD itself. The short-term success of behavioral interventions for weight loss has been repeatedly documented. Unfortunately, because weight re-gain is extremely common, a disappointingly small proportion of individuals achieve long-term weight control. Of the factors associated with sustained weight loss, one of the most important is continued intervention with frequent contacts. The Weight Loss Maintenance Trial (WLM) is a multi-center, randomized, controlled trial that determines the effects of two innovative behavioral interventions, each designed to maintain frequent contacts, compared to a self-directed usual-care control group. Overweight and obese individuals (~60% women, ~40% African-Americans) who are taking medication for hypertension and/or dyslipidemia enter a 5-month weight-loss program. Those individuals who lose at least 4 kg (N = 800) are then randomized into one of three groups: a Personal Contact (PC) Intervention that provides monthly personal contacts with a trained interventionist, primarily via telephone; an Interactive Technology (IT) Intervention that provides frequent contacts through a state-of-the-art interactive Web-based program supplemented by other communication technologies; or a Self-Directed/Usual Care control group (SD/UC). The primary outcome is weight change from the end of the initial weight-loss program to the end of the 30-month weight maintenance intervention period. Other outcomes include weight change in subgroups, control and prevalence of CVD risk factors, measures of behavior change, and cost of implementation. For each outcome, the PC and IT interventions are compared to SD/UC and, if either is different from SD/UC, to each other. To successfully combat the obesity epidemic, clinicians and health care systems must have options that are effective and feasible, and that can be provided to large numbers of individuals. The purpose of this study is to develop and test two such interventions, which, if effective, should complement ongoing efforts to stem the obesity epidemic and ultimately prevent obesity-related CVD.

2. Specific Aims

Overweight and obesity are the second leading cause of preventable death, primarily through effects on CVD risk factors (hypertension, dyslipidemia, and type 2 diabetes).[1,2] Extensive research has documented that weight loss is achievable (at least in the short term), and weight loss can control each of these CVD risk factors. In response to this overwhelming evidence, national health organizations recommend weight control as a core component of treatment guidelines for hypertension, dyslipidemia, and type 2 diabetes. Likewise, the Surgeon General, the NIH, and the medical research community consider weight control to be one of the highest public health priorities. And yet the obesity epidemic continues to grow, affecting over 90 million Americans.

A major factor contributing to this escalating epidemic is re-gain of weight after initial weight loss. Indeed, despite abundant evidence that weight loss can be achieved over the short term, re-gain of weight is disappointingly common. The most promising strategies to prevent re-gain involve continued behavioral intervention with frequent contacts.

Health care systems are reluctant to devote resources to weight-loss programs in part because of the high probability of weight re-gain and the anticipated costs of long-term behavioral interventions. In order to successfully combat the obesity epidemic, clinicians and health care systems must have options that are effective and feasible in high-risk and general populations. The objective of this trial is to develop and test two distinct behavioral interventions, each designed to maintain weight loss through continued intervention with frequent contacts.

The Weight Loss Maintenance Trial (WLM) is a randomized, controlled trial that compares the effects of two maintenance interventions to a self-directed usual care control group, in overweight or obese individuals who are at high risk for CVD (defined by use of medication for hypertension and/or dyslipidemia). During an initial 5-month period (Phase I), approximately 1600 individuals receive a behavioral lifestyle intervention designed to accomplish weight loss. In Phase II, those individuals (N = 800) who lose a minimum of 4 kg are then randomized to one of the following three groups:

1. **Self-Directed/Usual Care (SD/UC)**: advice and information at randomization, with minimal contact at 12 and 30 months;
2. **Personal Contact (PC) intervention:** behavioral intervention using Motivational Interviewing, delivered primarily through personal phone calls and to a lesser extent by in-person visits;
3. **Interactive Technology (IT) intervention**: Web-based, individually tailored behavioral intervention, supplemented with Interactive Voice Response phone calls.

In the development of both the PC and IT interventions, consideration was given to the cost of implementation, balancing the necessity for frequent and intense intervention contacts with the resources required to provide them.

The duration of the post-randomization weight-maintenance period is 30 months. The primary outcome variable is weight change from the end of Phase I (the initial weight loss period), to the end of Phase II follow-up (30 months post-randomization).

Primary specific aims:

1. Test the hypothesis that the PC intervention is more effective than SD/UC in maintaining long-term (30-month) weight loss.

2. Test the hypothesis that the IT intervention is more effective than SD/UC in maintaining long-term (30-month) weight loss.

We hypothesize that each of the two active interventions (PC and IT) will be superior to SD/UC. There is no basis in the literature for developing an *a priori* hypothesis about which active intervention will be superior to the other; hence this contrast is a secondary aim.

Secondary specific aims:

3. Test the hypothesis that the PC intervention differs from IT in maintaining long-term weight loss.
4. Compare the effects of PC, IT, and SD/UC on weight maintenance in subgroups defined by race, sex, age, CVD risk factors, and baseline body mass index.
5. Compare the effects of PC, IT, and SD/UC on the prevalence and control of major CVD risk factors.
6. Compare the effects of PC, IT, and SD/UC on measures of behavior change (e.g., physical activity, aspects of diet).

Other aims:

7. Compare the effects of PC, IT, and SD/UC on weight change from entry (prior to Phase I) to the end of the post-randomization maintenance phase (Phase II).
8. Determine behavioral, psychosocial, and physiological factors associated with both initial (Phase I) and sustained (Phase II) weight loss.
9. Estimate the direct costs of implementing the PC and IT interventions outside of the research environment.
10. Explore patterns of weight loss on trial outcomes.
11. Establish a bank of biological specimens (including serum, plasma, and DNA) for future analyses.

3. Background and Significance

Weight and CVD risk factors

An estimated 65% of U.S. adults are overweight or obese.[1,2] The prevalence of these conditions has increased dramatically in recent years and continues to rise.[3,4] The deleterious effects of obesity are enormous and include increased risk of morbidity and mortality from cardiovascular disease[5-9] in large part through the striking effects of obesity on CVD risk factors. The prevalence of hypertension, diabetes, and dyslipidemia is generally 1.5-2.9 times higher among overweight adults than normal-weight adults.[4,10,11] Fifty million adults have hypertension, 40 million have dyslipidemia, and 16 million have diabetes.[12-15] The human and financial costs of obesity and related conditions are staggering.[16,17] Three hundred thousand deaths each year are attributed in part to overweight and obesity.[18] Total direct and indirect costs related to obesity and its consequences amounted to $117 billion in the year 2000.[18]

Surgeon General Satcher has said that failure to address the problem of obesity could wipe out some of the gains we've made in controlling heart disease in recent decades, and he identifies increased research aimed at controlling the obesity epidemic as one of the nation's top health priorities.[19] Indeed, at this time in history, developing behavioral strategies for sustained weight loss can be considered a public health mandate.

Fortunately, the effect of obesity/overweight on CVD risk factors is reversible. Weight loss lowers total and LDL-cholesterol, lowers triglycerides, and raises HDL-cholesterol.[20] Several studies demonstrate the ability of relatively modest amounts of weight loss to lower blood pressure.[21,22] In individuals with high-normal blood pressure, weight loss can prevent the development of hypertension.[23] Similarly, weight loss lowers blood sugar in both diabetic and non-diabetic individuals, and two recent randomized trials[24,25] prove that weight loss can prevent the development of type 2 diabetes. All of these studies employed behavioral approaches to achieve weight loss, and in at least one[25] this approach was superior to medication.

Need for research focusing specifically on maintenance of weight loss

Behavioral interventions for weight loss and reduction of CVD risk factors have been recommended in numerous national guidelines and consensus statements.[1,18,26-28] These guidelines stress the need for treatment with a combination of reduced energy intake, improved dietary patterns, increased physical activity, and behavioral therapy. The reports acknowledge that weight loss is especially difficult to maintain, and thus further recommend that weight-loss programs should be followed by a weight maintenance program of prolonged duration. Yet remarkably little is known about the necessary structure, content, and mode of delivery of programs that lead to successful maintenance of weight loss.

This knowledge gap exists because, even though many weight loss trials have lasted several years, few studies have tested alternative strategies designed to sustain weight loss once it has been achieved.[29-31] Most studies falling under the rubric of "maintenance studies" have simply followed individuals over a period of time after they participated in weight loss, dietary change, or physical activity programs. The interventions may have been prolonged, but the studies were not specifically designed to test alternative strategies for weight maintenance. In addition, most previous studies have provided long-term weight management interventions for the purpose of achieving some other endpoint (e.g., blood pressure or diabetes control). Thus they are primarily tests of the effect of weight loss on another outcome, rather than testing alternative strategies for achieving and maintaining weight loss *per se.* This context may constrain the intervention so that it is less than optimal for maintenance of weight loss. For example, in the Trials of Hypertension Prevention (TOHP) minor emphasis was placed on physical activity to avoid the confounding

effects of physical activity on the study's primary outcome (blood pressure).[32,33] Another limitation of previous weight loss studies is that they have generally compared a single strategy to usual care rather than comparing alternative strategies to each other. Direct comparisons of interventions specifically designed to maintain weight loss are needed.

In response to this problem, national health organizations have stressed the need for comprehensive research aimed at maintenance of lifestyle modifications. *The NHLBI Strategic Plan* (2001-2005)[13] includes testing interventions for maintaining long-term health behaviors as a part of its goals. *The NHLBI Strategic Plan to Address Health Disparities* (2000)[34] highlighted the need to find innovative approaches to promote weight loss, physical activity, and healthy dietary practices among minorities, and to conduct intervention studies that test the effectiveness of these practices in ensuring long-term maintenance of health-promoting behaviors. Similarly, recommendations for research on the maintenance of weight loss and lifestyle changes are advocated in the 1997 *Surgeon General's Report on Physical Activity and Health,*[35] the 1995 *NIH Consensus Statement on Physical Activity and Cardiovascular Health,*[36] and the 1998 *NHLBI Clinical Guidelines for the Identification, Evaluation and Treatment of Overweight and Obesity in Adults.*[1] Furthermore, a 1998 national workshop convened by NHLBI, *Maintenance of Behavior Change in Cardiorespiratory Risk Reduction,*[29] stressed the critical need for research on specific strategies for long-term maintenance of dietary changes, physical activity, and weight loss. The recent *NHLBI Task Force on Research in Prevention of Cardiovascular Disease* considers the development of long-term solutions to the obesity epidemic a "top tier" priority.[18] These recommendations highlight the need to conduct randomized studies to compare different long-term intervention approaches.

This need can be seen clearly in the general pattern of weight change observed in previous studies. In most studies, intensive intervention leads to behavior change (and weight loss) over a relatively short period of time (usually 6 months or less). But the intensive phase is generally followed by a less intensive period of "support," which is associated with high rates of weight re-gain. For example, in TOHP II participants lost an average of 4.4 kg during the intensive intervention phase, but their average weight returned to baseline after 3 years.[33] Many other studies exhibit the same pattern. Even studies designed to provide a long-term intervention (rather than just a "support" phase after an intensive intervention) show a similar pattern of behavior. For example, the Activity Counseling Trial (ACT) provided a consistent level of intervention intensity throughout the 2-year intervention, and yet demonstrated increased physical activity over the first 6 months, followed by declining physical activity during the remainder of the trial.[37] An exception to this pattern is seen in the Trial of Non-pharmacologic interventions in the Elderly (TONE) study, in which participants lost an average of 5 kg during the intensive phase and were able to maintain that weight loss over 30 months.[22] The TONE study population was older adults on blood pressure medications, and the goal of the study was control of hypertension without medications. The demographics of the study population (older and retired) and their motivation for participating in the study (getting off medications) were the likely reasons for sustained weight loss. Thus the improved pattern of weight change in TONE may have been related to the study population rather than the intervention itself, but these findings suggest the possibility of successful weight loss maintenance. Unfortunately, the interventions that have been tested to date in a general population at risk for CVD do not lead to maintenance of weight loss. New interventions must be developed and tested, with long-term maintenance of weight loss as the primary goal and outcome.

Maintenance of weight loss in minority populations
Surgeon General Satcher has drawn attention to racial disparities in the obesity epidemic.[19] Minority populations, particularly African-Americans, are affected disproportionately.[12] The African-American population has a greater prevalence of obesity, a greater increase in prevalence over time,[4] and a greater prevalence and severity of obesity-related CVD risk factors[38] than other groups.[16,39] Unfortunately, African Americans also have derived less benefit from existing strategies for weight loss and its maintenance.[23,40] Therefore, the development and evaluation of new strategies for maintaining weight loss must specifically address the potential for controlling obesity in African Americans.

Maintenance of weight loss in high-risk populations
Sustained weight loss is an important goal for all overweight and obese individuals, but it is a more urgent issue in certain populations. Specifically, individuals who have obesity-associated cardiovascular risk factors are most at risk for the consequences of overweight/obesity and have the greatest motivation for altering their lifestyle. Individuals on medication have an additional incentive: to minimize the need for medication for these risk factors, with its attendant cost and potential side effects. Therefore, we believe that a priority should be placed on maintenance research in the high-risk population of overweight/obese individuals with hypertension and/or dyslipidemia.

Factors associated with maintenance of behavior change
Despite the dearth of trials that address weight maintenance, several important factors have been identified in clinical trials and observational studies. Important considerations include an emphasis on both dietary pattern and physical activity, use of behavioral theory and methods, and the frequency and duration of intervention contacts.

Emphasis on both dietary pattern and physical activity is important in maintaining long-term weight loss.[41-46] Ideally, the dietary pattern should include reduced calories and fat and increased fiber, fruits, and vegetables. Increasing physical activity has been associated with both the maintenance of weight loss and improvements in CVD risk factors such as hypertension.[26,47] Maintenance of weight loss may require higher levels of physical activity than what is recommended for general health. Although the current general physical activity recommendations are 30 minutes of at least moderate intensity activity on most days of the week,[48] data from the National Weight Control Registry and clinical trials suggest that individuals who are successful at maintaining weight loss engage in substantially greater amounts, on the order of 200 minutes/week.[49,50] Hence our goal for the maintenance phase (as opposed to the weight loss phase) of this trial is 225 minutes/week. In addition to this empiric evidence, physical activity in a weight maintenance intervention has a strong physiological rationale: Weight loss leads to decreased resting metabolic rate, resulting in lower energy requirements, which may contribute to weight re-gain. Interventions that address this issue (e.g., by emphasizing physical activity to preserve lean body mass and thus preserve resting metabolic rate) are likely to have greater success than those that ignore this important factor.

Behavioral approach: Specific behavioral strategies found to be most effective in maintaining lifestyle change include: self-monitoring, stimulus control, problem-solving, relapse prevention, environmental engineering, reinforcement management, social support, targeting motivational variables, offering choices, and individualizing feedback.[7,21,30,31,33,41,45,51-57]

Although published reports support the effectiveness of these various behavioral maintenance techniques, none stands by itself as a means to promote maintenance. Instead these techniques tend to be used in combination, i.e., in a multi-component approach. As reflected in recent theoretical overviews on maintenance,[58-60] consensus is growing that the weight loss phase of

weight management may require different behavioral approaches than the maintenance phase. Dietary education and skills acquisition may be more important for weight loss, while techniques for detecting lapses, enhancing motivation, and coping with obstacles may be more relevant for the maintenance phase.

An important innovation in behavioral techniques is the use of motivational interviewing.[61,62] The motivational interviewing strategy was first developed for use in addictions counseling[61-63] and was subsequently adapted for health behavior change, including nutrition counseling in several large clinical trials such as Dietary Intervention Study in Children,[64] the Trials of Hypertension Prevention Phase II,[65] the Women's Health Initiative (unpublished data), and, most recently, PREMIER.[66] Maintaining or developing motivation and overcoming resistance may be key issues for individuals attempting to maintain weight loss and is incorporated into the interventions.

Frequency and duration of intervention contacts: The most effective intervention strategies are those that extend the length of initial intensive intervention and then provide frequent and continued contact.[30,54] Perhaps the most dramatic example of this effect was a randomized trial comparing a 20-week series of group meetings to a 40-week series of group meetings.[67] The mean weight loss in the 40-week treatment was greater than the 20-week treatment, but after the cessation of treatment the rate of weight re-gain in both groups was the same. Definitive, comprehensive reviews of the weight loss literature consistently show that interventions with longer initial intervention phases, and more frequent and intensive follow-up contacts, show better long-term results.[42,68] Frequent, regular contact has been repeatedly documented as effective in the literature. Furthermore, in exit interviews therapists and participants commonly acknowledge the vital importance of this factor.

The data reviewed above and more comprehensive reviews of weight loss and maintenance studies by Kumanyika[51] and Jeffery[42] support the importance of physical activity, healthy dietary pattern, use of behavioral and motivational strategies, and frequent, regular contacts. Unfortunately, previous studies have tended to focus on a single or limited repertoire of approaches. Given the limited success with maintenance of weight loss, such a uni-dimensional approach may not be ideal. Weight maintenance interventions must optimize both the theoretical construct and the mode of delivery.

Feasibility and logistics of implementation

Developers of maintenance interventions must also consider feasibility and logistics for both participants and health care systems. For individuals, site-based programs (e.g., group sessions) pose logistic barriers such as travel, childcare, and scheduling. Although regular, frequent contact may help maintain weight loss and associated behavior changes, attendance at group sessions can be difficult to sustain over a prolonged period. Innovative approaches for increasing contact and sustaining motivation are needed. With regard to feasibility for health systems, the cost of providing the intervention is the major concern. Costs will ultimately need to be evaluated in the context of the population targeted (i.e., high risk or general), recognizing that high-risk populations may justify interventions of greater intensity. In addition, costs of maintenance interventions must be evaluated in the context of the direct and indirect costs of obesity and its consequences.[16,17] To advance this evaluation, this study includes plans for a cost analysis.

Telephone interventions

It may be possible to minimize logistical barriers and intervention costs by using personal telephone contacts to deliver a behavioral intervention. Telephone contacts offer many of the advantages of face-to-face contact, including an individualized approach and social support from

the counselor. In addition, telephone contacts offer some advantages over face-to-face encounters. For example, they offer flexible scheduling and no need to travel. In recent years, health researchers and health systems have turned to telephone systems to improve adherence to complex medical regimens and lifestyle changes. Such applications include triage systems for nurse advice lines, telephone banks of health educators to encourage physical activity, and interventions to promote smoking cessation.[69] Personal telephone calls have been shown to improve adherence to physical activity,[70] promote self-monitoring of dietary intake and physical activity,[71] increase smoking cessation rates,[72] and improve diabetic self-care and glycemic control.[73] The telephone provides an alternative mechanism for delivering a behavioral intervention that incorporates regular, frequent, and in this case, personal contact with on-going personal encouragement and support, and this mode of intervention delivery is the basis of the PC intervention.

