

**Pactice Based Opportunities for Weight Reduction
(POWER) Trial
at Penn**

**PROTOCOL
Version 7.0**

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ASCVD	Atherosclerotic cardiovascular disease
CCA	Clinical Care Associates
CHD	Coronary heart disease
CHF	Congestive heart failure
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements and the applicable regulatory requirements.
CRF	Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CS	Clinically significant
CV	Coefficient of variation
CVD	Cerebrovascular disease
DPP	Diabetes Prevention Program
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
End of Study (Trial)	End of study (trial) is the date of the last visit shown in the Study Schedule of the last participant active in the study.
GCP	Good clinical practice
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
Interim Analysis	Any analysis intended to compare treatment groups at any time prior to the formal completion of a trial.

IRB	Institutional review board: a board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the participants participating in a clinical trial are protected.
LC	Lifestyle Coach
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
NCS	Not clinically significant
PCP	Primary care provider
PI	Principle Investigator
PRC	Protocol Review Committee
PVD	Peripheral vascular disease
RV	Randomization visit
Study Terms	Screen The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained
	Consent/Enter The act of obtaining informed consent for participation in a clinical trial from participants deemed eligible or potentially eligible to participate. Participants entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
	Enroll/Randomize The act of assigning a participant to a treatment. Participants who are enrolled in the trial are those who have been assigned to a treatment.
SV1	Screening Visit 1 (first screening visit)
SV2	Screening Visit 2 (second screening visit)
T2DM	Type 2 diabetes mellitus
V6	Six month study assessment visit
V12	Twelve month study assessment visit
V18	Eighteen month study assessment visit
V24	Twenty-four month study assessment visit

1. ABSTRACT

Obesity, defined by a body mass index (BMI) ≥ 30 kg/m², affects more than 31% of American adults. Additionally, nearly one-quarter of U.S. adults meet criteria for the metabolic syndrome, a clustering of clinical signs (i.e., elevated waist circumference, blood pressure, glucose or triglycerides, decreased HDL cholesterol) that is associated with increased risk of cardiovascular death. Behavior modification programs and pharmacologic interventions for obesity typically result in an 8% to 10% loss of initial body weight. Losses of this magnitude are associated with clinically significant improvements in metabolic parameters among obese persons. The availability of traditional behavioral weight control programs, however, is limited as many of these programs are based in academic medical centers. Furthermore, pharmacotherapy is seldom covered by third-party payers. Thus, there are concerns about the accessibility of these interventions to the many obese individuals who could benefit from weight loss.

The purpose of the proposed study is to improve the management of obesity in primary care practice, where obesity is commonly encountered but infrequently addressed. Three hundred and ninety persons at 6 primary care practices within the University of Pennsylvania Health System will be randomized to one of three 2-year interventions: Usual Care, Brief Lifestyle Counseling, or Enhanced Brief Lifestyle Counseling. After training in obesity management and intervention strategies, each site will enroll approximately 65 individuals with a BMI of 30-50 kg/m² plus two or more components of the metabolic syndrome. Participants in the Usual Care condition (N=130) will receive educational materials plus quarterly visits with a primary care provider (PCP). Those in the Brief Lifestyle Counseling condition (N=130) will receive the same PCP visits, plus 26 brief counseling sessions with an auxiliary health care provider (e.g., a medical assistant), on-site or by phone. Participants in the Enhanced Brief Lifestyle Counseling condition (N=130) will additionally receive the same treatment as those in the Brief Lifestyle Counseling group, plus the choice of adjunctive meal replacements or pharmacotherapy.

Two-year changes in weight will be compared across groups. Participants who receive the Brief Lifestyle Counseling and the Enhanced Brief Lifestyle Counseling interventions are predicted to achieve greater weight loss than those who receive Usual Care. A secondary hypothesis is that participants in Enhanced Brief Lifestyle Counseling condition will lose significantly more weight at month 24 than participants in the Brief Lifestyle Counseling group. Secondary analysis will also compare changes in the metabolic syndrome (and its individual components), mood, quality of life, dietary intake, eating behavior, appetite, physical activity and sexual function, as well as cost-effectiveness, among the three conditions. Intervention protocols and study results will be disseminated to other health care providers and payers.

Relevance

The availability of evidence-based weight management programs is limited. This study will test the effectiveness of weight loss therapies delivered in primary care settings. The results of this study have the potential to influence the standard of care for obesity and the metabolic syndrome, thereby improving the general public's access to evidence-based care of these very prevalent conditions.

2. SPECIFIC AIMS

The goal of this research is to improve the management of obesity in primary care practice through the adaptation and extension of a theory-guided behavioral intervention that was successfully employed in the Diabetes Prevention Program. In this latter investigation, diet and exercise counseling were provided to study volunteers by highly trained registered dietitians and other staff in academic medical centers. Both patients and staff were highly selected. The proposed study, by contrast, will be conducted in six primary care practices. Weight management will be provided to a total of 390 obese patients (who have 2 or more components of the metabolic syndrome) by their own primary care providers, in conjunction with the practices' auxiliary health professionals, including medical assistants.