New technology applied to health management and maintenance

A potentially effective and innovative alternative to a personal contact intervention could be based on new technology, particularly the Internet. Interventions using Internet-based technology have the potential to reach millions of Americans and to be available "on demand." The rapid growth of Internet access, expanded Web content, and new developments in Internet appliances have all increased the feasibility of providing health behavior change and maintenance services to patients in their homes.[74,75] E-mail, interactive phone technology, and interactive Web sites provide mechanisms for increased frequency of contacts, self-monitoring, feedback, social support, and individually tailored advice.[76]

In this emerging field, only limited data on use and effectiveness of Internet applications for health management and behavior change are currently available.[76-78] Several encouraging studies have used computer-mediated and Internet interventions for behavior change and chronic disease management. Programs using e-mail and Internet Web sites have been shown to improve diabetes self-management,[79,80] promote physical activity,[81] and improve quality of life in AIDS patients.[82]

A recent study compares an Internet-based intervention with a therapist-led group intervention for maintenance of weight loss. After an initial 15-week intervention program followed by 22 weeks of the maintenance intervention, weight loss was comparable in the two groups.[83] This small study (n=44) demonstrates that an Internet-based intervention is feasible and acceptable to participants: only 8% of volunteers were excluded because they did not have Internet connections or computer equipment, and complete follow-up data was available in 87% of participants in this study.

An important key to effective computer-assisted participant intervention is the design of the user interface. User interface design refers to how humans interact with the computer system. The user interface enables interactivity and tailored interventions,[84,85] which are particularly applicable to the maintenance of behavior change. In efforts to increase satisfaction with services and effectiveness of interventions, methods to make medical information and health behavior change more personal for participants have been extensively explored.[86,87] Several studies have shown that tailored materials are more effective than traditional generic materials.[47,88,89] Some recent examples of automated interventions that tailor content to the user's individual characteristics include smoking cessation,[90,91] semi-automated dietary counseling,[89,92-95] mammography screening,[96] and materials for various types of cancer screening.[97] Several approaches to tailoring advice and feedback have focused on theoretical constructs of health behavior change, participants' perceived benefits and barriers associated with a health

behavior,[98] the participant's readiness to change,[99] and the participant's perceived causes of success or failure in undertaking a new health behavior.[100]

These technological approaches may be particularly relevant to maintenance of weight loss over the long term.[41] By using e-mail, the Internet, and automated telephone counseling, more frequent contacts may be feasible without one-on-one involvement of professionals, which would result in reduced costs. Individuals can use the Internet when it is convenient for them, which may mean greater satisfaction and more involvement in behavior change. With these Web-based technologies, key components of cognitive behavioral interventions can be delivered.[76] These technologies appear especially well suited for delivering components emphasized in the interventions: self-monitoring, motivational enhancements, social support, reinforcement, and prompts. The capabilities for providing immediate and personalized feedback may enhance participation and reinforce behavior change, thus contributing to the maintenance of the initial weight loss and changes in diet and physical activity.[86,92] Continued self-monitoring has also been associated with improved weight maintenance.[23,101] Using Internet technology, immediate feedback can be provided on self-monitoring data and can be used to reinforce positive changes. This technology may also offer flexibility in the approach to monitoring, which is a common issue in intervention programs. An Internet-based behavior change intervention can even provide social support, which is derived from chat rooms and message boards that allow participants to express their concerns to others with similar problems and to share advice.[102] Systems that include on-line social support, such as the Comprehensive Health Enhancement Support System (CHESS) used for AIDS/HIV and breast cancer patients,[82] have shown high usage and improvements in quality-of-life measures. Other studies of on-line social support for health concerns include Weinberg's system for cancer patients[103] and Radin's breast cancer support system.[104]

A second important key to successful use of Internet technology for weight maintenance is access. Internet technology has the potential to make behavior change and maintenance interventions available to a very large population. Although access is not universal at this time, and certain important groups are under-represented, year 2000 U.S. census data indicate that 54% of households contain a computer, and 42% of households use the Internet. Although the proportion of African-American households that currently have Internet access is lower than for white households, the proportion of households with access has been rising steadily in both groups. Overall, Internet access has increased by 233% since 1997,[105] and continues to grow at a remarkable pace.[106] By many measures, it is now considered a "mainstream" technology.[107-109] Informed projections show that Internet access will be very common for both black and white households within a decade. Although the spread of Internet technology has been much faster than that of the telephone, or even television, the adoption of Internet use has many similarities to these earlier communications systems. Both telephone service and broadcast television started as luxuries that many people thought would never become widely used, and then became virtually universal throughout the population. A survey of participants from the PREMIER trial, a study currently being conducted by the same research centers conducting WLM, indicates that 78% of African-American and 88% of non-African-American participants have Internet access in their home, suggesting that our plan to study an Internet-based intervention is feasible (unpublished observations).

Summary

Review of existing literature and of national health priorities highlights the need for research that develops and tests strategies for sustaining weight loss. This trial specifies maintenance as the primary outcome, focuses on a high-risk population (including those with CVD risk factors and

African Americans) that will benefit most from the interventions, and emphasizes behavioral strategies associated with sustained maintenance of behavior change (such as regular, prolonged contact). An intervention delivered through telephone contacts offers the advantages of personal contact without the logistical disadvantages of face-to-face interactions. A technology-based intervention offers advantages of wide availability, economy of scale and access on demand. Compared to the current lack of effective maintenance strategies, both of these interventions are likely to significantly increase the proportion of individuals who successfully sustain weight loss.

4. Research Design and Methods For Phase I and Phase II

Overview of methods

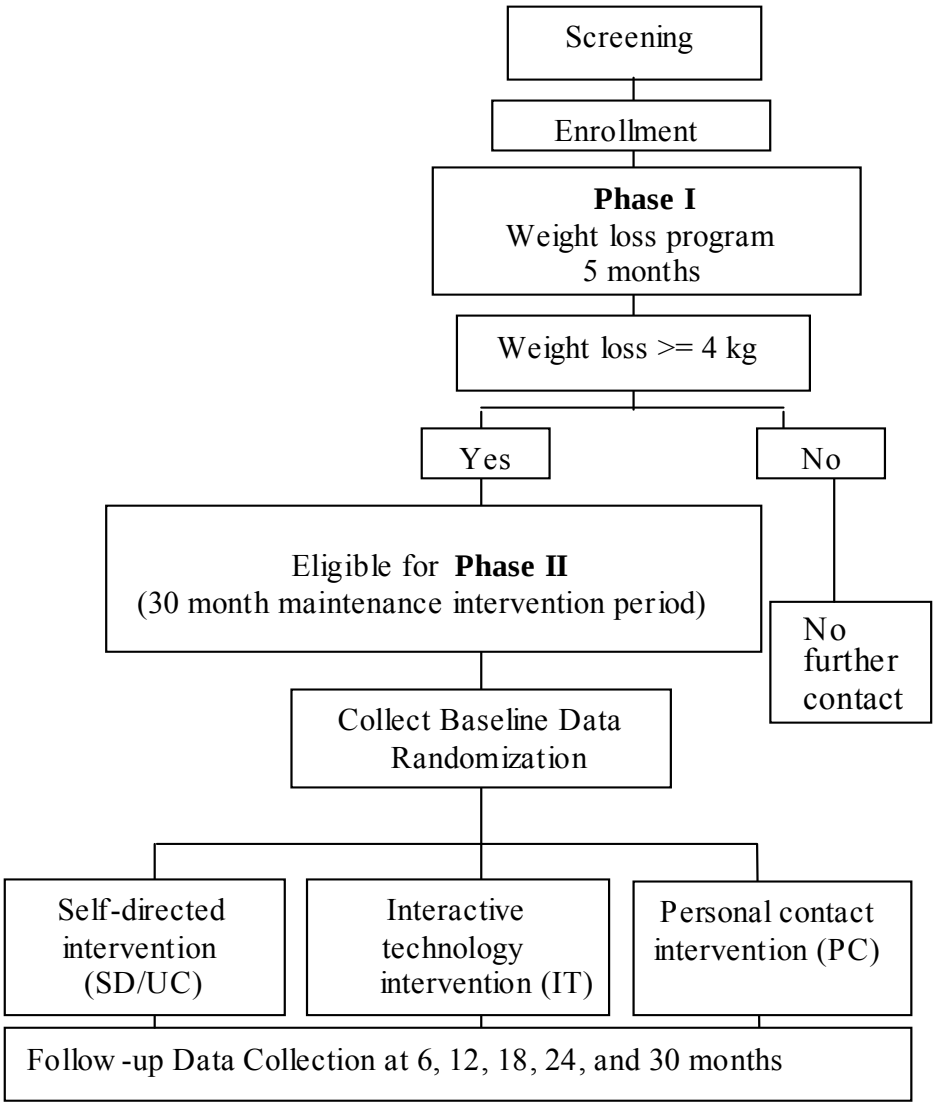
WLM tests two maintenance strategies: a Personal Contact (PC) intervention that includes monthly interaction with a counselor primarily using phone contact supplemented by face-to-face visits, and an Interactive Technology (IT) intervention that accomplishes frequent, individualized contact through largely automated systems. These maintenance interventions will be compared to a self-directed (SD/UC) control group. During "Phase I," individuals are screened for eligibility, and entry data are collected. All eligible individuals (n~1600) are enrolled in a 5-month weight-loss program. Subsequently, all individuals who have successfully lost at least 4 kg (n = 800 based on projections from PREMIER) are eligible for "Phase II," a randomized comparison of three maintenance interventions. Baseline data are collected at the beginning of Phase II (prior to randomization), and follow-up data after 12 and 30 months of the Phase II maintenance interventions. Methods for Phase III are described in chapter 15.

The maintenance strategies tested in this trial are designed to maximize the potential for rapid, widespread implementation in both the public health sector and the medical care environment. To this end, we have designed the interventions to be sufficiently flexible that government organizations, health care providers, and health insurance companies could adopt each intervention. Furthermore, we include a cost analysis in our trial to ascertain direct costs of implementation from a variety of perspectives. The interventions in this trial are developed in such a way that they can serve as prototypes for rapid translation of our research findings into practical applications. Such translation can lead to significant reduction in CVD morbidity and mortality through sustained weight loss.

Many of the recruitment, data collection, and intervention procedures used in WLM are based on the PREMIER trial. PREMIER was a randomized clinical trial designed to determine the effects of two multicomponent lifestyle interventions, relative to an advice-only control condition, on blood pressure (BP). Although numerous organizations recommend multiple lifestyle changes to control BP and potentially prevent hypertension, comprehensive strategies that simultaneously implement all lifestyle recommendations have yet to be developed and tested. A brief description of PREMIER is provided here; a more detailed description has been published.[66] Funding for PREMIER started in September 1998 and the final 18-month assessment visits for the last cohort of participants were completed in November 2002.

PREMIER participants were 25 years of age or older, with systolic blood pressure (SBP) of 120-159 mmHg, diastolic blood pressure (DBP) of 80-95 mmHg, and BMI 18.5-45 kg/m^2. Sixty-two percent of the 811 randomized participants are women, 34 percent African Americans, 37 percent have blood pressure classified as stage 1 hypertension, and 95% were overweight or obese (BMI >25). After three screening visits, participants were randomly assigned to one of two lifestyle interventions or to an "advice only" control group. Both of the lifestyle change groups included a series of group sessions designed to help participants lose weight, increase physical activity, and reduce sodium intake and make a variety of dietary changes to reduce blood pressure. One of these groups was given advice and assistance to adopt the DASH eating pattern, and the other group was not given that advice. The primary outcome was the change in SBP at 6 months, with change in SBP at 18 months, change in DBP at 6 and 18 months, and weight loss as secondary outcomes. The intervention programs developed for PREMIER formed the basis for the Phase I weight loss program in WLM.

Figure 1. Study Design



Study design

The study design for WLM is illustrated in Figure 1. The study population consists of overweight or obese adults who are taking medication for hypertension and/or dyslipidemia. Eligible participants first enter an intensive 5-month weight-loss program (Phase I). This behavioral intervention promotes weight loss through decreased calorie consumption and increased physical activity. Participants are also encouraged to follow the DASH (Dietary Approaches to Stop Hypertension) diet, which has been shown to reduce blood pressure and have a desirable effect on lipids. The high-fiber and low-fat content of the DASH diet make it particularly appropriate for weight loss.

After an intensive 5-month program, participants who have lost weight (at least 4 kg) are eligible for randomization into one of three maintenance interventions (Phase II). The three interventions are: 1) self-directed/usual care (SD/UC); 2) a Personal Contact (PC) intervention; and 3) an Interactive Technology (IT) intervention. The interventions are described in more detail below. Each of the active interventions (PC and IT) will be compared to the self-directed/usual care control group, and, if significantly different from control, they will be compared to each other. The maintenance interventions continue for 30 months; primary outcomes are assessed at 12 and

30 months following randomization. The primary outcome variable is weight change from randomization to the end of the 30-month follow-up period. Throughout the follow-up period, there are additional weight and safety measurements at 6-month intervals.

All participants provide written informed consent in accordance with local Institutional Review Board specifications. As was done in PREMIER and other lifestyle intervention trials, we use a 2-stage consent process, with the initial consent obtained prior to randomization.

We hypothesize that both PC and IT will be superior to SD/UC as a means to sustain weight loss. However, we are less certain of the relative effects of PC and IT. The greater frequency of contact may favor IT, while the personal contacts of PC, albeit less frequent than IT, may favor PC. Ultimately, the real-life utility of both interventions will be a function of both efficacy and costs of implementation; therefore the study plan includes a cost analysis.

The beneficial effects of weight loss on blood pressure, glucose tolerance, and lipids have been repeatedly documented. Therefore, WLM focuses its resources on implementation of the trial interventions and collection of data that might explain maintenance of weight loss. In view of this focus and the difficulty of assessing change in risk factor levels over the long term when many participants are taking medication, we assess control of CVD risk factors as categorical outcomes defined as percentage of participants whose risk factor status is at or better than levels established as normal by expert panels.

5. Eligibility

The target population is overweight or obese adults who are taking medication for hypertension and/or dyslipidemia, and who are able to lose at least 4 kg during an initial 5-month weight loss program (Phase I). The randomized population is expected to include approximately 60% women and 40% African Americans. Eligibility criteria for entry into the initial 5-month intensive weight-loss program are summarized in Table 1. A second eligibility requirement occurs after completion of this program: loss of at least 4 kg compared to entry weight. Based on our experience in PREMIER, which had a similar intensive weight loss phase, we anticipate that approximately 50% of those who enter Phase I will lose at least 4 kg of weight and elect to be randomized. To randomize 800 participants, we therefore estimate that approximately 1600 individuals will need to enter the Phase I weight-loss program.

Although overweight/obese individuals with type 2 diabetes would benefit from a weight loss program, there is a significant risk of hypoglycemia induced by weight loss and increased physical activity in diabetics treated with oral medication or insulin. The monitoring and clinical oversight that would be required to ensure their safety is beyond the scope of this project. In addition, another large clinical trial (LookAHEAD) is specifically studying long-term weight control in type 2 diabetics. Therefore, individuals with medication-treated diabetes are excluded. Individuals who report a history of diabetes but are not taking medication for it may be eligible as noted below.

Table 1. Phase I Eligibility Criteria

Inclusion criteria for Phase I

- Age 25+
- BMI of 25-45 kg/m^2 (inclusive)
- Currently taking prescription medication for hypertension and/or dyslipidemia
- Personal physician permission required if diabetes present or if participant had a prior CVD event (note: CVD event within past 12 months is an exclusion)
- Non-positive stress test or other diagnostic test for CAD required if diabetic or if history of CVD. The stress test can be waived for participants who enter WLM currently engaging in vigorous physical activity
- Willing to follow a healthy dietary pattern
- Willing not to use weight loss medications for the duration of the trial
- Able and willing to give informed consent and participate in the interventions
- Access to telephone and the internet
- Demonstrated ability to access a specific web site
- Demonstrated ability to receive and respond to email
- Willing to come to phase I sessions
- Willing to lose 4kg in phase I
- Able to keep a complete 5-day food record during screening

Exclusion criteria for Phase I

Medical history

- Contraindication to weight loss (e.g., malignancy or other serious illness)
- Cardiovascular event within the past 12 months
- Current symptoms of angina (by Rose questionnaire), unless we have both physician permission and a non-positive stress test or other diagnostic test for CAD
- Evidence of active cancer diagnosis (except for non-melanoma skin cancer) or treatment in past 2 years, defined as any diagnosis or any treatment within the past 2 years
- Medication treated diabetes. If unmedicated diabetes, eligible if HgbA1C <8 *and* with both MD permission and a non-positive stress test or other diagnostic test for CAD. The stress test can be waived for participants who enter WLM currently engaging in vigorous physical activity.
- Self-reported history of renal disease (other than kidney stones)
- Psychiatric hospitalization within the last 2 years
- Consumption of more than 21 alcoholic drinks per week or binge drinking
- Weight loss of > 20 lbs in the last 3 months
- Any history of gastric bypass surgery or fundoplication (commonly called “stapling”) for obesity, or scheduled surgery for this purpose
- Liposuction in the past 12 months

Medications

- Use of prescription weight loss medications in the 3 months prior to screening.
- Current use of medications for treatment of psychosis or manic-depressive illness
- Current use of medication for the treatment of diabetes

Other

- Planning to leave the area within three years
- Pregnant, breast feeding, or planning pregnancy prior to the end of participation
- Current participation in another clinical trial
- Weight Loss Maintenance Trial staff member
- Household member of a Weight Loss Maintenance Trial staff person

Table 2. Phase II Eligibility Criteria

Inclusion criteria for Phase II

- Weight loss of at least 4 kg during Phase I
- Willing not to use weight loss medications for the duration of the trial
- Willing to be randomized to maintenance phase
- Able and willing to give informed consent and participate in the interventions

Exclusion criteria for Phase II

Medical History
- Contraindication to weight loss (e.g., malignancy or other serious illness)
- Cardiovascular event since entry
- Current symptoms of angina (by Rose questionnaire), unless we have both physician permission and a non-positive stress test or other diagnostic test for CAD.
- Evidence of active cancer diagnosis (except for non-melanoma skin cancer) or treatment in past 2 years, defined as any diagnosis or any treatment within the past 2 years
- Self-reported history of renal disease (other than kidney stones) since entry
- Psychiatric hospitalization since entry
- Gastric bypass surgery or fundoplication (commonly called "stapling") for obesity since entry, or scheduled surgery for this purpose
- Liposuction since entry, or scheduled liposuction

Medications
- Use of prescription weight loss medications
- Current use of medications for treatment of psychosis or manic-depressive illness
- Current use of medication for the treatment of diabetes

Other
- Planning to leave the area within 30 months
- Pregnant, breast feeding, or planning pregnancy prior to the end of participation
- Weight Loss Maintenance Trial staff member
- Household member of a Weight Loss Maintenance Trial staff person

6. Recruitment and Screening

Each clinical center uses multiple recruitment strategies. Mass mailings of brochures, coupons, and flyers are the primary source of participants, as they were in the PREMIER and DASH studies.[110] Sources of mailing lists include commercial vendors and local governments (for lists of registered voters and drivers). In addition to mass mailings, clinical centers use other strategies, including printed advertisements in local newspapers, radio advertisements, e-mail broadcasts, screening events, and word-of-mouth. In this trial, physician referrals may also be effective.

Prior to the recruitment drive, recruitment coordinators from the four clinical centers work together to refine strategies and prepare prototype materials. During the recruitment period, they routinely share their experience and plans on recruitment subcommittee conference calls. As in each of our prior recruitment drives, the Steering Committee monitors yield closely, particularly the fraction of Phase I participants who are randomized into the trial. While a 50% yield is based on our experience in the PREMIER trial, a higher or lower yield is possible and will lead to adjustments in the number of participants who enter Phase I. The proportion of minorities and women who are randomized is also monitored, and recruitment strategies are adjusted according to initial results.