All participants in this 3-arm, 24-month randomized controlled trial will receive Usual Care from their primary care providers (PCPs). Usual Care visits will be scheduled approximately quarterly, will address the management of any obesity-related co-morbidities, and will include handouts on weight management. In addition to these PCP visits, participants assigned to a second condition, Brief Lifestyle Counseling, will have individual monthly, 10-15 minute visits with a medical assistant who will support participants' efforts to modify their eating and activity habits, following a curriculum adapted from the Diabetes Prevention Program. Medical assistants will weigh participants at each visit and review their food and activity records. Participants in a third condition, Enhanced Brief Lifestyle Counseling, will receive the same program of PCP visits and of diet and activity modification from the medical assistant. In addition, they will receive either meal replacements or weight loss medication to improve the induction and maintenance of weight loss (as proven effective in previous studies). The choice of meal replacements or medication will be left to participants in consultation with their PCP.

Primary Aims

- 1) To test the hypothesis that the Brief Lifestyle Counseling condition is more effective than the Usual Care intervention in reducing weight (kg) at 24 months and to estimate the magnitude of the effect.
- 2) To test the hypothesis that the Enhanced Brief Lifestyle Counseling condition is more effective than the Usual Care intervention in reducing weight (kg) at 24 months and to estimate the magnitude of the effect.

Secondary Aims

- 3) To test the hypothesis that Enhanced Brief Lifestyle Counseling is more effective than Brief Lifestyle Counseling alone in reducing weight (kg) at 24 months and to estimate the magnitude of the effect.
- 4) To test the hypothesis that the pooled Lifestyle Counseling conditions (i.e., Brief Lifestyle Counseling plus Enhanced Brief Lifestyle Counseling) are more effective than the Usual Care intervention in reducing weight (kg) at 24 months and to estimate the magnitude of the effect.
- 5) To compare the effects of the three treatment conditions (each pairwise contrast in specific aims 1-3) on a selected set of cardiovascular disease-related outcomes at 24 months:
 - a) prevalence of the metabolic syndrome and its individual components
 - b) glucose, insulin, and insulin resistance (as estimated by HOMA)
 - c) high sensitivity C-reactive protein (hsCRP)
 - d) lipid levels (LDL-C, HDL-C, and triglycerides)
 - e) blood pressure
 - f) waist circumference

- 6) To compare the effects of the three treatment conditions (each pairwise contrast in specific aims 1-3) on a selected set of measures that assess the following psychosocial and behavioral variables:
 - a) mood
 - b) health-related quality of life
 - c) sexual function
 - d) dietary intake
 - e) appetite and eating behavior
 - f) physical activity
- 7) To estimate the direct costs of implementing all three interventions and to conduct a cost-effectiveness analysis.

Other Aims

- 8) To conduct the above aims using outcome data at months 6 and 12
- 9) To conduct the above aims using % change in initial body weight
- 10) To conduct subgroup analyses based on age, gender, ethnicity, and education
- 11) To disseminate the results of the trial

3. BACKGROUND AND SIGNIFICANCE

Obesity is one of our nation's most pressing public health problems. Fully 31% of adult Americans are now obese,¹ as judged by a body mass index (BMI) of 30 kg/m² or greater, and an additional 35% are overweight, defined as a BMI of 25-29.9 kg/m². As a result, millions of Americans now suffer from weight-related health complications that include coronary artery disease, non-insulin dependent diabetes, several cancers, and osteoarthritis which cost our nation approximately \$100 billion a year.²⁻⁵

Health Benefits of Modest Weight Loss

A large body of literature has shown that a loss of 5% to 10% of initial weight is associated with significant reductions in cardiovascular risk factors including blood pressure, blood glucose, triglycerides, and LDL cholesterol.⁶⁻⁸ Intentional weight loss also appears to be associated with a reduced risk of cardiovascular mortality, as suggested by observational studies.^{6,9,10} The Look AHEAD (i.e., Action for Health in Diabetes) study is currently investigating this hypothesis in a 12-year, randomized trial of 5,000 overweight individuals with type 2 diabetes.^{11,12} The study is powered to detect an 18% difference in time to occurrence of both fatal (and nonfatal) myocardial infarction and stroke in persons assigned to a control group (i.e., Diabetes Support and Education) or a lifestyle intervention, designed to induce a loss of $\geq 7\%$ initial weight and to increase physical activity to ≥ 175 min/week. Look AHEAD builds upon findings of the Diabetes Prevention Program (DPP), which has provided the strongest evidence to date of the health benefits of lifestyle modification.⁸ Overweight participants with impaired glucose tolerance who lost approximately 7% of initial weight and exercised 150 minutes a week decreased their risk of developing type 2 diabetes by 58%, compared to control participants, and by 31% compared with individuals treated with metformin. Improvement was observed across all age, gender, and ethnicity subgroups. The lifestyle intervention also was associated with a significantly greater reduction in the incidence of metabolic syndrome, as compared with both metformin and placebo.¹³

Metabolic syndrome. As defined by the National Cholesterol Education Program (Adult Treatment Panel III),¹⁴ the metabolic syndrome is characterized by having three of the following five characteristics: 1) waist circumference > 88 cm in women or >102 cm in men; 2) triglycerides ≥ 150 mg/dl; 3) fasting blood sugar ≥ 110 mg/dl; 4) blood pressure $\geq 130/85$ mm Hg; and 5) high density lipoprotein (HDL) cholesterol < 40 mg/dl in men or < 50 mg/dl in women. Approximately 24% of adult Americans meet the criteria for metabolic syndrome, with rates increasing to 44% in persons 60 years or older.¹⁵ The metabolic syndrome is associated with an increased risk of developing type 2 diabetes, as well as with increased risk of mortality from cardiovascular disease.^{16,17} Recent findings showed that the combination of type 2 diabetes and metabolic syndrome was associated with a 2-fold increased risk of cardiovascular death in women, and a 1.5-fold increase in men, as compared with the risk conferred by type 2 diabetes alone.¹⁶ Other studies have found similarly increased risks associated with metabolic syndrome,¹⁷⁻²⁰ leading the National Heart Lung and Blood Institute (NHLBI) and the American Heart Association to call for the management of this condition.¹⁶ Among obese individuals seeking weight reduction therapy, 40% to 68% of individuals have been found to have the metabolic syndrome.^{13,21,22} Weight loss is associated with significant remission in the prevalence of metabolic syndrome.^{13,21,22}

Current Status of Obesity Management

Lifestyle modification. A program of diet, physical activity, and behavior therapy (i.e., lifestyle modification) is the cornerstone of treatment for most obese individuals,²³ as recommended by the NHLBI's Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.²⁴ In trials conducted in academic medical centers, persons treated by a 1200-1500 kcal/d diet, combined with regular exercise and a comprehensive program of group or individual lifestyle modification, lose approximately 7%-10% of initial weight in 20-26 weeks.^{25,26} Lifestyle modification has been incorporated in popular commercial programs such as Weight Watchers,²⁷ which was found in a randomized trial to induce a loss of 5.3% of initial weight in the

first 26 weeks (and 3.3% at year 2).²⁸ Diet and exercise interventions are increasingly delivered by Internet programs, the most effective of which has induced a loss of about 4% of initial weight in 6 to 12 months.^{27,29,30} The reduced efficacy of lifestyle modification in these two cases is probably attributable to the use of large group sessions (50 or more people) which limit individual attention (in Weight Watchers) and to the lack of frequent, face-to-face weigh-ins (in Internet programs) which improve participants' adherence to diet and activity recommendations.³¹

Pharmacotherapy. Following the NHLBI's stepped care algorithm for obesity treatment,²⁴ pharmacotherapy is an option for persons who have a BMI ≥ 30 kg/m² (or ≥ 27 kg/m² in the presence of comorbid conditions) and who are unable to lose 10% of initial weight with lifestyle modification alone. Two medications are currently approved by the Food and Drug Administration (FDA) for the "induction and maintenance of weight loss."³² Sibutramine is a combined serotonin-norepinephrine re-uptake inhibitor that acts in the hypothalamus to increase satiation (i.e., fullness) and decrease hunger, thus, reducing food intake and body weight.^{33,34} The medication is associated with mean increases in pulse of 4 to 5 beats per minute (BPM) and in systolic and diastolic blood pressure of 1 to 2 mm Hg, thus, making it inappropriate for persons with uncontrolled hypertension ($>140/90$ mm Hg) or with cardiovascular disease.³⁵⁻³⁸ These side effects can be controlled by monitoring vital signs regularly and by decreasing the dose of medication, typically from 15 mg/d to 10 or 5 mg/d. Orlistat is a gastric lipase inhibitor that reduces the absorption of fat contained in a meal by about 30%.^{37,39,40} The medication's principal side effects are gastrointestinal events (e.g., oily stools, flatulence with discharge, fecal incontinence) that result from the drug's mechanism of action. Orlistat is provided in 120 mg capsules that are taken within 1 hour of meals. In the summer 2007, the FDA approved an over-the-counter version of orlistat, known as AlliTM, that comes in 60 mg capsules. The 60 mg dose, compared to the 120 mg dose, is associated with significantly fewer gastrointestinal side effects, as well as a 1% smaller weight loss at 6, 12, and 24 months (data on file, Roche Laboratories). These findings suggest that orlistat might be more acceptable to patients if introduced in the 60 mg dose. Users are advised to take a multi-vitamin supplement to avoid possible deficiency in fat soluble vitamins (i.e., A, D, E, and K).^{40,41} The side effects of orlistat may be reduced by patient's consuming no more than 20 grams of fat at a meal and limiting daily fat intake to 60 grams. Both sibutramine and orlistat, when combined with diet and exercise counseling, produce a loss of approximately 8% to 10% of initial weight in 6 months.^{32,34,40,41} Sibutramine appears to be more efficacious than orlistat, as revealed by meta-analyses⁴² and one head-to-head comparison.⁴³ Placebo-subtracted weight losses for the two medications are 4.5 kg and 2.9 kg, respectively.⁴²

Improving the Treatment of Obesity

Investigators are currently addressing three principal issues in weight management: 1) increasing the size of initial weight losses; 2) improving the maintenance of lost weight; and 3) increasing the availability of treatment. These issues are selectively reviewed here as they apply to the proposed study.