Recruitment of minorities and women. Given the high prevalence of overweight in African Americans and the concomitant burden of CVD in that population, a major trial population goal is to randomize a population sample consisting of 40% African Americans. In most behavioral intervention studies, African Americans lost less weight than non-African Americans. Therefore, to ensure that we meet our randomization goal, we will over-recruit African Americans during the initial 2 cohorts of the trial and track yields closely in order to guide subsequent recruitment efforts.

Screening. At the initial contact with potential participants, a telephone prescreen questionnaire is administered to determine preliminary eligibility and interest. Those who remain eligible after prescreening are invited to attend a series of screening visits prior to starting Phase I in order to determine eligibility and to collect entry measurements. The number and content of these visits are determined locally; however, all eligibility data must be collected prior to study entry. Measurements made during this screening period include weight, height, and physical activity (via accelerometry). A fasting blood specimen is also obtained, and participants complete a series of questionnaires and interviews to help assess eligibility, including their commitment and ability to participate, as well as to gather entry data. Computer entry of all required data elements must be completed prior to start of Phase I.

After screening is completed, eligible participants are entered into the study to begin Phase I, the 5-month intensive weight-loss program. This program is described in the next section.

7. Weight Loss Program (Phase I)

Intensive weight-loss program (Phase I)
Individuals participate in a behavioral weight-loss program for 5 months prior to randomization. This weight-loss program is based on the intervention developed and used in the PREMIER trial. This program is delivered through weekly group sessions, and is designed to achieve a minimum weight loss of 4.5-6.8 kg. This amount of weight loss is associated with significant improvements in CVD risk factors.[1,21,111]

Lifestyle recommendations and targets. The Phase I intervention is designed to achieve weight loss through calorie reduction (dietary change) and increased energy expenditure with physical activity. The specific intervention targets include reducing weight by 4.5-6.8 kg (or more if desired), engaging in 180 minutes per week or equivalent of moderate physical activity, and following a healthy dietary pattern (the DASH diet) aimed at reduction of CVD risk factors.[112] This weight loss program is based on the current clinical practice guidelines established for obesity treatment and for individuals at increased risk for CVD: those with high BP and elevated serum cholesterol.[1]

Behavioral principles and theoretical foundation. The weight-loss program is based on key theoretical constructs developed over the past decades to guide health behavior change efforts and on practical applications from our previous trials of successful weight loss and CVD risk reduction.[7,21,22,32,33,113,114] This approach is derived from social cognitive theory[115] and techniques of behavioral self-management[116] and was constructed using the transtheoretical, or stages-of-change model,[99,117] and motivational enhancement approaches.[61,118] These approaches emphasize the importance of the individual's ability to regulate behavior by setting goals, developing specific behavior change plans, monitoring progress towards the goals, and attaining skills necessary to reach the goals. Self-efficacy (one's confidence in performing a given behavior) and outcome expectancies (one's expectations concerning the outcome of that behavior) are critical mediators of behavior change.[115,119] The transtheoretical model recognizes that behavior change is a dynamic process of moving through different motivational stages of readiness for change. During the program different behavioral strategies are emphasized, depending on the individual's stage of change.

Implementation of weight-loss program. Specific implementation strategies for this weight-loss program focus on frequent contacts, participant centered group and individual facilitation approaches, individual contacts that tailor the intervention to the individual's preferences and readiness to change, group interactions and social support, goal-setting and self-negotiation, acquisition of new information and skills, and problem solving. Examples of new behavioral options and decision-making approaches are presented, with careful attention to cultural appropriateness for minority populations.

Specific strategies targeting weight loss include: 1) self-monitoring of diet and physical activity, 2) development of personalized dietary and physical activity plans, 3) moderate caloric reduction, 4) reducing portion sizes, substituting alternative foods, and modifying the original items to be lower in calories and fat and focusing on fruits and vegetables and increased fiber intake, 5) increased physical activity (PA), 6) identifying problematic situations for undesired behavior and developing and rehearsing specific plans of action to deal with those situations, 7) graphing individual weight and behavioral progress, and 8) developing core food-choice competencies.

This program places a major emphasis on increasing moderate-intensity (3-6 METS) PA. The program helps participants determine how best to fit physical activity into their lives and takes into account each participant's initial motivation and current activity patterns.

Self-monitoring is a key component of the weight-loss program. Participants are encouraged to routinely monitor food intake, calories, and physical activity. The essential components of successful self-management include setting reasonable short-term goals, formulating specific plans of action to achieve those goals, developing reinforcement and social support for carrying out each major element of the plan, keeping a record to assess progress, and regularly evaluating and modifying plans using the self-management records.[116]

Group Sessions
The sessions are designed to be participant centered with active input and discussion rather than didactic lectures. Small group activities foster problem solving, support, and program ownership. Intervention staff are trained in motivational enhancement techniques and group facilitation concordant with this approach. Groups are 1.5 - 2 hours in length with 18-25 participants per group. Opportunities for guided physical activity or food demonstrations are included in many of the group sessions.

Individual Sessions
If needed, supplemental individual contacts by phone or in person may be scheduled to assist participants with weight loss and behavior change. Individual contacts focus on enhancing motivation, identifying specific behavior change goals, and problem solving.

Standardizing the weight-loss program. The intervention staff are provided with standardized program materials and guides including: program content and activities for each session as well as presentation aids and supplementary participant materials; and data collection forms for collecting attendance and process data. An Interventionist Workgroup comprised of interventionists from each center convenes monthly by teleconference call to review Phase I activities, clarify procedures, and to make any refinements needed to the process and organization of the intervention. Quality control site visits are conducted by the Coordinating Center.

Interventionist training for the weight-loss program. Both centralized and local training is conducted throughout the study. Prior to beginning the Phase I weight-loss program, all interventionists participate in a central training session that covers intervention procedures during Phase I. Training focuses on motivational enhancement and interviewing methods and group facilitation approaches. Training also covers methods for enhancing physical activity and physical activity demonstrations. The training program is organized to provide opportunities for staff to practice different techniques, role-play, and have peer discussion and evaluations.

Cultural training. The Minority Implementation Committee organizes and conducts a minority training program for all trial interventionists. This training program focuses on the cultural differences of African Americans and European Americans and the ways in which the maintenance interventions (both the initial weight-loss program and the subsequent maintenance interventions) can be best adapted to the needs and expectations of both groups.

8. Randomization

Following completion of Phase I (initial weight-loss program), those participants who have lost at least 4 kg are eligible to be randomized for Phase II. Prior to randomization, study staff reconfirm eligibility (table 2), review the study requirements with the participant, answer questions, administer the randomization consent, and collect baseline data (section 10, table 4).

Randomization assignments are generated on-site using software developed by the Coordinating Center. These assignments are stratified by clinic, race (African-American vs. non African-American), and weight loss during phase I. Allocation assignments are also blocked within these categories to provide a balance in treatment assignments over time. As part of the randomization process, the computer program verifies eligibility and the completeness of entry and baseline data. Individuals lacking proper documentation of eligibility or key data elements are not randomized.

Participants learn their treatment assignment from a staff member who is not involved in follow-up data collection.

Blinding

WLM study participants know their intervention assignments, as do clinical center staff that are involved in delivering the interventions. However, all clinical center staff involved in follow-up data collection are kept blinded to participants' treatment assignments, and all intervention staff are kept blinded to participants' official study measurements. Participants receive a complete set of weight measurements, along with a summary of their other clinical measurements and their laboratory measurements, at the conclusion of their follow-up period.

9. Maintenance interventions (Phase II)

Introduction and Rationale. Several key issues emphasized in the NIH-NHLBI Clinical Guidelines on the Identification and Treatment of Overweight and Obesity[1] serve as the impetus for this study. These guidelines recognize obesity as a major chronic disease and as such acknowledge that long-term contact following weight loss is critical. The report notes that frequent contacts between participant and provider should be utilized whenever possible to improve maintenance of weight loss. Furthermore, obesity treatment should be a priority for high-risk participants (e.g., those with CVD risk factors or disease). The interventions tested here are based on emerging methods for chronic disease management and widespread trends in health care delivery and intervention technology.[120-124] The use of interactive technologies for communication and delivery of health care and use of telephone contacts and counseling to improve participant outcomes are viewed as potentially successful strategies in the long-term management of obesity and its associated chronic diseases.[125] The comparison condition is a self-directed/usual care program in which participants receive advice for strategies to maintain their weight loss.[69,76]

The two active WLM interventions incorporate key theoretical constructs of maintenance (motivation, support, problem solving, and relapse prevention). Although the theoretical foundations of the active WLM interventions overlap with those of the initial weight-loss program (Phase I, pre-randomization), which focuses on weight loss and acquisition of new information and behaviors, the two active maintenance interventions focus on the maintenance of weight loss through problem solving and motivational enhancement. The WLM active interventions are based on previous studies that have identified factors associated with sustained weight loss (frequent contacts, self-monitoring, regular physical activity, and accountability), and emerging participant counseling methods (motivational interviewing) designed to enhance participant involvement and adherence.[42]

The physical activity and dietary recommendations for participants will be the same for both of the active maintenance interventions. As much as possible, the other content of these interventions will also be the same. That is, counseling strategies for making and maintaining behavior change, including self-monitoring and feedback, maintaining social support for desired behaviors, and sustaining motivation for maintaining long term behavior change will be the same for both active interventions.[61,118,126]

The WLM delivery approaches (PC and IT) were chosen as two alternative practical applications that many health care settings could adopt. These interventions explore new opportunities for improving weight loss maintenance by focusing on communication technologies: either personal contact (PC) primarily using personal telephone calls, or interactive technology (IT) using the Internet and automated phone-based technology. Both interventions are tailored specifically to the participant's needs. The PC intervention provides regular, scheduled personal contact, while the IT intervention allows participants unlimited access. Both delivery approaches feature frequent contacts—the factor most strongly associated with maintenance.[42] Both reduce participant burden of time and travel associated with regular or routine in-person visits, factors that are strongly associated with reduced participation and disengagement in long-term intervention programs. Both interventions are based on the same theoretical constructs and use the same core components to address specific maintenance issues. However, because each uses different communication technologies, they adapt the content and behavioral tools to the specific mode of delivery. Table 3 provides an overview of the three intervention arms, contact frequency and type, and information on intervention goals and core components.

Table 3. Description of 30-Month Phase II WLM Randomized Intervention Arms

Intervention Arm	Self Directed Usual Care	Personal Contact PC	Interactive Technology IT**
Description and Approach	Advice and Information	Behavioral counseling using Motivational Interviewing, delivered through personal phone calls and in-person visits	Web-based, individually tailored behavioral intervention supplemented with automated phone call reminders.
Frequency and Type of Contacts			
Overall Frequency of Study-initiated Contacts	Annually	Monthly	Continuously available, encourage at least weekly contacts
Types of Contacts			
Internet-Web site	0	0	Self-management and self-assessment modules and record-keeping tools.
E-mail	0	0	Welcome messages and reminders to return to website, if needed
IVR Phone Calls	0	0	Reminders to return to website, if needed
Personal Phone Calls	0	9/year*	Prompts to return to website, if needed
In-person Visits	~1/year	3/year	1 orientation at randomization; annual booster sessions
Contact flexibility	N/A	Scheduled personal	Unlimited electronic
Goals			
Physical Activity	225 min/wk moderate intensity activity		
Total Calorie Intake	Reduced, individually tailored to maintain prior weight loss		
Diet	DASH Dietary Pattern		
Core Components			
Self-Monitoring	None	F&F diaries, report during monthly contacts	F&F diaries with Web entry of weight, minutes of exercise, total daily calories and number of F&F diaries kept, at least weekly
Feedback	None	Quarterly reports, Motivational Interviewing and support at monthly contacts	Printable progress reports and graphs of self-reported data, tailored welcome messages, reminder prompts (e-mail and phone) based on website usage.
Problem solving	None	Tailored responses to problems identified at monthly contacts	Customizable action plans from interactive problem-solving, self-management modules.
Relapse prevention	None	Skills provided at monthly contacts	Customizable action plans from interactive relapse prevention, self-management modules.
Social Support	None	Phone	Bulletin board
Information on Diet and Physical Activity	Provided at annual visit	Available at each contact	Available on the Web site

IVR = Interactive Voice Response Telephone
F&F = Food and Fitness Diary for monitoring diet, physical activity, and weight
* 15-minute calls
** See Figure 2, which illustrates implementation of IT components

Cultural appropriateness of the interventions for African Americans. The Minority Implementation Committee works closely with all of the Intervention Committee working groups in developing procedures and materials appropriate for African-American participants. This cultural adaptation starts with what we have learned from focus groups, participant feedback, and direct intervention experience in our previous studies, most notably the DASH studies and the PREMIER trial.

Cultural adjustments include diversity training for all intervention staff, inclusion of African-American interventionists, using culturally appropriate food, making sure that "soul food" is included in the food guides, providing reduced fat and sodium recipes for popular African-

American dishes, conducting group exercise during group sessions (popular with most participants, particularly with African-American participants) and special intervention sessions where families are encouraged to attend and participate (our experience has been that African-American participants typically prefer much more family involvement than do white participants.)

Formative work on the PC and IT interventions begins in the first half of year 01 and includes beta testing of early versions of these interventions. Feedback from these beta tests is used to improve and refine these interventions.

Intervention goals. All participants in each of the three treatment arms are provided with the same intervention goals for physical activity, dietary pattern, and calorie levels.

Caloric levels. All participants are provided with individualized goals for energy intake. These goals are based on participants' current needs for weight maintenance or, if they choose, for further weight loss. Calorie ranges will be determined using standard formulas and tailored to participants' activity level.[127]

Physical activity. The physical activity recommendation for all WLM interventions is to increase moderate intensity physical activity to an average of at least 45 minutes per day at least five times each week (i.e., $\geq$ 225 minutes per week), an average increase of 45 minutes/week over the Phase I goal of 180 min/week. Maintenance of weight loss is associated with higher levels of physical activity than levels required for maintaining or improving health. While the current physical activity recommendations to maintain health are 30 minutes of at least moderate intensity activity on most days of the week,[48] data from the Weight Loss Registry of individuals who have successfully sustained weight loss suggest that a substantially greater level of physical activity is needed to maintain weight loss.[44] Physical activity can be performed either at one time or in multiple bouts as short as 10 minutes. Long bouts (40 minutes/day) and short bouts (10 minutes/day) have similar effects on weight loss.[50] Problem-solving approaches are employed in both interventions to determine how participants can fit this amount of physical activity into their daily lives and overcome barriers they may face. Because the primary recommendations are to engage in at least moderate intensity activity 5 days per week, 45 minutes each day, problem-solving strategies discussed in the PC and prompts from the IT arm will focus on this behavior. General messages about increasing daily activity (e.g., taking the stairs instead of the elevator) to increase caloric output are also included, although these activities are not emphasized as the primary physical activity strategies because there are no data to suggest that this type of activity alone will maintain weight loss.

Dietary pattern. We have chosen to include the DASH dietary pattern as a part of our weight-loss program and all active WLM interventions because, although this pattern by itself has not been proven to result in weight loss, it is fully compatible with a weight loss dietary pattern. The ultimate goal of weight loss is control of CVD risk factors and prevention of cardiovascular disease. Therefore, dietary guidelines for a weight maintenance program, anticipated to apply for a lifetime, must be consistent with recommendations for CVD prevention. The DASH dietary pattern is rich in fruits, vegetables, low-fat dairy and whole grains, is reduced in total and saturated fat and cholesterol, and is consistent with recommendations for the prevention of heart disease. Its high fiber and low fat content make it appropriate for weight loss, and it was successfully used in PREMIER as a part of a comprehensive weight-loss program.[128] DASH has been shown to lower blood pressure,[112,129] total and LDL cholesterol,[130] and homocysteine levels,[131] and the DASH dietary pattern is also consistent with recommendations to prevent osteoporosis and certain cancers.[132,133]

WLM interventions. The following sections provide detailed information on the three 30-month interventions that follow randomization (Self-Directed/Usual Care, Personal Contact, and Interactive Technology).

***Self-Directed/Usual Care (SD/UC) condition*.** Following randomization, participants assigned to this arm receive support and encouragement with a minimal contact schedule. At randomization, participants meet with a study interventionist to discuss the randomization assignment and motivation for returning for future measurement visits. Participants receive printed lifestyle guidelines with diet and physical activity recommendations. Participants then meet with a study interventionist after the 12-month visit, and again after the 30-month assessment visit (after all data collected has been completed), for a brief meeting to discuss their role and continued participation in the study. While this contact pattern exceeds what is typically covered as part of routine medical care for overweight or obesity, we chose this approach for the control condition because it is likely to be the minimum acceptable contact pattern for those who complete the Phase I program.

Personal Contact (PC) intervention

Overview of PC. The PC intervention offers person-to-person guidance and support to assist participants in avoiding or overcoming obstacles that would attenuate maintenance of weight loss. This approach acknowledges that weight maintenance is a difficult task and is built on the premise that success is more likely with the assistance of a health counselor, e.g., nurse, dietitian, or physical activity coach, (i.e., a "case management approach"). It uses brief individual monthly contacts, primarily via telephone, and several face-to-face sessions to deliver an intervention composed of core elements.

Core elements. The core elements of the Personal Contact (PC) intervention include methods and strategies to assist participants in adhering to health behaviors for maintaining weight loss. These methods and strategies include frequent contacts, a mechanism for self-monitoring, tailored reinforcement messages, social support, problem solving, and relapse prevention. Motivational Interviewing approaches are used by the interventions to conduct these contacts.

Contact schedule. Participants in the PC Intervention have monthly contacts with an interventionist for 30 months. The face-to-face (FTF) intervention contacts occur approximately every four months, with telephone contacts during the intervening 3-month periods. One of the three annual face-to-face contacts should be a group session with other PC participants. If needed, there may be two additional contacts (face-to-face or by phone) at the interventionist's discretion. This frequency of contact is based on information from previous trials on what may be an appropriate contact frequency to enhance maintenance,[42] from experience in disease management programs,[120] and suggested frequency of face-to-face contacts from the Medicare Medical Nutrition Therapy Amendment Act of 2001.[134]

Motivational Interviewing (MI) strategies are based on the work of Miller and Rollnick[61,118] and emphasize a client-centered counseling approach to help participants explore and resolve ambivalence and to enhance commitment and confidence for behavior change[135]. Major techniques used in MI include: using reflective listening to build empathy for the participant, showing no discrepancy between the participant's goals and his or her current problem behavior, and providing objective feedback. Sessions using MI are designed to avoid argumentation by assuming that clients are responsible for their decisions. The technique emphasizes supporting self-efficacy and optimism for change. The MI framework also recognizes that readiness to change is not fixed, but fluctuates as a product of interpersonal interaction, and that the intervention relationship functions best as a partnership rather than an expert/recipient relationship. Motivation to change is elicited from the client, not imposed by the interventionist.

In this method, the participant articulates and resolves his or her ambivalence. The counselor is directive in helping the client examine and resolve ambivalence. The interventionist uses a variety of tools and techniques to facilitate this process.