Increasing initial weight losses. Although losses as little as 5% of initial weight are associated with improvements in health, larger losses are generally associated with greater improvements in glycemic control,⁴⁴ blood pressure,⁴⁵ and lipids.⁴⁶ The use of portion-controlled servings of conventional foods,^{47,48} as well as liquid meal replacements,^{49,50} is effective in increasing initial weight losses by approximately 3 kg, as compared with the prescription of a self-selected diet of conventional foods with the same calorie goal. Portion-controlled servings, by providing foods of pre-determined quantity and energy content, reduce obese individuals' tendency to underestimate their calorie intake,²⁶ which has been found to be as great as 50% when a self-selected diet of conventional foods is consumed.⁵¹ The use of liquid meal replacements and snack bars contributed to the 8.6% reduction in initial weight achieved in the first year of the Look AHEAD study.⁵² The addition of pharmacotherapy to lifestyle modification also increases initial weight loss by approximately 4 to 6 percentage points (e.g., from 6% to 10%), compared with lifestyle modification alone.^{40,53,54,55} This additive benefit is observed whether participants receive a modest program of lifestyle modification (e.g., a few visits with a dietitian)⁵³ or a comprehensive program (i.e., weekly group meetings).⁵⁵

Improving the maintenance of lost weight. Weight regain remains the Achilles Heel of behavioral treatment.^{25,26,56} Obese adults, on average, regain one-third of their weight loss in the year following treatment, with increasing regain over time. Four treatment strategies have been shown to improve the maintenance of lost weight. The first is providing long-term patient-provider contact, following the period of initial weight loss. Perri and colleagues⁵⁷⁻⁶⁰ have shown in a series of studies that twice monthly contact, whether in person or by telephone or mail, significantly improves weight maintenance, compared with no contact. Second, high levels of aerobic activity (≥ 200 minutes/wk) are associated with improved maintenance of lost weight.⁶¹⁻⁶³ Recent research has investigated the efficacy of lifestyle activity for weight maintenance.⁶⁴⁻⁶⁶ Pedometers provide an excellent method of tracking lifestyle activity;⁶⁷ the goal is to increase the number of steps taken throughout the day, without regard for the intensity of the activity. Third, the long-term use of sibutramine and orlistat, significantly improves the maintenance of lost weight, as compared with placebo, for periods up to 2-4 years.^{34,40,68} Fourth, there is growing evidence that long-term use of meal replacements may facilitate the maintenance of lost weight. This was revealed by Flechtner-Mors et al,⁶⁹ who found that persons who replaced one meal and one snack a day with shakes or meal bars for 4 years maintained an 8% reduction in initial weight at the end of this time. Any effort to induce and maintain a loss $\geq 5\%$ of initial weight for 2 years should include one or more of these four strategies.¹²

Improving the availability of treatment through translational research. A third critical area of research is increasing the availability of weight reduction for the millions of Americans who need it. This includes translational research, designed to extend findings from randomized controlled trials to primary care and community practice,⁷⁰ as well as ensuring that interventions are culturally appropriate for different populations.⁷¹⁻⁷³ This is particularly needed with African-American and Hispanic-American women, in whom the prevalence of obesity is approximately twice as great as in Caucasians.^{1,73}

Management of Obesity in Primary Care Practice

Obesity is the most frequently encountered problem in primary care practice and the one least likely to be addressed. Primary care physicians, by their own report (or that of their patients) do not discuss weight management with 50% or more of their overweight and obese patients.⁷⁴⁻⁷⁸ Physicians' inactivity in this area appears to be attributable to multiple factors including providers' perceptions that: 1) discussing obesity is uncomfortable for both patient and provider; 2) most therapies are ineffective; and 3) treatment is not adequately reimbursed.⁷⁹⁻⁸³ Practitioners also believe they lack the training and time to provide adequate weight counseling.^{81,82} Many of these concerns are understandable when the interventions delivered in randomized trials (in academic medical centers) are examined more closely. The Diabetes Prevention Program is an excellent example of an efficacy study in which participants were provided intensive treatment, without regard for cost.⁸ During the first 26 weeks, each participant had 16 individual visits with a registered dietitian, followed by monthly contact in clinic or by telephone until the study's conclusion. Few primary care practices are equipped to provide such treatment.

Weight control in primary care practice. Numerous studies have shown that primary care providers, through brief interventions, can facilitate patients' efforts to stop smoking^{84,85} and reduce alcohol intake.^{86,87} By contrast, there has been remarkably little research on primary care interventions for weight management. Martin et al⁸⁸ recently reported a mean loss of 2 kg (in 6 months) in overweight and obese African-American women who had six brief (15 minutes) monthly visits with their primary care provider. Jeffery et al⁸⁹ similarly reported a loss of approximately 2 kg (at 1 year) in persons who participated in a 10-session weight control program that was delivered either by telephone or surface mail. While results of both studies are encouraging, mean weight losses probably would have been significantly greater (and more clinically significant) if participants had been asked to keep daily records of their food intake and physical activity (absent in Martin's study) and if they had "weighed in" at the clinic on a monthly basis (absent in Jeffrey's study). Multiple studies have shown that these two behaviors facilitate weight loss.^{31,55,90-92}

Two other investigations, conducted in primary care, obtained larger weight losses by providing participants weekly or twice monthly counseling from registered dietitians, combined with meal replacements.^{93,94} These, however, were efficacy studies that would be difficult to replicate in most primary care practices. The proposed study seeks to correct the shortcomings of these previous investigations and, by relying on the use of auxiliary health providers to support physicians, should provide weight management at a lower cost. We believe that auxiliary health care providers, such as nursing assistants and medical technicians, can be trained to provide weight counseling during brief contacts. This belief is based on findings that virtually all commercial weight loss programs (including Weight Watchers) employ lay persons who are trained by the company.²⁷ In addition, there appear to be few differences in the success of trained professionals versus lay persons in inducing weight loss.⁹⁵ Commercial programs hire persons who have natural empathy and enthusiasm and enjoy helping others.²⁷