Self-monitoring. Participants are encouraged to weigh themselves on a weekly basis, keep track of daily minutes of physical activity, and self-monitor dietary intake. Several types of monitoring forms (including the Food and Fitness Diaries used in Phase I) are available for the participant to choose from, or they may devise their own method. Participants choose both the method they wish to use for monitoring food intake, and the format they wish to use for recording this information. For example, for dietary intake some participants choose to only monitor food intake, while some participants chose to record food intake and score calories. Participants discuss the self-monitoring approach chosen during their PC contacts and include this information in their action plans.

Problem solving has been used successfully to promote weight maintenance.[57] This technique incorporates active methods by the interventionist in assisting the participant through a 5-stage problem-solving process for specific barriers encountered.[136] These stages include: problem orientation, problem definition, and generation of alternative solutions, making a decision, and implementing and evaluating the solution. FTF sessions focus on problem-solving techniques that are practiced in telephone contact sessions. Using MI techniques, the participant identifies topics and issues to be addressed during the contact, and the interventionist guides him or her through the problem-solving steps.

The relapse prevention model[137] has also been shown to be effective in the promotion of long-term weight maintenance by teaching participants a set of behavioral skills to plan for and respond to "high risk" situations that might challenge the behaviors that promote maintenance of weight loss.[138] Although we do not attempt to conduct formal relapse prevention therapy, we select relapse prevention topics for review and discussion during the FTF sessions. The relapse prevention model identifies several components such as instruction in the process and emotional aspects of lapses, the identification of personal high-risk situations for slips and lapses, step-by-step methods (including problem-solving) for coping with high-risk situations, and cognitive restructuring strategies to prevent a "slip" from becoming a full-blown relapse.

Telephone contacts. MI techniques are used to deliver these contacts. Interventionists use a telephone contact form to guide, structure, and document each contact. Following a brief interval of conversation to establish rapport, the interventionist conducts a general review of the participants' diet and activity efforts for the previous month. Participants' reported data on frequency of self-monitoring and amount of physical activity are recorded**.** There is particular attention to having participants identify barriers or difficulties encountered during the past month. These may include barriers to maintaining exercise, dietary recommendations, or self-monitoring. The participant selects a specific barrier or difficulty for discussion. The interventionist helps the participant focus on problem-solving techniques, guiding the participant through the five-stage process to address the specified barrier.

During a phone contact, participants may request additional information (such as recipes or nutrition information), and the interventionist may mail or e-mail them materials as needed or direct them to additional resources. Common types of materials/resources are identified for the trial, and copies of materials are provided to the centers.

Face-to-face (FTF) contacts. FTF contacts last about 45 minutes and consist of three components: *Check-in, Training, and Action Planning*. *Check-in* includes a weigh-in, a review of self-monitoring and participant goals, and a brief review and feedback on the previous month's

performance (10-15 minutes). The *Discussion and Training* portion of the FTF session consists of brief topical discussions, and covers methods for anticipating, avoiding, and coping with high-risk situations and possible lapses in the participant's diet and activity plans (20-30 minutes) and problem solving tailored to the participant's choice, and need. The specific topics discussed are to be based on the problem solving and the relapse prevention models discussed above. A series of topics focusing on practical maintenance elements is identified to guide and prompt discussion. The interventionists use discussion guides and case scenarios for each topic to facilitate these contacts. The final component of each FTF session, *Action Planning*, highlights weight maintenance strategies for the subsequent month (5-10 minutes). The interventionist continues using the motivational interviewing techniques and strategies (e.g., assessing motivation and confidence, negotiating action plans) to assist participants in identifying diet and activity goals for the subsequent month.

PC intervention implementation and process flow. Standardized materials and procedures guide the PC contacts. Interventionists use a contact guide to record data, to guide the contact and the topical discussions, and for documentation of the discussion for use with subsequent calls. A series of case scenarios for the problem solving topics and for specific situations and barriers that participants commonly experience is used for guidance. These scenarios serve as examples for the interventionist to use when identifying approaches to use in the participant discussions. They also provide triggers for the type of questions and supportive comments they may use.

A variety of techniques are used to ensure completion of the telephone contacts. The first call is prescheduled as a phone appointment. Phone contact appointment reminders are mailed or provided by phone or e-mail. Each subsequent call is scheduled at the time of the current call.

Some PC participants use e-mail to communicate with their interventionist. However, these contacts are not initiated by the interventionist (except to schedule an appointment) and are not considered substitutions for FTF contacts or personal phone calls. Thus Internet technology is used for communication but not for delivery of the PC intervention.

Training for the PC intervention. Training of all intervention staff is conducted centrally once a year. This training focuses extensively on the motivational interviewing techniques and on methods for implementing problem solving and relapse prevention approaches.

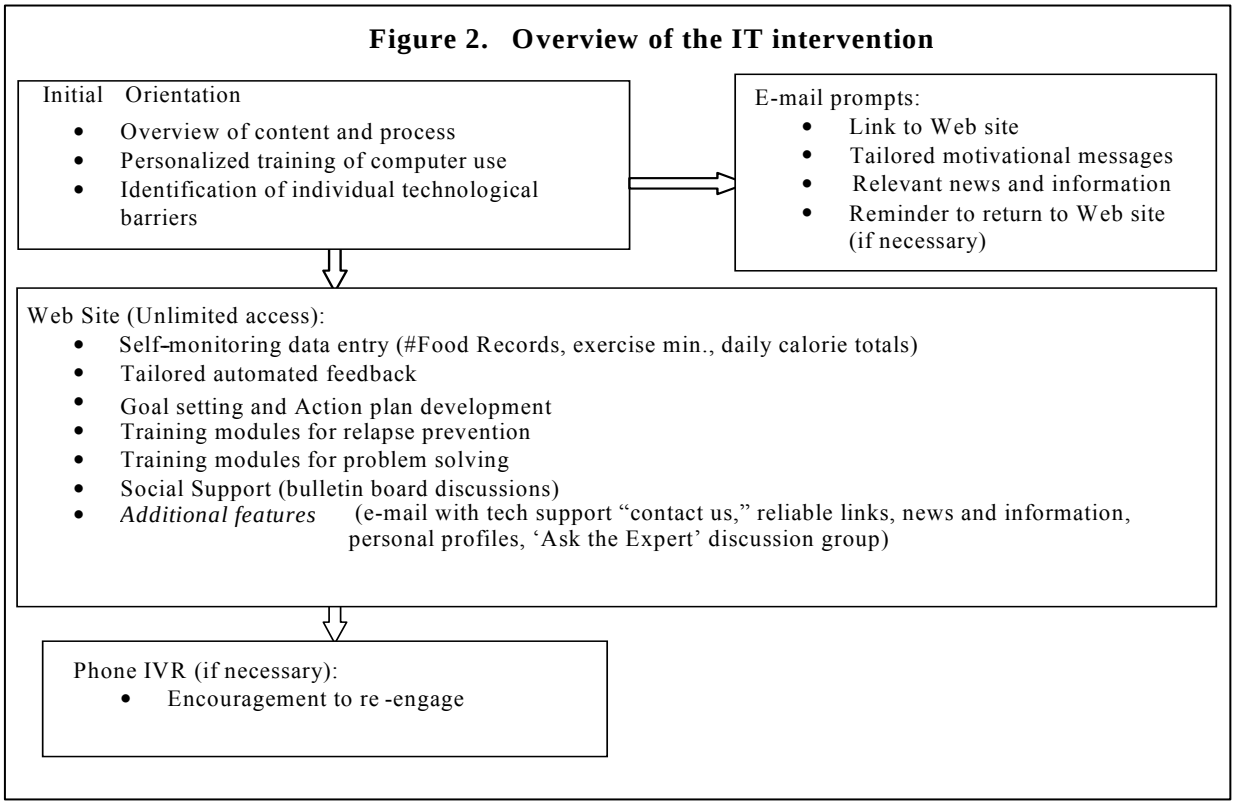
Interactive Technology (IT) intervention

Recent advances in technology make it feasible to develop automated and personalized support systems to aid in the management of chronic diseases. Such systems have the potential to reach large populations at a much lower per-participant cost than comparable personal-contact systems. Our IT intervention takes advantage of the new developments and capabilities of interactive communications technology to maintain weight loss. The synergistic use of the Internet and Interactive Voice Response (IVR) automated phone technology allows us to provide frequent and timely reminder messages and prompts for participants to return to the project website.

IT intervention overview.

Like the PC intervention, the IT intervention is based on core behavior-change components (goal setting, self-monitoring, training in relapse prevention and problem solving, feedback, and social support), but utilizes Internet and automated phone technology to enhance the frequency and timeliness of feedback. In addition, several website features keep participants engaged and provide an enriching experience. Such features include encouraging weekly tips, establishment of a personal profile, links to reliable health and weight-loss related information, and printable program materials and resources.

Figure 2. Overview of the IT intervention



After an initial face-to-face orientation, participants are encouraged to input data on weight, keeping food records, physical activity, and goals and plans on a regular basis. They initially use the Web to construct a personal action plan. We use collaborative goal setting and problem-solving techniques to identify contingent action plans for perceived barriers and triggers. This action plan can be updated anytime. We use e-mail reminders, with the IVR phone system as back up, to prompt participants to visit the Web for self-monitoring and motivational modules. In addition, at any time, participants have the option of logging on to the Web site to enter data, communicate with other participants via a bulletin board, or to seek other information. Figure 2 displays an overview of the content and process of the IT intervention.

Core elements of the IT intervention. The core elements of the Interactive Technology intervention include strategies to assist participants in adhering to health behaviors for maintaining weight loss. These strategies include frequent contacts, encouragement for self-monitoring, social support, and training in problem solving and relapse prevention.

Interactive goal setting and updating of personal action plan. This component of the WLM Web allows participants to set and record personal goals for diet and physical activity behaviors. The participants use this feature in the beginning of the maintenance intervention to establish goals and to define a personal action plan for diet and physical activity based on these goals. The personal action plans are viewable as a single Web page and are printable.

Self-monitoring**.** The self-monitoring module consists of a calendar-type data form for current weight, physical activity, and food records. The participants are encouraged to enter these data at least once per week. However, over time the need for self-monitoring may wax and wane in each individual; participants are encouraged to increase self-monitoring at times of threatened "relapse" or after slips.

Tailored messages. To reinforce weight loss maintenance and the use of the WLM Web site, we use automated e-mails as frequent reminders for self-monitoring input. Each e-mail includes a direct link to the WLM Weight Loss Web site to make data input as easy as possible.

Training in relapse prevention and problem-solving. This interactive motivational module takes advantage of materials developed for the telephone contacts in the PC intervention, and adapts them for interactive use on the Internet. Participants step through an interactive process of assessing the situation, identifying the problem, determining a strategy and creating a plan.

Social support. We offer threaded message boards with other study participants for the social support component of the technology intervention. A study interventionist reviews the message board ensuring the appropriateness of the posted messages. However, the discussion and problem solving is generated by the study participants themselves. This service is provided from the Coordinating Center. Participants from all regions of the study use the same message board.

Additional Optional Web features for sustaining participant interest.

Ask an expert / FAQs. The Web site includes a section for posting nutrition and physical activity questions to an expert. Replies are posted to the website, and include opportunities for further discussion and comment by participants. Again, this service is provided by the Coordinating Center.

Information modules. This reference section of the Web site consists of links to articles on nutrition and physical activity topics. We also provide links to other recommended related Web pages.

Orientation and training. As outlined in Figure 2, the IT intervention is initiated with an orientation session, conducted by a local interventionist trained by the Coordinating Center. At this time, participants receive information about the process and goals of the research study. In addition, they are trained to use the features of the WLM Web site, set up goals and action plans and practice using the data entry screens for weight, food records, and exercise minutes.

Participants are also encouraged to use the Web to monitor their personal action plan on a weekly basis. Additionally, the session is orientated to increase the participant's confidence using the Website and troubleshooting technical issues.

Methods to enhance use of the WLM Web site. One of the challenges of incorporating technological enhancements and Internet components into health behavior change programs such as WLM is to keep participants using the Web site. Several approaches to the Web site design and program delivery are made to facilitate continued Web site use. For Web site design this means enhancing many aspects of the user interface and improving "usability" and interactivity. Our goals are to make the content relevant, provide feedback, and to keep the site interactive and "fresh." As Internet technology advances and the experience of the designers and users increases, principles regarding effective design have evolved.[139] Principles for usability are incorporated into all design activities for the site, pages, and content, and for navigation and search approaches.

The IT intervention takes advantage of unique features of the Internet to enhance contacts, motivation, and maintenance of behavior change. Relevancy and personalization are key features we will use to enhance Web site use.[78,139] They are also the underpinnings of our approach to support maintenance of behavior changes.[79,94,140,141] Cultural relevancy is also important for enhancing Web site use and promoting maintenance of behavior change. The Minority Implementation Committee is involved in our IT design activities, and our formative evaluation activities include cultural issues for minority groups. The Web site features for self-monitoring

and tracking allow participants to maintain awareness of diet and activity and to chart their progress. Automated feedback in the form of weight and exercise graphs, personalized messages, and tailored progress summary reports provide tailored to participants' goals and progress. The content and features of the Web site focus on the needs and interests of the WLM population. A variety of approaches are used to obtain feedback and input from participants during the development stages. New material (assessments and content pieces on physical activity, diet, special occasions, motivation) is added monthly to keep the site "fresh," interesting, and timely.

Description of the user model and tailoring algorithms. The participant database contains the initial assessment information and all subsequent monitoring data. These data contain estimates of the following features, maintained on an on-going basis in the participant database:

- Weight (average current weight – target; trend summary)
- Activity (target – weekly minutes)
- Time since last contact (current time since contact – target time)

IT intervention security and confidentiality. We take a multi-faceted approach to ensure data security from the point of entry via the Web to the master database. The CHR maintains protocols, procedures, and review on security for all Web applications. Security steps include custom programming to secure individual access to forms and other documents, and data packet encryption to ensure that confidential data cannot be revealed even if packets were intercepted in transmission. Our authentication process consists of assigned user login IDs and initial passwords that we distribute at the orientation meeting. Users then have the option of changing their password upon first entry to the system. Users enter their password for each new login to the system. Additional security for data entry transactions is applied by using the role-based security model in Microsoft Transaction Server. The SHHS server sits behind the CHR's standard configuration of firewall/proxy server with access via encrypted Virtual Private Network (VPN) connections

The interactive WLM Web site is not a public site, and any individual's data is available to only that individual and the study interventionist who provides the phone support. For message board use, the users choose a display name for their postings. Security issues are monitored and evaluated as part of the regular administration of the project.

Ongoing evaluation and updates of Web-based program. Throughout the intervention, we monitor and evaluate the performance of the Web and IVR phone systems. We monitor pages visited and time spent per page. Through this feedback and the contact us function, we are able to update the design for improved usability. We continue to update the educational and informational aspects of the Web site throughout the intervention, as would be done in any commercial release of a Web service. We record the professional time and costs associated with these activities throughout the intervention, so that we are able to model the costs of scaling the intervention to a larger population.

Annual follow-up. IT participants will be invited to attend an in-person session approximately 12 months after randomization and then annually. The purpose of this visit will be to familiarize the participants with new features on the Web site.

10. Outcome Measures and Data Collection

The *primary outcome* is change in weight from baseline to end of follow-up**.** For our intervention goals and for our primary outcome variable, we chose weight loss expressed in absolute terms (kilograms), rather than weight loss expressed as a percent of baseline, for several reasons. First, the general relationship between change in CVD risk factors and change in weight appears similar whether weight is expressed as an absolute value or as percent change. This is well documented for blood pressure.[25] Absolute weight loss, rather than percent change, has the advantage of being the measure used routinely in clinical settings. From an intervention perspective, it can be discouraging for heavier participants to lose the same amount of weight as other participants and yet be told that their weight loss is less. However, we recognize that percent of body weight change is a commonly used measure of merit, and we therefore plan to present the weight loss data both ways in our outcome papers.

Secondary outcomes include measures of behavior change (total energy intake and minutes of physical activity), process measures (attendance and self-monitoring), psychosocial variables, costs, and the control, prevalence, and medication treatment of CVD risk factors (hypertension, diabetes, and dyslipidemia).

Masking. All outcome measures are made by clinic staff that are masked to intervention assignment. Staff members who inadvertently become unmasked to a participant's assignment no longer obtain outcome measures on that participant. All intervention-related data forms are kept separately from outcome data and are not accessible to masked staff. Participants are reminded frequently to avoid talking with outcome data collectors about intervention assignment. Of necessity, local interventionists are aware of some participants' weight changes, since tracking such information is an integral part of the PC intervention and, to a lesser extent, SD/UC. However, interventionists are masked to the official weight measurements that are used in data analysis and to all other clinical measurements. All masking procedures are reviewed annually during Coordinating Center quality control site visits.

Data collection schedule. Eligibility and demographic data are collected at study entry during screening visits, prior to Phase I (the initial 5-month weight-loss program that all participants receive). The number of screening visits is not predetermined. Additional baseline data are collected at the end of Phase I for those individuals who qualify for randomization to Phase II (i.e., who have lost at least 4 kg) at additional clinic visits. The number of these clinic visits is also not predetermined. Comprehensive follow-up data are collected 12 and 30 months after randomization. Additional weight and safety measurements are obtained at 6, 18, and 24 months. The data collection schedule is summarized in Table 4. Measurement methods are described below.

Table 4. Data Collection Schedule							
	Entry Measures	Baseline Measures	Follow-up Measures				
	Phase I	End of Phase I/ Start of Phase II	Phase II (time since randomization)				
	Screening	Randomization	6 mo	12 mo	18 mo	24 mo	30 mo
Inf. consent	X	X[1]					
Demographics	X						
Internet ques	X						
Medical Hx ques	X						
Height	X						
Weight	X[2]	X[2]	X	X[2]	X	X	X[2]
Rose angina ques	X	X[1]	X	X	X	X	X
Medication ques	X	X[1]		X			X
FFQ*	X	X[1]		X			X
Accelerometry	X	X[1]		X			X
Blood pressure[3]		X[1]		X			X
Fasting blood[4,5]	X[4]	X[1]		X			X
Adverse event Q		X	X	X	X	X	X
Psychosocial Qs	X	X[1]		X			X
Perceptions ques	X[6]						
Beliefs ques	X[7]						

1 only collected for those eligible for Phase II. Weight and adverse event questionnaire are collected for everyone.
2 weight is collected on two separate days at entry, baseline, 12, and 30 months
3 blood pressure is collected on two separate occasions for each measurement point
4 includes serum for analysis of glucose and lipids. Aliquots of plasma, serum, and buffy coat are collected for long-term storage
5 only analyzed on individuals who are subsequently randomized to Phase II
6 once, preferably during screening, but may be collected later if unable to obtain
7 once during screening, but can be completed up to 4 months after the participant has enrolled in Phase 1
* FFQ = food frequency questionnaire

Measurement methods

Weight is the study's primary outcome variable. It is measured on two separate days at entry, baseline, 12, and 30 months, and once each at 6, 18, and 24 months. At each measurement visit, weight in light indoor clothes without shoes is recorded by a high-quality digital scale. Duplicate measurements are made to ensure accuracy. Weight is actually measured in pounds for ease of interpretation by the participants and subsequently converted to kilograms for data analysis. Scales are calibrated annually by the Bureau of Weights and Standards and quarterly by trained study personnel using standard weights. Study personnel are trained and certified to use their site's particular scale and to measure weight according to study protocol.