Rationale for Present Study

The present study builds upon previous investigations at the University of Pennsylvania to improve the management of obesity through brief counseling visits, provided by an auxiliary health provider or primary care physician. A first investigation showed that obese participants who received a copy of the LEARN Program for Weight Control⁹⁶ and had 11 brief visits (5 to 10 min) with a research assistant, at which participants were weighed and provided a new set of food records, lost 3.3 kg (4.0%) in 52 weeks.⁹⁷ This study was conducted at the Center for Weight and Eating Disorders and has the potential bias of having selected highly motivated volunteers who were followed by experienced research assistants. Thus, our research team currently is conducting a follow-up investigation in two primary care practices at the Hospital of the University of Pennsylvania.⁹⁸ Obese individuals from these practices have been randomly assigned to a usual care condition, which includes quarterly medical visits with participants' own primary care provider, or to the same schedule of usual care combined with brief lifestyle counseling. During the first 6 months, this counseling consists of 8 brief visits (10-15 minutes) with a medical assistant (from the primary care practice) who provides instruction in weight management, following an abbreviated version of the Diabetes Prevention Program. A total of 33 participants have completed the first 6 months of treatment. Those assigned to Usual Care gained 0.1 kg (0.0%) at the end of this time, while those who received Brief Counseling lost 3.8 kg (4.3%). (This study serves as the basis for the Brief Lifestyle Counseling intervention in the proposed investigation.)

A third study from our group showed the benefits of combining the weight loss medication, sibutramine, with brief lifestyle counseling.⁹¹ Participants who were prescribed sibutramine alone lost 5.0 kg at the end of 1 year, whereas those who received medication combined with 8 brief lifestyle counseling visits, conducted by a primary care physician, lost 7.5 kg. Larger weight losses were associated with a greater reduction in the odds of having the metabolic syndrome.⁹⁹ (This study provides support for the Enhanced Brief Lifestyle Counseling condition in the proposed investigation.) We will offer participants in the present study the choice of meal replacements, sibutramine or orlistat as part of the Enhanced Brief Lifestyle Counseling arm. Sibutramine is slightly more efficacious than orlistat but also is usually associated with more significant adverse events, including increases in blood pressure and pulse.

4. RESEARCH DESIGN AND METHODS

This is a multi-site, randomized controlled trial, in which obese participants will be assigned to one of three conditions: 1) Usual Care; 2) Brief Lifestyle Counseling; or 3) Enhanced Brief Lifestyle Counseling (see study design Table 1, page 18). These three conditions will be compared on changes in body weight (kg), the prevalence of the metabolic syndrome (and its individual components), selected eating and activity habits, and psychosocial status. The primary hypothesis is that participants in Brief Lifestyle Counseling and Enhanced Brief Lifestyle Counseling will both lose significantly more weight at month 24 than participants in Usual Care. A secondary hypothesis is that participants in Enhanced Brief Lifestyle Counseling, by virtue of receiving either meal replacements or a weight loss medication, in addition to behavioral counseling, will lose significantly more weight at month 24 than participants treated by Brief Lifestyle Counseling alone. This third treatment condition represents an intensification of treatment, as proposed by the NHLBI weight management algorithm. The present effectiveness-oriented study seeks to reflect clinical practice in which physicians and patients can select from a variety of medications and diets in intensifying treatment. A traditional efficacy study would limit participants to the use of only one treatment option (e.g., sibutramine), which we wished to avoid in the present investigation, given its divergence from clinical practice. Both weight loss medications and meal replacements have been shown to increase mean weight losses by approximately 3 kg or more as compared with traditional lifestyle modification alone.

Study Sites

A total of 390 participants will be enrolled, approximately 65 at each of 6 primary care practices in the Clinical Care Associates (CCA) practices of the University of Pennsylvania Health System. These sites were chosen in collaboration with Dr. Ron Barg, executive director of the CCA. Each site has at least two full-time primary care providers (PCPs) and at least two potential Lifestyle Coaches (e.g., medical assistants or other auxiliary health care providers) who will be trained to deliver the intervention. Each of the practices was visited by the research team prior to their selection as a study site. Thus, each practice has shown an interest in treating obesity and has the personnel and space required to conduct the study. In addition, each site has agreed to undergo monthly training sessions in which the research team will lead discussions of obesity and its treatment, as well as review implementation of the study protocol (see Standardizing Delivery of the Interventions page 24). After the first two years of treatment, training meetings will continue to take place on a regularly scheduled basis.

Inclusion of Minorities. Study sites were selected from CCA practices throughout the greater Philadelphia region to ensure a diverse sample of participants, both by ethnicity and by socioeconomic status. We anticipate that approximately 70% of participants will be non-Hispanic white, 25% African-American, and 5% of other ethnic origin (Latino or Asian). We also will attempt to recruit at least 30% men to ensure that the results obtained can be generalized to both genders.