The first of the two entry weights taken during screening is used to compute BMI for eligibility into phase I. The second entry weight, which must be measured no more than two weeks prior to the initial phase I intervention session, serves as the starting point against which the phase I weight loss eligibility criterion is assessed.

The first of the two baseline weights must be measured on or after G19 or the start of week 22, whichever is earlier. The second baseline weight is taken at least one week (7 days) following the first baseline weight, and no later than on the date of the randomization visit.

Both the first baseline weight and the second baseline weight must be at least 4 kg less than the second entry weight in order for the participant to be eligible for Phase II. The second of the two baseline weights defines the baseline weight for analysis of post randomization weight loss maintenance.

Height is measured once at entry using a calibrated, wall-mounted stadiometer. The participant stands shoeless on a firm, level surface, with his/her head in the horizontal (Frankfort) plane. Height is measured to the nearest 0.1 cm.

Body mass index is calculated as the Quetelet index (kg/m^2). Eligibility BMI for Phase I is based on height and weight during screening. Participant weight at the end of Phase I is used as the baseline weight for Phase II.

The Block Food Frequency Questionnaire (FFQ)[142] is used to determine customary dietary intake. This self-administered questionnaire has been extensively validated. It requires about 15 minutes to complete. Data are summarized by daily intake of kilocalories, specific nutrients (e.g., total fat, saturated fat), and food group servings (e.g., fruits and vegetables, low-fat dairy).

Physical Activity is measured objectively by accelerometry. Objective measures are not subject to the biases associated with self-reported physical activity assessments, but they do have limitations because: (1) they only assess physical activity during the time the participant is wearing the monitor, and (2) they cannot accurately assess all types of physical activity, particularly those activities in which there is limited vertical displacement (e.g., bicycling and during swimming). Nonetheless, for the purposes of WLM, in which physical activity level will have substantial intervention focus, an objective measure is preferred. It is widely reported that the most common type of physical activity among adults is walking,[143] an activity that is emphasized in the interventions and is measured by an accelerometer.[144] The accelerometer is about the size of a pager and can be strapped around the waist to record vertical acceleration and deceleration. This type of device provides an activity count that is used as an indicator of physical activity. It can be used to assess a global index of physical activity (i.e., total counts per day, time spent above moderate to vigorous physical activity thresholds per day.) It can process activity data in 1-minute intervals and can be programmed to start and stop at pre-selected times. Energy expenditure determined by an accelerometer and from treadmill exercise correlates at $r=0.80$,[144] and also correlates with daily physical activity assessed over a 3-week period.[145] Participants wear the monitor for 4 consecutive days, including a weekend day.

Psychosocial measures are considered both potential modifiers of intervention effects and potential outcomes of the trial. These measures are obtained using existing self-administered psychosocial instruments at entry, at baseline, at 12 months, and at the end of intervention (30 months). All questionnaires are self-administered and require a total of 30 minutes to complete.

Quality of life: QOL is assessed with the Medical Outcomes Study Short Form Health Survey (SF-36),[146] a widely used, generic health profile including 9 subscales (physical function, role function-physical, role function-emotional, bodily pain, general health, social function and psychological well-being /mental health, vitality health transition, and side effects checklist). This standardized instrument is comprehensive in scope, has been used in a variety of settings including studies of weight loss, has an extensive normative database, has undergone extensive validation[147] and has good psychometric properties.

Social support: Both active interventions are designed to provide social support through interactions with WLM staff or through on-line chat rooms. The instruments for measuring social support in WLM include the "Social Support and Eating Habits Survey" and the "Social Support and Exercise Survey."[148] These instruments are reliable, have high internal consistency,[148,149] and are associated with other measures of physical activity and dietary behaviors.[148,150]

Perceived stress: The active interventions may decrease perceived stress (relative to the self-directed group) by virtue of increasing physical activity levels and personal attention. On the other hand, the active interventions may increase perceived stress by placing too many demands on the participants. In addition, the two active interventions may differ with regard to their effects on perceived stress. Comparisons across intervention groups and with the Self-Directed group will clarify this issue. The 4-item "Perceived Stress Scale" (PSS) (a subset of the14-item scale)[151,152] is administered in WLM.

Depression: Depression is measured with the Patient Health Questionnaire (PHQ-8). This validated, self-administered questionnaire is widely used in the mental health community to screen for depression.

Beliefs and Attitudes of Participants Questionnaire This questionnaire is a validated assessment instrument for acculturation of African Americans. This questionnaire has been added to the WLM data collection battery by African American investigators interested in the associations between African American cultural identity and participation in weight loss clinical trials. This questionnaire will be administered only to African-American participants.

Perceptions of Participation in Clinical Research This questionnaire covers attitudes toward participation in clinical trials. Data from this questionnaire will be used in an attempt to better understand the differences between those who stay involved in long-term studies and those who choose to leave before completion of the study.

Blood pressure is measured on two separate days for all participants at baseline, 12- and 30-months. These readings are used to assess blood pressure control, which is defined by JNC-6 criteria, based on risk stratification, regardless of medication status.[26] On each measurement visit blood pressure is assessed twice with participants resting quietly in the seated position, and the average of the two readings is recorded. An appropriately sized cuff is applied after measurement of arm circumference, and measurements are made by trained staff using an ambulatory blood pressure monitor (using it as an automatic in-clinic device rather than as an ambulatory monitoring device.)

Hypertension is considered present if an individual is currently taking anti-hypertensive medication or has a systolic BP $\geq$ 140 mm Hg or a diastolic BP $\geq$ 90 mm Hg.

Lipids and glucose. Lipids and glucose are anticipated to be measured from plasma collected by venipuncture after an overnight fast and then stored at -70°. Blood is drawn at each time point (entry, baseline, 12, and 30 months). "Control" of dyslipidemia is defined by NCEP guidelines based on risk stratification.[47] Dyslipidemia is considered present if an individual is currently taking lipid-lowering medication or has a fasting LDL-C $\geq$ 130 mg/dl.

Diabetes is considered present if an individual is currently using hypoglycemic agents, or has a fasting glucose $\geq$ 126 mg/dl. "Control" of diabetes will be based on ADA guidelines.[153]

Biological specimens. Aliquots of plasma and serum are stored at -70^{o}C for future investigation of putative risk factors related to CVD and other chronic disease, as outcomes, predictors of outcomes, and as effect modifiers. Candidate assays that might be performed include nutrient levels, homocysteine, inflammatory markers, oxidative damage markers, sex

hormones, and leptin. Buffy coat is also extracted from the whole blood specimens and stored for future investigation of genetic modulation of intervention effect. Resources for these analyses will require independent funding.

Retention

Each clinical site implements local procedures to monitor and enhance retention. These procedures are based on strategies that have been successfully employed in other studies, including local case management systems, regular case review, monitoring of visit completion, and monetary reimbursement for attending clinical measurement appointments. Several committees promote and track retention. The Clinic Coordinators Committee designs and implements strategies to promote retention, the Measurement Committee reviews monthly reports of data collection and completion, and the Steering Committee routinely monitors retention rates on its monthly conference calls.

Minority Implementation

Because of the importance of cultural sensitivity in a study of lifestyle modification, WLM has a Minority Implementation Committee (MIC) that includes representatives from each site and external consultants in minority health. The MIC has a presence on each intervention committee to provide feedback and suggestions to enhance minority participation and retention. This committee is actively involved in the development of the intervention protocol and provides feedback on active Web pages and materials. They also review clinic follow-up rates and recommend additional procedures as needed. In addition, the Minority Implementation Committee conducts annual diversity and cultural sensitivity training for all recruitment, data collection, and intervention staff.

Cost analysis

For health systems, the very high prevalence of overweight and obesity suggests that efficiently delivered behavioral approaches to maintaining weight loss are likely to be more cost-effective than pharmacologic and surgical approaches. Successful lifestyle approaches provide additional clinical and financial benefits from reduced morbidity and pharmacotherapy for related conditions such as hypertension and diabetes. However, these benefits are constrained by the degree to which a behavioral intervention can be delivered systematically to large populations. Thus, the logistical barriers and the actual costs of implementation must be determined as part of an assessment of the value of weight maintenance interventions. Ultimately, the implementation costs of PC and IT can be compared to each other and to other therapies that might be used for weight maintenance (e.g., surgery or medication).

We will perform a cost analysis to assess the direct costs of implementing the PC and IT interventions, which generally refer to changes in resource use attributable to an intervention. We include participant costs of time and/or money in our definition of direct costs; conceptually, these do not reflect the value to the participant of the intervention itself, but rather represent the value of the participant's resources expended to participate in the intervention.[154]

We view intervention costs as conceptually falling into three categories: 1) development costs; 2) implementation costs, which may include adaptation ("tailoring") to a specific target population, as well as ongoing costs of operations; and 3) costs of research-related activities. This categorization helps us inform decision makers who are interested in different issues—e.g., the costs of implementing an existing version of one of the interventions vs. the costs of developing (or adapting) a program tailored to a specific target population.

A micro-costing approach to assess intervention costs is used because it allows others to determine how well the analysis matches their own situation, where patterns of implementation may differ.154 We will be able to prospectively collect data on the exact number and type of each resource consumed by a participant. Unit cost multipliers is then applied to the quantity of each service consumed, and the results summed to obtain total cost. Such multipliers are obtained from internal sources where available, and from external sources when necessary. Our model of intervention costs will be designed to allow appropriate analysis of parameter uncertainty that reflects the variations among different implementation settings. Estimates of implementation costs outside of research settings will include consideration of economies of scale.

11. Safety

Overview
This chapter describes measures to ensure the safety of participants in the WLM Trial, a study population that is at risk for complications of hypertension, diabetes, and/or dyslipidemia. In general, participants are carefully screened to insure that participation in the study does not put them at undue risk. The study's eligibility criteria serve to exclude those in whom more aggressive therapy is indicated or in whom the dietary and physical activity components of the WLM interventions might pose some risk. For example, individuals with a CVD event in the past year, and those with medication-treated diabetes are excluded.
Additionally, surveillance for serious adverse events and other relevant clinical events occurs by questionnaire at regularly scheduled intervals. This chapter describes safety monitoring and management of serious adverse events.

Serious Adverse Events (SAE) Surveillance
Surveillance for SAEs and other relevant clinical events that may be associated with study participation occurs at Randomization (prior to Phase II) and at every data collection visit thereafter through the 30-month visit. This is done via several methods: 1) the Rose angina questionnaire is a well-validated tool for detecting possible angina, 2) a medication questionnaire documents changes in the use of eligibility medications (i.e., for hypertension and dyslipidemia) that may result from changes in weight and/or physical activity, and 3) the medical events screening form captures information about new CVD events and other serious or life threatening events. Any positive response on these questionnaires is reviewed by a local site clinician. Specific guidelines determine what constitutes an SAE and when and if the participant should be referred to his/her provider for additional evaluation and treatment.

Confirmed serious adverse events are reviewed at the Coordinating Center and classified as gastrointestinal, cardiovascular, musculoskeletal, or "other" in nature. This information is then reported to the DSMB and NHLBI by site and treatment arm. Similar information reported by participants at other times (e.g., during Phase I group meetings) is noted and followed up as needed to assure participant safety.

Expected Events
Over the three-year duration of the study a number of medical events may be expected to occur, including cancer, routine surgeries, routine procedures, the development of chronic conditions, increased symptoms from a chronic condition, musculoskeletal problems, and motor vehicle accidents. Expected events that occur as a result of a protocol violation are treated in the same way as unexpected events and will therefore require expedited reporting to the NHLBI.

Serious Adverse Events are defined as the occurrence of any acute life-threatening event, a hospitalization for any cause other than routine delivery, prolonged or permanent disability, pregnancy resulting in a congenital abnormality or birth defect, a major cardiovascular event, or cancer other than non-melanoma skin cancer. Evidence of the occurrence of these events is based on participant self-report that a health care professional has diagnosed the condition, and no attempt is made to verify the diagnosis.

Participants are also monitored at every data collection visit through the 30-month visit for the occurrence of angina pectoris, TIAs, severe hypoglycemic episodes, severe hypotensive episodes, broken bones, and torn ligaments. All other outcomes that may be construed as

being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented, reviewed, and followed up by a study clinician as needed.

Physical Activity

Non-medicated diabetics, individuals with a prior history of a CVD event (> 1 year ago), and individuals with possible angina at baseline (based on the Rose questionnaire) are referred to their primary care provider for evaluation, and are eligible to participate in WLM only if they submit documentation of a non-positive exercise stress test or other diagnostic test for CAD within the previous 12 months and have been cleared by their personal provider and a WLM clinician. All other participants are eligible to participate in a moderate physical activity program. Because all participants have at least two CVD risk factors (overweight/obesity PLUS hypertension and/or dyslipidemia), any individual who, after the start of phase I intervention sessions, reports having started a new vigorous physical activity program are referred to their primary care provider for approval to continue vigorous exercise. Participants who enter WLM currently engaging in regular vigorous activity are allowed to continue vigorous activity without referral. Participants with non-medicated diabetes or prior CVD event who are engaging in regular vigorous activity require MD permission (and HgA1C < 8 for diabetics), but not a stress test.

The Steering Committee recognizes the need to minimize the potential risks of vigorous activity in previously sedentary individuals with CVD risk factors. In WLM, this responsibility must be met in the context of a lifestyle modification study in which 1) primary care is proved by the participant's own clinician and not by the study personnel and 2) we can recommend that participants follow safety advice but cannot force them to do so. In order to protect the participants' safety while respecting their autonomy, we will continuously reinforce our recommendation to engage in moderate-intensity physical activity and to undergo a safety evaluation if a participant wishes to progress to vigorous physical activity. Specific procedures include the following:

1. During Phase I (weight loss program with weekly group sessions), the interventionists will remind participants at regular intervals that we are recommending moderate rather than vigorous physical activity. Participants will also be reminded at these times that, should they wish to engage in vigorous physical activity, we strongly recommend an exercise stress test (EST) and clinician permission beforehand. Recognizing that we can't control whether a participant follows these recommendations or not and that they will potentially be engaging in a number of lifestyle behaviors not prescribed or sanctioned by the study, we will request documentation of EST and provider permission, but participants will remain in the study even if they do not provide it.

2. During Phase II (maintenance phase with less frequent contact), participants are asked, as part of the clinical measurement protocol every six months, whether they are engaging in vigorous physical activity and, if yes, are referred to their primary care provider as noted above. The coordinating center will notify the clinical sites whenever a participant is engaging in vigorous physical activity and approval for such activity has not previously been documented.

Participants are informed of the potential risks, such as musculoskeletal discomfort when new types of physical activities are started. Risk of injury is minimized by instruction on proper exercise technique. As a component of Phase I, participants are taught techniques for stretching,

warm-up, and cool-down. In the case of illness or injury during Phase I, interventionists advise the participants on adapting their physical activity program. For example, individuals who have been in automobile accidents may need to alter their physical activity patterns for a time period. This alteration in activity may require some assessment in order for the interventionist to be able to provide suggestions for adapting the participant's physical activity program. A study clinician is available to advise the interventionists on the need to refer for medical care if necessary. Musculoskeletal problems that occur during Phase II and are brought to an interventionist's attention are handled similarly; an unblinded clinician is available to advise the interventionist as needed.

If there is any question about the etiology of an injury or the need for treatment, the participant is referred to their provider for evaluation. If a participant is not willing to follow recommendations for referral care, the study clinician is notified and determines if further action is required. If appropriate, a serious adverse event report is created.

Nutrient Intake

Calorie restriction can theoretically lead to inadequate nutrition. To minimize this risk, participants are encouraged to eat a variety of foods from all food groups and to maintain an adequate calorie level. Participants are instructed not to reduce caloric intake below 1200 calories per day. During the intensive weight-loss program in Phase I, an interventionist periodically reviews food records and provides feedback on the adequacy of nutrient intake. The issue of adequate nutrient intake is discussed in the group and individual sessions. If nutritional deficiency is suspected and unresponsive to advice from the interventionist, the site clinician counsels the participant.

Participants may use extreme measures to lose 4 kg at the end of Phase I in order to be eligible for Phase II. Participants are reminded regularly of the importance of safe weight loss. Those who have a sudden, marked weight reduction are interviewed to determine if extreme measures have been taken. Interventionists are trained to detect evidence of extreme measures, and are given strategies for responding. The clinical site clinician is available to interview any participant if the interventionist or other study personnel suspects that the participant is using potentially unsafe methods.

Pregnancy and Other Exclusions

If a participant becomes pregnant during the study, she is excluded immediately from further participation in all study activities. If she has not yet seen a physician, she is immediately referred for standard prenatal care. If a participant develops any other exclusionary condition (e.g., cancer) following randomization, further participation is determined by a study clinician in conjunction with the participant's personal physician.

Contact with Personal Clinicians

The WLM investigators recognize the appropriateness and importance of securing the cooperation of personal clinicians. To this end, the personal clinicians of all participants are sent a letter describing the trial. These letters explain the study procedures and measures, and the circumstances that would lead to referral of a participant to her/his personal clinician. At screening, persons with non-medicated diabetes, individuals with a history of a CVD event more than 12 months prior, and individuals with possible angina based on the Rose questionnaire require explicit approval of the personal clinician and a non-positive stress test or other diagnostic test for CAD within the past 12 months in order to be eligible to participate. The

angina referral is made again at baseline if applicable. However, as noted above, a stress test may be waived for participants with non-medicated diabetes or prior CVD event who are already engaging in regular vigorous activity, have obtained MD permission to participate, have a glycosolated hemoglobin less than 8.0 (for diabetics only), and meet all other eligibility requirements. Screenees without a personal care provider are assisted in finding one.

All WLM participants will be on medication for hypertension and/or dyslipidemia. Weight loss and increased physical activity may necessitate reducing medications; other situations (e.g., new onset of one of these conditions; weight re-gain) may necessitate initiating or increasing medications. The decision to initiate or adjust drug therapy is a decision of the personal clinician, not a WLM clinician. However, formal criteria based on BP measurements or symptoms trigger referral for clinician evaluation. Clinical center staff track these referrals and this information is reported to the Data and Safety Monitoring Board.

Providers of participants who, after randomization, experience a CVD event are asked to make recommendations about what level of physical activity is safe to resume. These participants are still encouraged to attend regular follow-up clinical measurement visits. Participants who become pregnant following randomization are excluded from further participation in the study and their outcome data are censored as of their estimated date of conception.

Study Oversight

A Data and Safety Monitoring Board (DSMB) provides participant safety oversight for the trial. DSMB members, who include research scientists not otherwise connected with the study, are appointed by NHLBI. The expertise of members includes the disciplines and skills needed to initially review the protocol and then to monitor trial progress, quality of data, and safety of the participants by reviewing study reports. The DSMB serves in an advisory capacity to the NHLBI. Its members have access to unblinded outcome data during the trial, and can recommend early termination of one or more arms of the trial if the data suggest significant adverse risk to participants, if the questions posed by the trial appear to have been answered and there are no ethical or other reasons to continue the trial, or if continuation of the trial is futile.