5. INCLUSION/EXCLUSION CRITERIA

We seek to enroll a sample of patients that is representative of those encountered in primary care practice, while ensuring the safety of participants during weight reduction. Thus, we aim to enroll individuals with controlled weight-related co-morbidities, such as type 2 diabetes, hypertension, and hyperlipidemia. Conversely, we will exclude individuals with a recent cardiovascular event, as well as those with serious internal organ disease, in whom weight loss is contraindicated. In addition, participants are required to have had a relatively stable weight prior to enrollment. Thus, individuals who have lost $\geq 5\%$ of initial weight in the 6 months prior to enrollment will be excluded. The detailed inclusion and exclusion criteria are listed below. The requirement that participants have at least 2 of the 5 components of the metabolic syndrome is expected to result in a sample in which approximately half of participants meet criteria for the full syndrome (at least 3 out of 5 components).

Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age ≥ 21 years
- BMI 30-50 kg/m² and weight ≤ 400 lbs.
- At least 2 of 5 criteria for metabolic syndrome
 - Elevated waist circumference (> 102 cm for men, > 88 cm for women)
 - Elevated blood pressure ($\geq 130/85$ mmHg)
 - Impaired fasting glucose (≥ 100 mg/dl)
 - Elevated triglycerides (≥ 150 mg/dl)
 - Low HDL cholesterol (< 40 for men, < 50 mg/dl for women)
- Willing to change diet, physical activity and weight
- Willing to accept randomization to each group
- Able to give informed consent
- Patient of participating PCP

Persons with the following conditions are eligible with PCP approval:

- Diabetes mellitus
- Prior CVD event > 6 months before randomization
- Stable CVD or peripheral vascular disease

Exclusion Criteria:

- Serious medical condition likely to hinder accurate measurement of weight, or for which weight loss is contraindicated, or which would cause weight loss (e.g., end-stage renal disease on dialysis, cancer diagnosis or treatment within 2 yrs)
- Prior or planned bariatric surgery
- Chronic use (at least past 6 months) of medications likely to cause weight gain or prevent weight loss (e.g. corticosteroids, lithium, olanzapine, risperidone, clozapine)

- Unintentional weight loss within 6 months of enrollment ($\geq 5\%$ of body weight)
- Intentional weight loss within 6 months of enrollment ($\geq 5\%$ of body weight)
- Pregnant or nursing within past 6 months
- Plans to relocate from the area within 2 years
- Another member of household is a study participant or staff in the trial
- Consumes > 14 alcoholic drinks per week
- Current use of illicit substances
- Psychiatric hospitalization in last year
- Psychiatric condition likely to impair adherence to treatment (e.g., schizophrenia)
- Blood pressure $\geq 160/100$ mmHg; patient may be re-screened in 1 month
- Principal Investigator or PCP discretion

6. RECRUITMENT

Participants will be recruited from six University of Pennsylvania Clinical Care Associates practices in the greater Philadelphia area. Approximately 65 participants (or potentially more) will be enrolled at each site, yielding 130 participants in each of the three treatment conditions (study-wide N = 390).

Participants will be recruited during routine office visits. The majority of candidates will be identified by a Penn research assistant, who will regularly review lists of patients scheduled for the upcoming week and note those whom are thought to be eligible for the study. Simultaneously, PCPs seeing patients at their routine medical visits will discuss the study with appropriate individuals, determine the patient's interest in participating, and, as appropriate, direct the patient to the research assistant (who will be on-site for approximately 2 to 3 half-days per week). In both cases, the research assistant will complete a brief Patient Eligibility Checklist (see Appendix 2), which will be attached to patients' charts and will be confirmed by the PCP. Once a patient has been confirmed to be eligible, the assistant will review with the patient the nature and requirements of the study and emphasize that, in order to participate, patients must be willing to accept randomization to any of the three conditions, one of which would require them to consume at least two meal replacements a day for the first 4 months (and at least 1 per day thereafter) or to use weight loss medications. Written informed consent will be obtained by the research assistant or a trained Lifestyle Coach, and the next visit will be scheduled. Research assistants will track, with the PCPs, the numbers of patients who were identified as eligible and who ultimately declined, were excluded from, or achieved enrollment in the study.

Candidates also will be recruited by IRB-approved brochures, flyers, letters and other methods in the individual practices. Information sessions and research-study open houses potentially also will be held. Announcements will describe the study and direct interested persons to contact the research assistant, either on site or by phone at the Center for Weight and Eating Disorders. These individuals will be screened to determine eligibility in the same manner as described previously. Patients who are considered appropriate, and are approved by their PCP, will then be directed to meet with the research assistant to give their written informed consent to participate. The disposition of these candidates will be tracked in the same manner as described previously.

Recruitment goals include approximately 25% African Americans and 30% male. Three of the CCA practices selected, treat principally African-Americans, and thus, should ensure that we achieve ethnic diversity. The study-wide research team, as well as the participating sites, will use special recruitment strategies, as needed, to encourage the enrollment of minorities and men, who are typically underrepresented in weight loss trials.

7. RANDOMIZATION AND MASKING

Randomization

Random assignment to one of 3 groups will be generated by a computer program after confirming that all screening activities have occurred, that the participant meets all eligibility criteria, and that all required baseline data have been collected. Assignment will be stratified by clinics to ensure balance within each clinic. Randomly varying block sizes (3, 6 or 9) will be used to prevent predictability of assignment.

Once the participants' eligibility has been confirmed, the Investigational Drug Service at the University of Pennsylvania will be notified by fax. The Investigational Drug Service will assign the participant to treatment and fax back the completed randomization assignment form. The completed form will include the participants' ID number, study site code and randomization kit number. The randomization kits will be stored at each primary care practice in a pre-designated secure location. Only research personnel directly affiliated with this study will have access to the randomization kits.