Participant Closeout

The structure and content of close-out activities is left largely up to the individual sites, but in all cases includes personalized feedback, a summary of clinical measurements (e.g., weight, blood pressure), and counseling on heart disease prevention by qualified personnel (e.g., dietitian, nurse, health educator). Close-out activities can take place in the context of either an individual exit interview or a group counseling session. Clinical centers can make alternative arrangements to provide this information to participants who are not able or willing to attend the exit interview.

At the conclusion of the full trial, study participants are informed about the overall findings of the trial. This may occur in the context of an individual interview, group meeting, or mailing.

12. Statistical Analysis Plan

Analysis of Phase I Weight Loss Data
Complete results from the Phase I weight loss program will be available by the end of the second year of the study. Since these run-in data will be collected before randomization, they will be available for analyses and publication before the end of the trial. These secondary analyses will focus on the relationships between participant characteristics, adherence to the treatment program, and weight loss before randomization.

Analysis of Phase II Weight Loss Data
Primary Analysis sample
The planned primary analysis sample is intent-to-treat (ITT). In this approach, all persons who were randomized are included in the analysis in the assigned treatment group, regardless of actual treatment. If randomized individuals were not measured on the primary outcome post-randomization, we will impute an outcome for the ITT based on pre-randomization data and likelihood-based estimates (see missing data imputation, below).

We will exclude cases randomized in error or admitted to Phase I in error from the ITT analysis, except for those exceptions approved specifically by the Steering Committee for inclusion in the ITT analysis. Such exclusions can be carried out without biasing the outcomes analysis if they occur no more than 6 months after randomization, are objectively determined, carried out blinded to information about treatment assignment or outcome, and applied consistently to all affected participants. If a randomized participant is discovered to fail an inclusion/exclusion test that the Steering Committee has already waived for another participant, that second participant will also stay in the analysis sample.[133,153]

<u>Multi-person households</u>
This study is somewhat unusual in that a small subset of participants is same-household pairs (usually a married couple), in which one partner is randomized and the other is assigned to the same arm. So one partner is assigned non-randomly, and, since these pairs live together, outcomes are likely to be correlated. Through August, 2004, 16 couples were randomized, or less than 2.5% of the number randomized into Phase II. Partners were accepted for entry into the study in an effort to improve recruiting success for difficult-to-recruit subgroups, particularly African-American men.

We used a stratified randomization plan with the aim of balancing the distribution of selected features across the arms of the trial. Because the randomized person is assigned to arm in a way that balances the study and the non-randomized paired person is assigned to the same arm, the inclusion of the non-randomized person potentially creates an imbalance between the two arms. In addition, we anticipate that there may be numerical problems in attempting to model the covariance within household pairs because of the very small sample involved.

In view of these considerations, the Steering Committee decided not to include the non-randomized person in the primary ITT analysis. A secondary analysis will look at the impact of including these individuals.

Outcome measures
The **primary outcome** variable is weight in kilograms, which is measured six times--at baseline/randomization (W_R), end of follow-up after 30 months (W_F), and at 6-month intervals in between (6, 12, 18, 24 months).

The feature of weight that is of primary interest is the change over 30 months, $\Delta W_{R\text{-}F}$. If the 30-month measure is missing, we will impute the missing value (see below). In descriptive tables in our outcome papers, we will also report the weight loss data as percent loss from baseline, defined as $100*\Delta W_{R\text{-}F}/W_R$.

The first of the two baseline weights must be measured on or after G19 or the start of week 22, whichever is earlier. The second baseline weight is taken at least one week (7 days) following the first baseline weight, and no later than on the date of the randomization visit.

Both the first baseline weight and the second baseline weight must be at least 4 kg less than the second entry weight in order for the participant to be eligible for Phase II. **The second of the two baseline weights defines the baseline weight (W_R) for analysis of post randomization weight loss maintenance.**

Secondary outcomes, o*ther than costs,* include measures of behavior change, psychosocial variables, and prevalence of CVD risk factors. Many of these measures may also serve as covariates (mediators or moderators of weight change) in secondary covariate analysis. As for the primary outcome, the feature of interest is change from baseline to final measure, and the same modeling methods will be used to analyze these, but without replacing missing values through imputation. The measures are defined below.

1. Behavior change:
- *Total energy intake (kcal.)*, as measured by the Block FFQ;
- *Dietary intake* of various nutrients (e.g., fats) and food groups (e.g., fruits and vegetables) (from Block FFQ);
- *Physical activity*, as measured by accelerometry and self-reports of minutes of exercise.

2. Psychosocial variables:
- *Medical Outcomes Study Short Form Health Survey* (SF-36), 9 subscale scores (physical function, role function-physical, role function-emotional, bodily pain, general health, social function and psychological well-being /mental health, vitality health transition, and side effects checklist), plus overall scores for mental and physical well being;
- *Social Support and Eating Habits Survey* (2 subscores each for family, friends, total 4 scores);
- *Social Support and Exercise Survey* (2 subscores for family, 1 for friends, total 3 scores);
- *Perceived Stress Scale* (PSS) (4-item subset of the14-item scale, 1 score);
- *Patient Health Questionnaire (PHQ-8*, 1 score*).*

3. Prevalence of CVD risk factors:
The sample will be stratified based on baseline information into positive for the condition (i.e., medication treated or elevated) vs. neither.

- *Hypertension*: Individuals with prevalent hypertension (elevated BP or taking an antihypertensive medication at baseline) will be scored for improvement (0, neither of these is true at time F) vs. persistent hypertension (1). Individuals without hypertension at baseline will be scored as incident hypertension (1, defined by either elevated BP or taking an antihypertensive medication at time F) or persistent non-hypertension (0).
- *Hyperlipidemia*: Individuals with prevalent hyperlipidemia (fasting LDL-C ≥ 130 mg/dl or taking lipid-lowering medication at baseline) will be scored for improvement (0, neither of these is true at time F) vs. persistent hyperlipidemia (1). Individuals without hyperlipidemia at baseline will be scored as incident hyperlipidemia (1, fasting LDL-C ≥ 130 mg/dl or taking lipid-lowering medication) or persistent non-hyperlipidemia (0).
- *Diabetes*: Individuals with prevalent diabetes (fasting glucose ≥ 125 mg/dl at baseline or self-diagnosis of diabetes) will be scored for improvement (0, fasting glucose < 125 mg/dl) vs. persistent diabetes (1). Individuals without diabetes at baseline will be scored as incident diabetes (1, fasting glucose ≥ 125 mg/dl or taking diabetes medication) or persistent non-diabetes (0).

Design Variables
1. Treatment:
There are three treatment groups, parameterized so that SD/UC is the reference group.
2. Sites:
There are four sites. Portland will be coded as the reference group.

Primary Covariates
The following are *primary* covariates, which will be included in the initial models testing the effect of treatment on the above primary and secondary outcomes.
1. Demographic features
- *Age in years at randomization (R)*: continuous measure;
- *Gender*: Self-reported, female (code 1) vs. male (code 0);
- *Race*: Self-reported, African-American (code 1) vs. other (code 0);
- *Race x Gender* interaction.

Missing data
The analysis of the primary endpoint will be on the intent-to-treat sample, with all missing 30-month weights to be supplied by multiple imputation. We anticipate that we will have complete data on baseline measures including the primary covariates, so that the need for imputation will arise only with respect to the 30-month (final) measure. Only this measure will be imputed.

To fill in the missing 30-month weight, we will carry out multiple imputation using SAS PROC MI (which implements algorithms given by Schafer).[155] We will specify the variables in the MI model in advance and obtain the approval of the Steering Committee before proceeding with this process. The MI will be completed before outcomes analysis is begun.

The goals of this process[156] are
a) to assure a valid and efficient outcome analysis,
b) to assign plausible values to participants with a missing outcome given their observed values,
c) to preserve the correlational structure among the study measures, and

d) to incorporate into the inferential process the uncertainty inherent in replacing missing values.

In multiple imputation, the parameters (means and covariances) of the joint distribution of observed and missing variables is estimated in an iterative fashion, starting with the observed data and plausible values for the missing values. After an estimate of the parameters for all the variables is obtained, the imputed values of missing data points are updated, and the parameters are re-estimated.[155] The prior joint distribution is assumed to be multivariate normal but is otherwise not specified. Simulations (e.g., in NHANES data) have shown that inferences based on MI are robust to departures from this assumption "except when the fraction of missing information is high (in excess of 50%)".[155]

Once stable parameter estimates are achieved, each missing value is sampled from the final ("posterior") joint distribution and then further perturbed with random error. The selection of observed variables should be as inclusive as possible, in order to assure that any likely analyses involving the 30-month weights are nested within the MI model. For instance, by including any interim outcome measures (months 6-24) in the modeling, the within-subject trend over time is accounted for in the prediction process.[25]

The efficiency and unbiasedness of analyses based on imputed data rest on the assumption that the data are "missing-at-random", also called "ignorable". Without getting too technical, the "crucial assumption made by ignorable methods is not that the propensity to respond is completely unrelated to the missing data, but that this relationship can be explained by data that are observed".[155] This implies that the MI model should include all of the variables that may help predict the missing value, such as weight measured at months 6-24.

Schafer notes that ignorability is a "relative concept". To put this in perspective, it may be helpful to note that the validity and efficiency of complete-cases analysis depends on data "missing completely at random" (i.e., unrelated to any variable observed or not observed), that maximum likelihood estimation in a random-effects model also requires MAR, and that last-value-carried-forward (a widely used strategy for replacing missing values) ignores any trend in the outcome over time and reduces the standard error, thus inflating the likelihood of observing a significant result. In short, methods that do not use multiple imputation often have more stringent assumptions or less desirable effects on the analysis results.

Imputed values will be drawn several times (most likely 5, but this needs to be determined once the parameter estimates of the imputation process are known), thus creating several "complete" versions of the dataset. The planned primary outcome analysis will be repeated in exactly the same way in each of the imputed datasets. Finally, the results will be combined using Rubin's[157] rules (implemented in SAS PROC MIANALYZE) to produce the adjusted estimates and statistics from which inferences will be drawn. Only the results based on multiple imputation carried out on the cleaned and locked final data will be used in publications.

Primary Analysis statistical model

The trial's primary specific aim is to compare the effectiveness of each of two active interventions (PC and IT) versus self-directed/usual care in maintaining weight loss from randomization (R, at the end of the initial Phase I weight-loss phase of the trial) to the end of Phase II maintenance (F), 30 months post randomization. We use E to denote an entry measure (beginning of weight-loss program, or Phase I), e.g. W_E.

Formal hypotheses:
Null hypothesis: The PC [IT] intervention does not differ from SD/UC in the change in weight over the 30-months maintenance period; this is a joint hypothesis with two parts: $\beta_1 = 0$ and $\beta_2 = 0$.

Alternate hypothesis 1. The PC intervention differs from SD/UC in the amount of weight change over the 30-months maintenance period: $\beta_1 \neq 0$ (2-sided test).

Alternate hypothesis 2. The IT intervention differs from SD/UC in the amount of weight change over the 30-months maintenance period: $\beta_1 \neq 0$ (2-sided test).
The full model for the primary hypothesis test is

$$\Delta W_{R\text{-}F} = \beta_0 + \beta_1 PC + \beta_2 IT + \beta_3 \Delta W_{E\text{-}R} + \beta_4 W_E + \Sigma \alpha_i S_i + \Sigma \delta_i E_i + e_{ij} \quad (1)$$

where PC is an indicator of the personal contact intervention; IT is an indicator of the Web-based intervention; $\Delta W_{E\text{-}R}$ indicates the change in weight from Entry to Randomization, and W_E is the Entry weight. The S_i terms are indicators of the performance sites, the E_i terms are planned additional explanatory variables, and e_{ij} is a random "error" term assumed to be normally distributed with mean zero. The additional explanatory (E's) factors are 1) age, 2) female gender, 3) African-American ethnicity, and 4), gender x ethnicity interaction.

Under this model, β_1 represents the effect, after adjusting for all of the explanatory factors, of the PC intervention vs. SD/UC, and β_2 represents the corresponding contrast for the IT vs. SD/UC groups. Tests of the null hypotheses that $\beta_1 = 0$ and $\beta_2 = 0$ are thus the test of the primary hypothesis. Because the PC vs. IT contrast is a secondary aim, a test of the null hypothesis that $\beta_2 - \beta_1 = 0$ is done only if at least one of the previous two null hypotheses is rejected.

To preserve the experiment-wide Type I error rate at .05 for the primary outcome analysis, we will apply the Holm sequential testing procedure to the hypotheses $\beta_1 = 0$ and $\beta_2 = 0$[158,159] at overall level 0.05 (all two-sided tests). Under the Holm procedure, we first order the p-values for testing β_1 and β_2, then compare the smaller of the two p-values with $\alpha = .05/2 = 0.025$ for significance. The smaller p-value exceeds 0.025; neither comparison is considered significant. If the smaller p-value is less than 0.025, it will be considered significant, and the larger p-value will be considered significant if it is less than 0.05.

Secondary Analyses
Secondary aims
Secondary outcomes will be analyzed using the same approach as for the primary outcome analysis, but the specifics of modeling (such as error distribution assumed) will vary to reflect the type of outcome variable. We will not impute secondary outcome *variables*, but imputed 30-month weights will be used where these are involved in analyses of secondary *aims*. The critical value for significance will be .05 for all of the secondary outcomes analyses.

The following hypotheses relate to **secondary outcomes**, all have a null H of no difference:

Aim 3. The PC intervention differs from IT in maintaining long-term weight loss. This will be tested using Model 1 parameter estimates (above) only if either of the treatments is found to differ significantly from control; otherwise, we will conclude that it is non-significant.

Aim 5. Compare the effects of PC, IT, and SD/UC on the prevalence of major CVD risk factors (hypertension, hyperlipidemia, and diabetes), implies 2 alternate hypotheses vs. the null hypothesis of no difference between treatment groups:

- The final prevalence of major CVD risk factors is less in the PC intervention group than in SD/UC group;
- The final prevalence of major CVD risk factors is less in the IT intervention group than in SD/UC group.

In participants with a CVD risk factor at baseline, the risk factor may persist or may appear to improve (defined in this trial as no medication and no elevation of the corresponding physiologic measurement). For each risk factor, we will evaluate the relative risk of improvement among those with the prevalent risk factor at baseline. In addition, we will evaluate relative risk of cessation of medication within the stratum of individuals who use medication at baseline.

Finally, in the stratum of individuals without the risk factor at baseline, we will evaluate the relative risk of developing the risk factor (incident cases, defined by medication use or elevation of the corresponding physiologic measurement). We will compare arms within each stratum using a chi-square test.

Aim 6. Compare the effects of PC, IT, and SD/UC on measures of behavior change (e.g., physical activity, aspects of diet).

The following alternative hypotheses will be evaluated against the null hypothesis of no difference between treatment group and SD/UC.

- The PC intervention produces greater behavior change than does SD/UC
- The IT intervention produces greater behavior change than does SD/UC

Aim 7. Compare the effects of PC, IT, and SD/UC on weight change **from entry** (prior to Phase I) to the end of the post-randomization maintenance phase (Phase II).

While change in weight from R to F is of primary interest, comparison of the change in weight from initial entry (E) to final assessment (F) is an additional study aim. The logic behind this aim is that, if the maintenance interventions are successful in maintaining all or some of the original weight loss, then some of the original weight loss should persist to some extent through the end of the trial. The analytic model for this analysis is

$$\Delta W_{E\text{-}F} = \beta_0 + \beta_1 PC + \beta_2 IT + \beta_4 W_E + \Sigma \alpha_i S_i + \Sigma \delta_i E_i + \varepsilon, \qquad (2)$$

using the same conventions and statistical approaches as for Model 1. The imputed 30-month weights will be used in this analysis.

Secondary Covariate Analyses

The analyses in this section are motivated by an interest in factors that may moderate weight loss in the various treatment groups.

Aim 4. Compare the effects of PC, IT, and SD/UC on weight maintenance in **subgroups defined by race, sex, age, and baseline body mass index**.

Comparison of treatment effects across subgroups defined by race, sex, age, baseline body mass index, and potentially additional factors, will be approached using the same analytic model (1), with added terms to elucidate possible differential effects between subgroups, operationalized as interactions between treatment group indicators and subgroup indicators. The model is:

$$\Delta W_{R\text{-}F} = \beta_0 + \beta_1 PC + \beta_2 IT + \beta_3 \Delta W_{E\text{-}R} + \beta_4 W_E + \Sigma\gamma_i [XI_k]_i + \Sigma\alpha_i S_i + \Sigma\delta_i E_i + e_{ij} \quad (3)$$

where $\Delta W_{R\text{-}F}$ is the same variable as in model (1), based on imputed 30-month weights and $[XI]_i$ represents the interaction between a covariate X and indicator for treatment group I_k. The first step is to test whether the parameters on the interaction, γ_i, are all 0.[160] If this hypothesis is not rejected, modeling stops here. If this hypothesis is rejected, then the second step is to test whether the parameters on the interaction, γ_i, are the same across groups. The form of this model is

$$\Delta W_{R\text{-}F} = \beta_0 + \beta_1 PC + \beta_2 IT + \beta_3 \Delta W_{E\text{-}R} + \beta_4 W_E + \eta X + \Sigma\gamma_i I[XI_k]_i + \Sigma\alpha_i S_i + \Sigma\delta_i E_i + e_{ij} \quad (4)$$

where ηX represents the main effect of the covariate. If this test is not significant, modeling can stop here or, if desired, the term $\Sigma\gamma_i I[XI_k]_i$ can be dropped from the model and the estimate of treatment effects adjusted for the main effect of the covariate can be obtained. If the test is significant, this indicates that treatment effects are different for different values of X. For a categorical covariate, the estimates of treatment effects are obtained within each level of the covariate. For a continuous covariate, estimates will be obtained at several selected values of the covariate, e.g. 25^{th} , 50^{th}, and 75^{th} percentiles of the covariate. These estimates are obtained using model (3). We will use two-sided 0.05 tests on the regression coefficients.

Aim 8. Determine **process variables** that are associated with sustained weight loss [e.g., physical activity, dietary intake of various nutrients (e.g., fats), and food groups (e.g., fruits and vegetables)].

This analysis will be carried out by the same methods described above for the primary analysis with a priori covariates measured at baseline.

However, if there is interest in modeling the mediating effect of process variables measured during maintenance, a different analysis strategy is needed. Measures obtained during the 30-mo follow-up phase comprise time-dependent covariates that may mediate the subsequent course of weight loss maintenance. The impact of time-dependent covariates is easily handled in mixed models effects by constructing a repeated measures dataset with an observation for each time of the measurement and values of the covariates and outcome at that time. Time-dependent covariates cannot be incorporated in the conditional change model, which takes only baseline and final measures into account.

Some secondary outcomes also will serve as covariates in Aim 8 analyses of the primary outcome. These include the following:

1. Behavior change:
- *total energy intake*
- *dietary intake*
- *minutes of physical activity*

2. Psychosocial measures
- *SF-36*
- *Social Support and Eating Habits Survey*
- *Social Support and Exercise Survey*
- *PSS*
- *PHQ-8*

The following are design variables in Phase I, nested within site. In a secondary analysis, the possible moderating effect of these Phase I variables on outcomes in Phase II will be evaluated.

1. Intervention Group:
This is a random variable nested within sites during Phase I. The number of intervention groups varies between sites. There are three types of intervention groups, with sites varying in the number of each:
a. All African-American
b. Mixed African-American and other race/ethnic groups
c. No African-American (other race/ethnic groups).

2. Interventionist:
Interventionist is partially crossed with intervention group. They can also be grouped according to race/ethnicity, AA vs. other.

In addition, the following have been mentioned as potential covariates:
Process measures:
These will be defined as specific papers are planned.
- *Attendance*
- *Self-monitoring*,
- *Others to be determined.*

Table 5. Statistical Power

	Entire Sample			40% Sample			60% Sample		
SDE	0.8	0.85	0.9	0.8	0.85	0.9	0.8	0.85	0.9
0.40	1.2	1.3	1.4	1.7	1.9	2.0	1.4	1.5	1.5
0.45	1.4	1.5	1.6	2.0	2.1	2.3	1.6	1.7	1.8
0.50	1.5	1.6	1.8	2.2	2.3	2.5	1.8	1.9	2.1
0.60	1.8	2.0	2.1	2.6	2.8	3.0	2.2	2.3	2.4
0.65	2.0	2.1	2.3	2.8	3.1	3.2	2.3	2.5	2.7
0.70	2.2	2.3	2.5	3.1	3.2	3.5	2.5	2.7	2.9
0.75	2.3	2.5	2.6	3.3	3.5	3.8	2.7	2.9	3.1

Detectable Effects: Difference in $\Delta W_{R\text{-}F}$ between active treatment (PC and IT) and control (SD/UC) in kg, for powers 0.8, 0.85, 0.9 under various assumptions about the SDE (standard deviation of the estimate) and sample size. Figures for subgroups assume that the primary analysis will be in the expected direction.

Detectable effects/sample size

The sample size for the WLM trial (800 randomized participants) was designed to provide adequate power for subgroup comparisons as well as for the overall study comparisons. In particular, the trial has 90% power to detect about a 2.0 kg difference in weight change between either of the active intervention groups (PC or IT) and the self-directed group overall, and 80% power to detect treatment differences of about 2.7 kg among African Americans.

Because randomization occurs after the initial 5-month weight-loss phase of the trial, the sample size calculations are based on the number randomized, and not on the number who initially enter the trial. In order to randomize 800, we anticipate that we need 1600 participants to enter Phase I. This estimate assumes the following: 10% of those entering Phase I drop out before the 5 months ends; 35% complete the weight loss phase but fail to lose at least the 4 kg of weight required for randomization, and 5% are eligible but decline to be randomized. These estimates are based on the experience in the PREMIER study in which 6-month follow-up rates were 94%, and 50% of participants had lost 4 kg or more at the 6-month visit.

None of the calculations presented in this section factor in participant dropout following randomization, since we propose an intention-to-treat analysis and will impute data for those individuals who do not complete follow-up. The effect sizes shown in Table 5 should therefore be interpreted as net effect sizes after imputation.

The method used to estimate detectable effects was as follows. The PREMIER data (as of January 2002) were used for the purpose of estimating the standard deviation of the estimate (SDE) of treatment effects. Among those PREMIER participants who lost at least 4 kg in the first 6 months, their changes (12 mo. vs 6 mo, and 18 mo. vs. 6 mo.) were regressed on their entry weight, the 6-month change, gender, and two treatment group indicators. Thus, both the sampling method and the statistical method used to estimate detectable effects were identical to what we plan for the analysis of the WLM trial. Adjusted to the projected sample size of 800 participants, the SDEs were 0.45 and 0.52 kg, respectively. Since this indicates that the variability might increase with the length of the interval between measurements, the table above includes some values of SDE above 0.52. The table provides the detectable effects (kg) for three

powers (0.8, 0.85, 0.9) for the entire sample, for a 40% subgroup (appropriate for subgroup analysis in African Americans) and for a 60% sample (appropriate for subgroup analysis in women). These effects refer to the primary analysis in the left panel (comparison of weight change ΔW_{R-F} between PC and SD/UC, or between IT and SD/UC, taking the multiple tests into account, at significance level 0.05 two-sided) and the subgroups in the right panels (one-sided tests without multiple testing adjustment). Assuming that the 0.60 row were to be true, the sample size is sufficient to detect an effect in the 1.8-2.1 kg range with power 0.8-0.9 in the entire sample, and to detect effects in the range 2.6-3.0 kg with power 0.8-0.9 in a 40% sample, and effects 2.2 -2.4 kg with power 0.8-0.9 in a 60% sample.

13. Data Management and Quality Control

Data Management System. Data reaches the CC via several routes: distributed entry of eligibility and other data by the sites using a web based system developed by the CC; centralized entry of selected data by the CC; entry of selected intervention information directly by participants via the intervention web site; and secure file transfer of laboratory data using the web based system.

Distributed entry: Data entry is accessible via the web to any computer at the sites via Internet Explorer. Web based data entry systems include sophisticated range and cross checks, and primary outcome data is 100% verified.

Randomization: Randomization assignments for participants are generated by the web-based system when the sites randomize the participant. Prior to randomization, the system checks the master databases to make sure that all requirements for the study have been met.

Central entry: All data centrally entered by the CC are 100% verified. Long-term security of all study data is assured by the CHR's automated system of daily, weekly, monthly, and yearly backups, which are stored off-line on tape and/or laserdisk.

Data confidentiality: All data stored electronically are password protected. In addition, all CHR staff annually sign a confidentiality statement attesting to their understanding of, and willingness to abide by, the CHR's written policies on research ethics and confidentiality. Site access to the data entry website is password protected and restricted to site personnel trained to use the system.

Development of Web-based intervention applications: The CC Web development application team is responsible for the systems design, analysis, development, and implementation for all project-related application requirements. They design and develop the participant on-line intervention applications under the direction of the WLM investigators. The team also develops, tests, and deploys the business-tier components for data entry validation, transaction validation, and other special-use components. The CC also has application interface designers, who are responsible for the graphical user interface in the client tier for both participant and staff Web-based tools, including the production and implementation of client-side animation.

Trial monitoring and quality control. In addition to the systems referred to above, the CC uses a number of other quality control (QC) procedures as part of its on-going trial monitoring.

Trial monitoring reports: The CC produces and distributes reports covering all aspects of the trial, including enrollment, baseline data collection, project quality control, laboratory quality control, intervention participation, interim results, reported treatment side effects, and safety issues.

End-user reports: The data management system allows clinical center staff to generate a variety of site-specific QC reports using their desktop PCs. These reports allow sites to verify data, produce frequency distributions for selected variables, create recruitment projections, and generate closeout summaries for participants.

Site visits. The CC conducts combined annual site visits to the four clinical sites and distributes reports of these visits to the site PI, the study Chair, and the Project Officer. These site visits cover data validation and documentation; laboratory procedures; informed consent; certification and calibration of staff and equipment; follow-up visit observations, protocol, MOP, and forms manuals; observation of automated systems and their use; staff training and certification; and site-identified problems. These site visits also cover intervention delivery, including observation

of intervention sessions, observing selected individual counseling and telephone contacts, and interviewing local staff and/or participants as necessary.

Weight quality control: To ensure that our primary outcome data are of high quality throughout the study, all data collection staff are trained and certified annually, with central training/certification of master trainers from each site.

Closeout and data analysis phases.

Data analysis. The CC conducts all analysis of study data under the direction of a statistician. A statistician is assigned to all approved papers and works with the lead author to develop an appropriate analysis plan. Formal written analysis requests are reviewed for clarity and for appropriateness of the requested statistical analysis before work is begun. This procedure minimizes rework and thus makes most efficient use of staff resources.

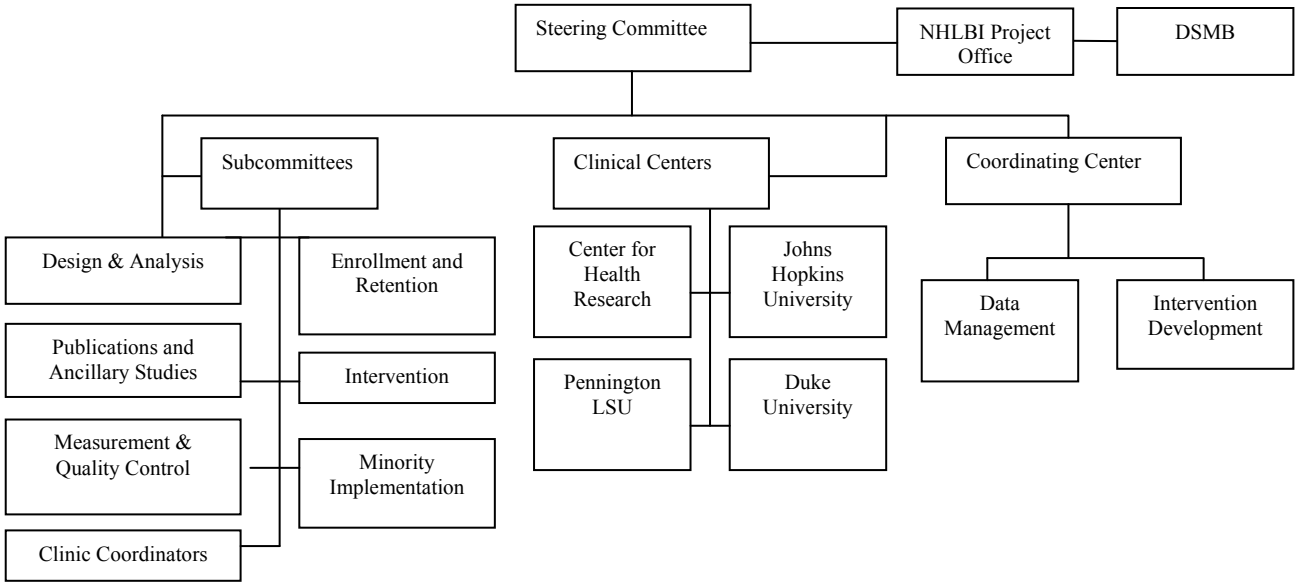
Analysis guide. To facilitate data analysis requests, the CC creates a detailed analysis guide for the study investigators. This guide provides detailed, organized documentation of all study variables along with a process that allows researchers to request analyses in a clear, concise fashion. A summary data set including the most frequently used variables is provided, with variables in alphabetical order. Copies of every data form used in the study are also provided, each labeled with the specific variable name in the response field.

Trial-wide data release. We recognize that the CC may not be able to perform all desired analyses by the time the trial is concluded. The CC therefore prepares and distributes a formal data release to the participating sites at the end of the study, and to the NHLBI project office, a limited access dataset for public use. As with the analysis guide, the data release documentation provides detailed, organized documentation of study variables and clear instructions on how to install and access the data.

14. Trial Administration

Trial organization
WLM is conducted by four participating clinical centers and a Coordinating Center with assistance from NHLBI. This research group acts together to implement a common protocol and to administer the trial.

Figure 3. WLM Organizational Chart



WLM sites. Participating institutions include the NHLBI Project Office, the Coordinating Center (Kaiser Permanente Center for Health Research in Portland, OR), and four clinical centers: Johns Hopkins University in Baltimore, MD, Pennington Biomedical Research Center in Baton Rouge, LA, Duke University Medical Center in Durham, NC, and a clinical center also located at the Kaiser Permanente Center for Health Research in Portland, OR.

Trial committees. The Steering Committee is the primary decision-making body for the trial. The composition and functions of the trial committees are described below.

Steering Committee. Voting membership on the Steering Committee include the principal investigators (PIs) from each of the four clinical centers and the Coordinating Center, and the NHLBI project officer. The steering committee clarifies the roles and responsibilities of participating institutions; reviews and approves all policies, protocols, and trial-wide procedures; monitors performance both overall and at each clinical center (enrollment, adherence, data collection, quality control, and data analysis), and reviews and approves ancillary studies and requests for study data.

Minority Implementation Committee. Membership includes the trial chair, and representatives from all of the other trial committees, as well as investigators, staff members, and consultants with a special interest and experience in minority health research. The concerns of this working group cut across all aspects of the trial, with a focus on recruiting and retaining minority participants and on adapting the intervention material to be culturally appropriate for African Americans. Responsibilities include conducting an annual training meeting for trial staff,

reviewing materials, protocols, and procedures for cultural appropriateness to African Americans, and making recommendations to the Intervention, Recruitment, Design and Analysis, Measurement, and Steering Committees for maximizing full participation of African Americans in the trial.

Clinic Coordinators. This committee includes the clinic coordinators from each clinical site and the Coordinating Center data manager. The committee is the primary forum for issues of data management and quality assurance. This committee also oversees implementation of training and certification procedures and is the forum for sharing experience and problem solving among clinic coordinators. To facilitate communication, representatives from the clinic coordinators committee serve on each of the other trial committees.

Design and Analysis Committee. This committee includes each site PI, all of the investigators at the Coordinating Center, the project officer, statisticians from the project office, and other investigators selected by the committee chair. The committee reviews proposed design and data collection changes and makes recommendations to the Steering Committee.

Recruitment Committee. This committee includes a representative from each clinical center and the Coordinating Center's project administrator. The committee meets by conference call to review enrollment at each clinical center, to monitor yields (especially the yield from entry to randomization), to share experiences, and to provide mutual assistance as needed.

Measurement Committee. The committee includes key trial personnel including representatives from each clinical center, the Coordinating Center, and the Project Office. The committee recommends to the Steering Committee measures, processes, and procedures for assuring quality control of the trial, including training, certification, quality control measures and procedures, and other activities directed at ensuring that data are valid and reliable.

Intervention Committee. This committee includes investigators and interventionists from each site, along with representatives from the Coordinating Center and project office. The committee makes recommendations to the Steering Committee regarding intervention development, implementation, and quality control. The intervention committee meets monthly by conference call and annually for interventionist training meetings. Working groups within the intervention committee include IT intervention workgroup, PC intervention workgroup, and Phase I workgroup.

Publications and Ancillary Studies Committee. Membership includes the PIs of each clinical site, the Coordinating Center, and a representative from the Project Office. This committee develops policies on publications and presentations and oversees the implementation of these policies. This committee also recommends policies for the conduct of ancillary studies, reviews all ancillary study proposals, and makes recommendations to the Steering Committee regarding ancillary study proposals.

Data and Safety Monitoring Board (DSMB). Described in section 11, the DSMB is appointed by NHLBI in an advisory capacity. Its role is to initially review the protocol and then to monitor trial progress, quality of data, and safety of the participants. In addition to the Board members, meetings are attended by representatives from the Coordinating Center, the Steering Committee (including the chair, vice-chair, and chair of the intervention committee), and the NHLBI. Only DSMB members have voting privileges. None of the clinical center investigators have access to blinded study data until the end of the trial and/or until the DSMB recommends unblinding. The DSMB meets at least annually throughout the trial. Minutes of the meeting are prepared by the NHLBI Executive Secretary, and a summary of the portion of the minutes related to participant safety is distributed to all principal investigators to forward to their individual IRBs.

Dissemination of project documents. WLM uses secure Web technology to provide staff access to all project documents. The Manual of Procedures (MOP), data collection forms, minutes from committee meetings, queries and answers, and other key documents are posted on the trial administrative website and are accessible to all authorized Coordinating Center and clinical center staff. Using this system, any authorized WLM staff member has access to the current version of the MOP, protocol, data collection forms, and all other documents. They also have access to all trial minutes and other communications. All documents on the WLM Web site are stored in a read-only format; that is, they can be read or printed at the local site, but not edited.

Staff training and certification. The Coordinating Center develops and conducts the training and certification modules for the data management system, trial communications, the protocol, MOP, forms manual, analysis guide, and all intervention activities. Clinical measurement staff are trained and certified in all key elements of the MOP, including height, weight, blood pressure, accelerometry, and lab measurements. Additional training covers forms administration and use of the data management system. Master trainers at each site receive central training by Coordinating Center staff or trainers designated by the Steering Committee. These master trainers in turn conduct local training and certification. Master trainers are re-certified at each training meeting. Training for delivery of the interventions includes all study interventionists. The Coordinating Center schedules all training sessions and keeps a record of staff that have attended trainings.

Trial communications**.** The CC coordinates all trial-wide communications, including distributing and archiving physical mail, electronic mail, and facsimiles; scheduling and documenting conference calls; and scheduling and arranging national meetings. The CC is represented on all committee meetings and conference calls and takes and distributes meeting minutes.

The Coordinating Center maintains a computerized infrastructure for communications between the clinical sites and the CC. A Microsoft Windows NT Web server at the CC is dedicated to data collection and information dissemination between the CC and clinical centers.

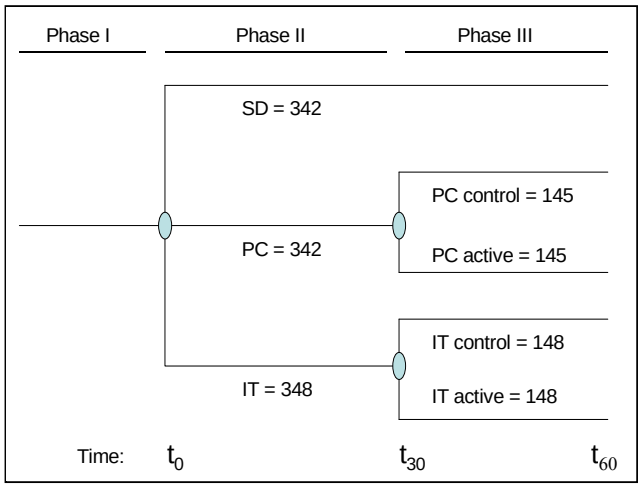
15. Phase III

Overview

The start of WLM Phase III was funded by an Administrative Supplement while waiting for the review of a competing continuation application. Re-enrollment for phase III was completed in June 2007. In late 2007 we learned that the continuation application would not be funded. All four clinical centers then conducted a follow-up data collection visit. In early 2008 one of the clinical centers closed out their participation in the trial, and the other three continued the trial using local sources of funding with the goal of continuing until their participants could attend a final data collection visit five years after randomization into phase II. In September 2010, the Coordinating Center received a grant to support the analysis of all of the Phase III data.

The goals for this third phase of WLM are to assess long-term results of the Phase I and II interventions, and to determine if continued intervention (either PC or IT) is necessary to maintain treatment effects. During Phase III, PC and IT participants were re-randomized to either continued intervention (PC-Active and IT-Active, respectively) or to no further intervention (PC-Control and IT-Control, respectively). Participants originally assigned to Self-Directed Care (SD) were assigned to the SD condition and received no further intervention.

Figure 4. Design of WLM Phase I, II and III



Aims	**Contrast**	**Phase** (time period)
Primary Aims	#1) PC Active vs. PC Control #2) IT Active vs. IT Control	Just Phase III (t_{30} to t_{42})
Secondary Aims	#1) PC Active vs. SD #2) IT Active vs. SD	Phase II and III combined (t_0 to t_{42})
Other Aims	#1) PC Active vs. IT Active #2) PC Control vs. SD #3) IT Control vs. SD	Phase II and III combined (t_0 to t_{42})

Aims addressed in Phase III:

PRIMARY AIMS

1. Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight of an additional 30-months of PC intervention (PC-Active) compared to no further PC intervention (PC-Control).
2. Compare the 60-month weight loss maintenance experience of participants in the PC-Active intervention versus those in the SD condition.