Masking

The research assistants who collect the outcome data will not be masked to the participants' intervention assignment. This is practically unfeasible given the limited number of study staff responsible for the collection of outcome data at the primary care sites. More importantly, such masking is not needed for the primary outcome of weight change, because weight is objectively measured with an electronic scale. In addition, the research assistants will collect outcome data without having knowledge of previously collected measures. This will prevent any digit bias that may otherwise occur.

8. INTERVENTION METHODS

Introduction

The interventions proposed in this study extend previous research that has shown that primary care practitioners, during brief office visits, can assist patients in changing health habits. These include curtailing cigarette smoking, increasing physical activity, and reducing body weight. The present study employs auxiliary health professionals (e.g., medical assistants) to provide weight management counseling in conjunction with primary care physicians. The study includes an evaluation of different intensities of obesity care, following a stepped-care algorithm proposed by the NHLBI.

Brief Overview of the Interventions

Participants will be randomly assigned to one of three treatment conditions with the following objectives. All interventions will last 2 years:

Usual Care. Participants in this group will receive usual medical care, provided by their own primary care providers (PCPs). PCPs also will provide participants recommendations for weight management at quarterly-scheduled visits. This condition includes what we believe is a stronger standard for weight management in usual care, (as compared with what is normally provided) against which the effects of the two other interventions will be compared.

Brief Lifestyle Counseling. These participants, like those in the first group, will receive usual medical care from their PCPs, at approximately quarterly sessions, and will receive the same recommendations for weight management. In addition, these participants will have brief, monthly sessions with a medical assistant who will instruct them in behavioral methods of weight management, following the protocol adapted from the Diabetes Prevention Program.

Enhanced Brief Lifestyle Counseling. These participants will receive the same intervention as those in the second condition, including quarterly PCP visits and monthly sessions with a medical assistant who will instruct them in lifestyle modification. These individuals also will select, in consultation with their PCP, the use of either meal replacements or weight loss medication, to facilitate the induction and maintenance of weight loss.

Theoretical Rationale/Model Underlying the Interventions

The two lifestyle interventions proposed in this study are derived principally from social cognitive and behavioral self-management theory. Both theories view participants as active problem solvers who are capable of regulating their affect, behavior, and cognition. Self-monitoring is used to identify times, places, emotions, people, and events associated with eating (or exercising) appropriately or inappropriately. Goal setting is facilitated by specifying behaviors to be adapted and when, where, how, and with whom they will be performed. Behavior change is reinforced by increased self-efficacy, by the inherent rewards in reaching a goal (i.e., weight loss or improved fitness), by social support (including encouragement from medical personnel) or by the use of external rewards. The provision of long-term treatment, including the addition of meal replacements and pharmacotherapy, recognizes that obesity, for most individuals, is a chronic condition that requires long-term care.

The delivery of the two interventions in primary care practice is guided by Wagner's Chronic Care Model. Using a team approach (i.e., PCPs and medical assistants), obese participants will be provided an evidence-based intervention (i.e., the Diabetes Prevention Program) that is translated to the demands of traditional office practice. Medical assistants will be trained to guide and support participants'

efforts to improve their eating behavior and physical activity. In this regard, the intervention seeks to engender a “productive interaction” between an “informed, activated patient” and a “prepared, proactive treatment team.”

COMMON GOALS AND METHODS ACROSS THE INTERVENTIONS

Table 1 below summarizes: 1) the schedule of participants’ intervention contacts; 2) the diet, activity, and lifestyle modification prescriptions for each intervention; and 3) other shared characteristics. As seen, participants in all three conditions will have brief quarterly visits with their PCP at which they will receive usual care for existing medical conditions. All participants also will receive the same diet and activity prescriptions, and accompanying handouts, but only those in the Brief Lifestyle Counseling and Enhanced Brief Lifestyle Counseling groups will meet with the medical assistant to develop behavioral strategies to meet these recommendations. Participants in the two lifestyle counseling groups will receive the same program of treatment, delivered on the same schedule, with one exception. Participants in the Enhanced Brief Lifestyle Counseling group, in consultation with their PCPs, will select either meal replacements or pharmacotherapy as part of their intervention.

Table 1. Comparison of Three Treatment Conditions

Treatment Component	Usual Care	Usual Care + Brief Lifestyle Counseling	Usual Care + Enhanced Brief Lifestyle Counseling
Quarterly Visits with Primary Care Provider	√	√	√
NHLBI Handouts: “Aim for a Healthy Weight”	√	√	√
Dietary goal: Kcal goal based on body weight	√	√	√
Exercise goal: ≥ 180 min/week of moderate intensity activity	√	√	√
Record Food Intake and Activity		√	√
Brief Monthly Counseling Sessions with Medical Assistant		√	√
DPP Lifestyle Modification Curriculum		√	√
Meal Replacements*			√
FDA-Approved Weight Loss Medication*			√

* Participants in this group will select the use of meal replacements or medication.

DESCRIPTION OF THE THREE INTERVENTIONS

Usual Care Condition

Goals. This condition will serve as a control group against which the efficacy of the two lifestyle counseling interventions will be assessed. It is intended to reflect usual medical care, while also meeting the needs of patients participating in a randomized controlled trial.