SECONDARY AIMS

3. Compare the 60-month weight loss maintenance experience of the PC-Active versus PC-Control arms and of the PC-Control versus SD arms.
4. Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight of an additional 12-months of IT intervention (IT-Active) compared to no further IT intervention (IT-Control).
5. Compare the 42-month weight loss maintenance experience of the IT-Active and IT-Control interventions versus each other and versus the SD condition.
6. Compare the 42-month weight loss maintenance experience of the PC-Active and PC-Control interventions versus each other and versus the SD condition.
7. Compare the 42-month weight loss maintenance experience of the PC-Active and IT-Active interventions.
8. Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight at 60 months of an additional 12 months of IT intervention (IT-Active) compared to no further IT intervention (IT-Control).
9. Compare the 60-month weight loss maintenance experience of the PC-Active and IT-Active interventions.

Rationale for Phase III

NHLBI has identified the need to test long-term weight loss maintenance strategies of at least 5 years duration.[161] The 2½-year timeframe of WLM Phase II, while longer than most weight loss trials, is nonetheless insufficient to address the critical issue of whether the interventions, if successful, should be continued. The "natural history" of weight loss would suggest that weight re-gain occurs in the vast majority of individuals without continued intervention. The issue of whether or not weight loss maintenance interventions must be continued has enormous implications for public health strategy. For certain conditions (e.g. elevated blood pressure, alcoholism), treatment is lifelong, whereas for other conditions (e.g. cigarette smoking), successful treatment does not require sustained intervention. Information about the necessary duration of weight loss maintenance intervention has important implications for allocation of health care and community resources, and for setting realistic expectations for individuals who are attempting long-term weight loss maintenance. Without evidence on long-term effects to guide them, organizations implementing a weight loss maintenance intervention might truncate the intervention after 2½ years despite possible benefits of continuing, or alternatively, might continue intervention despite lack of benefit.

The addition of Phase III to WLM offers an ideal opportunity to get added value from the ongoing WLM trial. The WLM study population already enrolled is large (n=1032) and demographically heterogeneous (38% African-American, 63% female). Trial participants were successful at achieving initial weight loss (mean 8.4 kg) and are now demonstrating an impressive commitment to the study (follow-up rate of 90% one and one half years after initial

weight loss). Furthermore, participants have hypertension and/or dyslipidemia, and hence are a high-risk population in whom long-term weight loss maintenance would likely lead to improved health outcomes.

Research Design and Methods For Phase III

Overview

Figure 4 shows the overall study design (i.e., Phases I, II, and III) of the Weight Loss Maintenance Trial, as well as the contrasts associated with the aims of the proposed extension. The following sections summarize the research methods for Phase III, which includes re-enrollment of all eligible participants, re-randomization of participants originally assigned to PC and IT, continued intervention, and follow-up data collection.

Study Population

All WLM participants who have not previously terminated their involvement in WLM were invited to continue into Phase III. The only exclusions were women who were pregnant or nursing and any individuals for whom we were unable to collect outcome data (weight) at the end of Phase II.

Re-Randomization, Re- Enrollment and Consent

Each participant who agreed to re-enroll in WLM signed a consent form specifically for Phase III. A separate consent form was required for participants from each Phase II treatment condition (PC, IT, SD). Phase III was initiated with an administrative supplement from NHLBI, pending review and funding of a Competing Continuation grant proposal. Hence, the consent process informed prospective participants of the possibility that the Competing Continuation would not be funded. The consent document indicated that, in the event the Continuation was not funded, their participation in the trial would end with the termination of the current WLM grant, and that a final, limited data collection visit occur at that time.

All individuals who were randomized to PC or IT in Phase II were re-randomized for Phase III, using a randomization scheme blocked by site, Phase II treatment group, and Phase II weight change. PC participants were re-randomized to continued intervention (PC-active) or to no further intervention (PC-control). Similarly, IT participants were re-randomized to continued intervention (IT-active) or to no further intervention (IT-control). Individuals were only informed of their new randomization assignment after they signed Phase III consent. SD participants were re-enrolled in their current control condition (SD). Individuals who do not enroll in Phase III were asked to sign a separate consent allowing us to conduct a final outcome assessment (weight measurement and an adverse events questionnaire). Thus all participants who re-enroll were included in analyses for Aims 1 and 2, above, and all participants who were originally randomized into Phase II will be included in analyses for Aims 3 and 4.

Phase III Intervention

Overview. The Phase III active interventions (PC-Active and IT-Active) are extensions of their Phase II counterparts that were designed to support the participants' behavioral self-management programs. Rather than simply supplying information or giving instruction on diet and exercise, they provide personal accountability, prompting and reinforcement for behaviors that support continuing efforts to maintain weight loss or lose more weight. Both the Phase III active PC and IT interventions were designed to be practical, easy to implement in a variety of settings, and amenable to broad dissemination.

As a part of the randomization process, we conducted an orientation session for all participants explaining their new study assignment. This included an intervention orientation for IT-active

and PC-active participants, and discussion of the importance of follow-up data collection for the IT-control and PC control participants.

Self-Directed (SD) control condition: Phase III participants in the self-directed control condition did not receive lifestyle change counseling in Phase III, but returned for data collection visits.

PC-Control and IT-control: Participants randomized from PC into PC-control and from IT into IT-control receive no further intervention during Phase III, but will return for data collection visits.

PC-Active: The Phase III personal contact intervention (PC-active) begin with four weekly group sessions conducted by a trained WLM interventionist and modeled after the Phase I intervention group sessions. These Phase III group sessions were designed to serve as "booster sessions" for these participants who have been attempting weight loss maintenance for 30 months during Phase II. After the initial booster sessions, PC-active employed the same contact schedule, format, and general content as PC in Phase II. Each participant had monthly contacts with an interventionist throughout Phase III. These contacts used a case-management approach and motivational interviewing to offer person-to-person guidance and support for avoiding or overcoming obstacles to maintaining weight loss. Participants were counseled to monitor food intake and physical activity, weigh at least weekly, and continue to follow the DASH dietary pattern. Group visits allow for social support among participants, identifying adherence barriers and providing a supportive environment for problem-solving discussions. To provide accountability, weight and self-monitoring data were be collected at each contact.

IT-Active: Participants randomized to the IT-Active intervention in Phase III also attended booster sessions similar to PC-active (but conducted separately from the PC-active participants). After the initial booster sessions, IT-active participants continued to have unlimited "24/7" access to the WLM interactive website with encouragement to log onto the site at least once per week. Self-monitoring was built in to the website (e.g., participants must enter weight at least weekly), as were goal setting, feedback, relapse prevention training, social support, and problem solving. Participants scheduled their own next check-in date, and received automated e-mail and phone prompts when the check-in date is missed until the IT site was taken offline which occurred at approximately the participants 42-month visit. Participants with prolonged absence from the site enter a case management protocol to help them re-engage in the intervention.

Phase III Data collection

All Phase III participants were invited to a 42-month data collection visit at which a weight and a weight management strategies questionnaire was collected. Participants from the three clinical sites that continued with the study using local funding conducted a five year (60-month) follow-up visit at which a weight, summary medications form, blood pressure, and weight management strategies questionnaire was collected.

Analysis Plan for Phase 3 of the WLM Trial

All sites conducted a 42-month phase III data collection visit with a window from 36 to 48 months following phase II randomization. Three of the sites conducted final phase III data collection with a window from 50 to 68 months. That is we obtained an average an additional 30 months of follow-up beyond phase III randomization.

NOTATION

E = entry
R1 = first randomization (start of phase 2, also called baseline)
R2 = second randomization (start of phase 3, 30 months post R1)
FU42 = first phase 3 FU (42 months post R1)
FU60 = second phase 3 FU (60 months post R1)

IMPUTATION

To maximize the stability of the imputation process, we will conduct separate imputations for the FU42 and FU60 data, with the latter excluding participants from Portland. Further, because binary data are extremely hard to impute reliably and tend to make the imputation matrix unstable, we will not impute any data from form 210, which asks about various weight loss behaviors undertaken since R1. We will, however, try to impute binary indicators of med use for each of hypertension, dyslipidemia, and diabetes. We will also impute weight for FU42 and FU60 and BP at FU60. We will not, however, include individuals in our analysis after they have died. That is, we will not impute hypothetical weights for such individuals.

MULTIPLE COMPARISON CONSIDERATIONS

Given the Phase 1 and 2 results of WLM, we view (a) the conditional 30-month test of PC-Active verus PC-Control among those willing to be re-randomized at R2 and (b) the unconditional 60-month test of PC-Active versus SD as the questions of primary interest for Phase 3 of the trial. We also have a number of secondary hypotheses that we wish to address, as well as some purely exploratory analyses.

In what follows we therefore distinguish between primary aims, secondary aims, and exploratory analyses. The Steering Committee has determined that none of these analyses will be adjusted for multiple comparisons. Instead we will make clear in our papers our *a priori* hierarchy of analysis aims and focus on the presentation of effect size estimates and confidence intervals. Although we will present 95% confidence intervals, the papers will include standard errors for our effect size estimates so that readers can compute broader confidence intervals if desired.

ABSOLUTE VS. PERCENT CHANGE

We will focus on absolute weight change, but will likely present key analyses with percent change as well. When computing percent change, the relevant absolute weight changes will always be expressed as a percent of entry weight. In this way all weight changes, regardless of how they are expressed, will be additive over time. This in turn will provide some convenient equivalencies for model fitting as noted below. For simplicity, in this document we will simple speak of weight change without specifying whether this is absolute weight change or percent weight change.

PRIMARY AIMS

1. **Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight of an additional 30-months of PC intervention (PC-Active) compared to no further PC intervention (PC-Control).**

This question very specifically takes the health plan perspective and asks, among the subset of PC participants who want to continue in such an intervention after an initial 30 months, whether doing so for an additional 30 months has any further benefit. The analysis will therefore focus on the 196 PC participants from Baton Rouge, Baltimore, and Durham who were re-randomized into phase 3. However it also will include the 208 IT participants from these sites who were re-randomized so that a single "unified" model will thus allow us to test this primary aim as well as a secondary aim of interest (see aim #8).

We will assume an ITT analysis and use imputed values for all participants who do not provide a FU60 weight measurement.

Outcome variable = change in weight from R2 to FU60 ($\Delta W_{R2\text{-}FU60}$).

Analytic model:

$$\Delta W_{R2\text{-}FU60} = \beta_0 + \beta_1 PCA + \beta_2 ITA + \beta_3 \Delta W_{E\text{-}R2} + \Sigma \beta_i X_i \ , \qquad (1)$$

where PCA and ITA are binary indicators of the PC-Active and IT-Active conditions, respectively, and the X_is are a series of adjustment variables that include indicators for the four race-gender groups and for site. Since weight changes are additive over time, this model can be rewritten as

$$\Delta W_{E\text{-}FU60} = \beta_0 + \beta_1 PCA + \beta_2 ITA + \beta_3^* \Delta W_{E\text{-}R2} + \Sigma \beta_i X_i \ , \qquad (2)$$

where $\beta_3^* = (\beta_3+1)$. The other coefficients in the two models are identical. Thus so long as we condition on change in weight from entry through R2, it makes no difference if we use as our outcome phase 3 weight change or total weight change over the 66 months since entry. The primary aim is evaluated by testing whether $\beta_1=0$.

2. Compare the 60-month weight loss maintenance experience of participants in the PC-Active intervention versus those in the SD condition.

Unlike the previous analysis, which was limited to (i.e., conditioned on) those who were re-randomized into phase 3, this "unconditional" analysis will look at all PC and SD participants, regardless of their phase 3 consent status. However we will still exclude Portland participants. Similar to aim 1, we will fit a unified model that allows us to test both PC and IT related hypotheses, so that the analysis will actually include all 740 participants from Baton Rouge, Baltimore, and Durham who were initially enrolled into phase 2, including those randomized to the IT condition.

For the PC participants, we will effectively assume not that they were randomized to a single 30-month PC intervention, but rather that they were randomized to one of two 60-month interventions (PC-Active or PC-Control). Since assignment to these latter two arms was done at random, the 3-arm randomization framework is valid so long as we retroactively "randomize" those PC participants who opted out of phase 3 (or provided a "data only" consent) into either the PC-Active or PC-Control conditions. 18% (44/240) of the PC participants from these two sites will need to be randomized in this manner.

Similar considerations hold for the IT arm, 18% of whom (46/254) will need to be retroactively randomized.

We will use an ITT analysis and use imputed values for all participants who do not provide a FU60 weight measurement.

Outcome variable = change in weight from R1 to FU60 ($\Delta W_{R1\text{-}FU60}$).

Analytic model:

$$\Delta W_{R1\text{-}FU60} = \beta_0 + \beta_1 PCA + \beta_2 PCC + \beta_3 ITA + \beta_4 ITC + \beta_5 \Delta W_{E\text{-}R1} + \Sigma \beta_i X_i \ , \qquad (3)$$

where PCA, PCC, ITA, and ITC are 0/1 indicators of the PC-Active, PC-Control, IT-Active, and IT-Control conditions, respectively, and the X_is are indicators for the four race-gender groups and for site. Since weight changes are additive over time, this model can be rewritten as

$$\Delta W_{E\text{-}FU60} = \beta_0 + \beta_1 PCA + \beta_2 PCC + \beta_3 ITA + \beta_4 ITC + \beta_5^* \Delta W_{E\text{-}R1} + \Sigma \beta_i X_i \ , \qquad (4)$$

where $\beta_5^* = (\beta_5+1)$. The other coefficients in the two models are identical. Thus so long as we condition on phase 1 weight change, it makes no difference if we use as our outcome phase 2 plus phase 3 weight change or total weight change over the 66 months since entry. Aim #2 is evaluated by testing whether $\beta_1=0$.

SECONDARY AIMS

3. Compare the 60-month weight loss maintenance experience of the PC-Active versus PC-Control arms and of the PC-Control versus SD arms.

These analyses also can be tested using model (3). The β_1-β_2 comparison tests PC-Active versus PC-Control, while β_2 alone is used to test PC-Control versus SD.

4. Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight of an additional 12-months of IT intervention (IT-Active) compared to no further IT intervention (IT-Control).

Analogous to aim 1, this question asks, among the subset of IT participants who want to continue in such an intervention after an initial 30 months, whether doing so for an additional 12 months has any further benefit. The analysis will therefore be limited to the 277 IT participants from all four sites (i.e., including Portland) who were re-randomized into phase 3. It also will include the 277 PC participants from these sites who were re-randomized so that a single "unified" model can be fit that will allow us to test multiple hypotheses of interest.

We will assume an ITT analysis and use imputed values for all participants who do not provide a FU42 weight measurement.

Outcome variable = change in weight from R2 to FU42 ($\Delta W_{R2\text{-}FU42}$).

Analytic model:

$$\Delta W_{R2\text{-}FU42} = \beta_0 + \beta_1 PCA + \beta_2 ITA + \beta_3 \Delta W_{E\text{-}R2} + \Sigma \beta_i X_i \ , \qquad (5)$$

where again the X_is are indicators for the four race-gender groups and for site. Also as before, this model can be rewritten as

$$\Delta W_{E\text{-}FU42} = \beta_0 + \beta_1 PCA + \beta_2 ITA + \beta_3^* \Delta W_{E\text{-}R2} + \Sigma \beta_i X_i \ , \qquad (6)$$

where $\beta_3^* = (\beta_3+1)$ and the other coefficients in the two models are identical. Aim #4 is evaluated by testing whether $\beta_2=0$.

5. Compare the 42-month weight loss maintenance experience of the IT-Active and IT-Control interventions versus each other and versus the SD condition.

The unconditional analysis used to address this aim will parallel that used to address aims #2 and #3, but focusing only on data through FU42. A unified model will again be fit so that we can address a similar aim related to the PC intervention arms. Since Portland participated in the FU42 data collection, the analysis will include all 1032 randomized participants. Hence all IT and PC participants from Portland who were not originally re-randomized (41/191) will also need to be retroactively re-randomized as was done for the other sites. All SD participants are included, though they don't require re-randomization per se.

We will use an ITT analysis and use imputed values for all participants who do not provide a FU42 weight measurement.

Outcome variable = change in weight from R1 to FU42 ($\Delta W_{R1\text{-}FU42}$).

Analytic model:

$$\Delta W_{R1\text{-}FU42} = \beta_0 + \beta_1 PCA + \beta_2 PCC + \beta_3 ITA + \beta_4 ITC + \beta_5 \Delta W_{E\text{-}R1} + \Sigma \beta_i X_i \ , \qquad (7)$$

where PCA, PCC, ITA, and ITC are 0/1 indicators of the PC-Active, PC-Control, IT-Active, and IT-Control conditions, respectively, and the X_is are indicators for the four race-gender groups and for site. Since weight changes are additive over time, this model can be rewritten as

$$\Delta W_{E\text{-}FU42} = \beta_0 + \beta_1 PCA + \beta_2 PCC + \beta_3 ITA + \beta_4 ITC + \beta_5^* \Delta W_{E\text{-}R1} + \Sigma \beta_i X_i \ , \qquad (8)$$

where $\beta_5^* = (\beta_5+1)$ and the other coefficients in the two models are identical. Tests of $\beta_3=0$ and $\beta_4=0$ are used to evaluate the IT-Active vs. SD and IT-Control vs. SD contrasts, respectively, while a test of $\beta_3-\beta_4=0$ is used to evaluate the IT-Active versus IT-Control contrast.

6. Compare the 42-month weight loss maintenance experience of the PC-Active and PC-Control interventions versus each other and versus the SD condition.

Model (7) is also used to test these contrasts. Tests of $\beta_1=0$ and $\beta_2=0$ are used to evaluate the PC-Active vs. SD and PC-Control vs. SD contrasts, respectively, while a test of $\beta_1-\beta_2=0$ is used to evaluate the PC-Active versus PC-Control contrast.

7. Compare the 42-month weight loss maintenance experience of the PC-Active and IT-Active interventions.

Model (7) is also used to test this contrast as well. The relevant test is β_1-β_3=0.

8. Determine, among those willing to continue after the initial 30-months of intervention, the effect on weight at 60 months of an additional 12 months of IT intervention (IT-Active) compared to no further IT intervention (IT-Control).

This is the analog of aim #4 for FU60. Due to the fact that the IT-Active intervention was not continued beyond FU42, this aim will only be evaluated if we see a significant effect in aim #4. It can be evaluated by testing β_2=0 in model (1).

9. Compare the 60-month weight loss maintenance experience of the PC-Active and IT-Active interventions.

This is the analog of aim #7 for FU60. Due to the fact that the IT-Active intervention was not continued beyond FU42, this aim will only be evaluated if we see a significant effect in aim #7. It can be evaluated by testing β_1-β_3=0 in model (3).

EXPLORATORY ANALYSES

Additional exploratory analyses that are planned include subgroup analyses and correlates of 5-year weight change.

Power

Due to the now pilot nature of the Phase III analysis, with a very wide measurement window no power calculations are presented for this analysis.

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