Description and delivery of the intervention. Participants in this group will receive usual medical care from their PCPs (for existing conditions). In addition, PCPs will provide general recommendations for weight management, based on nine handouts from “Aim for a Healthy Weight,” developed by the National Heart, Lung, and Blood Institute (NHLBI). The provision of the NHLBI

materials may be viewed as increasing the standard for weight management during usual care visits. In addition, the provision of “Aim for a Healthy Weight” should reduce participants’ likelihood of seeking treatment elsewhere during the 2-year study.

Frequency, duration, and format of intervention contacts. Participants in this condition will meet approximately quarterly with their PCP (at months 0, 3, 6, 9, 12, 15, 18, 21, and 24) during the 2-year trial. (A time window of ± 6 weeks is acceptable for scheduling of visits.) This schedule of visits was selected in consultation with several PCPs and is believed to approximate the number of yearly visits made by obese individuals with two or more components of the metabolic syndrome (as required in this study). Additional visits, required by emergent medical issues, are expected in a subset of patients but, otherwise, participants in all three conditions will attend visits on approximately this schedule. These visits, which are expected to last approximately 15 minutes each, will focus largely on the management of weight-related co-morbidities (including components of the metabolic syndrome) and any other medical concerns that participants present. However, weight management also will be briefly addressed at each scheduled visit, with PCPs providing a handout from NHLBI’s “Aim for a Healthy Weight” booklet. PCPs will review and respond to patients’ weight changes (e.g., “Congratulations on your weight loss”) but will not provide specific techniques or instructions to facilitate behavior change or weight loss (e.g., recommend the use of food or activity records). In addition, PCPs will not recommend the use of meal replacement products or prescribe weight loss medication.

Dietary goals. Participants in all three conditions will be prescribed a daily calorie goal based on body weight. Following recommendations of the Diabetes Prevention Program, persons who weigh ≤ 114 kg (≤ 250 lb) will be prescribed 1200-1499 kcal/d and those ≥ 114 kg (≥ 250 lb) 1500-1800 kcal/d. All participants will be encouraged to aim for the lower end of their range. Usual Care participants will be instructed to consume a diet of conventional table foods with $< 30\%$ of calories from fat (including $< 10\%$ from saturated fat), approximately 15%-20% of calories from protein, and the remainder from carbohydrate. This includes a goal of consuming up to 2.0 cups of fruits and 2.5 cups of vegetables a day. Participants in this group will be provided a calorie guide (e.g., Calorie King) to use as they wish.

Physical activity goals. Participants in all three conditions will be instructed to engage in moderately intense physical activity (principally walking or similar aerobic activity), building to ≥ 180 minutes a week in the first 6 months. At month 6, participants also will be provided pedometers. They will be instructed to gradually increase to 10,000 or more steps/day by the end of year 2. Following guidelines of the American College of Sports Medicine and Centers for Disease Control (ACSM/CDC), participants also will be informed of the benefits of strength/resistance training. They will be provided handouts that illustrate simple methods of engaging in strength training at home.

Lifestyle modification goals. The “Aim for a Healthy Weight” booklet provides information about decreasing portion sizes, reducing fat in the diet, practicing stimulus control, self-monitoring and related topics. Participants will be provided readings but no instructions in adopting such behaviors. Participants will also receive a Community Resource Guide. The Resource Guide will list community resources, physically near each practice, that may facilitate participants’ efforts to lose weight and increase their activity. Exercise resources, for example, might include a list of parks, community centers, and commercial fitness centers. The guide will be distributed to all participants upon enrolling in the study.

Assessment of participants’ adherence to Usual Care. Participants’ adherence to this treatment condition will be assessed by tracking their attendance of scheduled visits with their PCP. Additional sick visits also will be tracked by reviewing participants’ medical charts at regular intervals.

Brief Lifestyle Counseling Intervention

Goals. The goals of this intervention are to induce a loss of 5% or more of initial weight and to increase participants' physical activity to ≥ 180 minutes per week and to maintain these improvements over 24 months. These goals will be achieved by providing participants a program of lifestyle modification, delivered by a medical assistant in conjunction with the patient's PCP.

Description and delivery of the intervention. Participants in this group will meet with their PCPs on the same schedule as those in the Usual Care group and receive the same attention for their co-morbid conditions, as well as the weight management handouts.

In addition to Usual Care, participants in this condition will receive a program of lifestyle modification based on the curriculum used in the Diabetes Prevention Program (DPP). The lifestyle modification program will be delivered to participants during brief, approximately monthly individual visits conducted by medical assistants (Lifestyle Coaches). We elected to use the DPP materials because they have been shown to be effective across a wide range of participants and provide tailored dietary menus for African Americans and other ethnic minorities. The DPP materials have been adapted for delivery in primary care practice by medical assistants and have obtained a loss of approximately 3.8% of initial weight during 6 months of treatment.⁹⁸

Frequency, duration, and format of intervention contacts. During the first year, participants will have 14 lifestyle counseling sessions, scheduled at approximately monthly intervals (i.e., at months 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12). Each visit will last approximately 10 to 15 minutes and will begin with participants being weighed and informed of their weight change. At each visit, the participant and Lifestyle Coach (i.e., medical assistant) will review the participant's completion of food and activity records since the previous visit. This will include examining the number of calories consumed and minutes walked each week, as well as any other homework assignments. The Lifestyle Coach will assist participants with problem solving and will then introduce the lesson from the DPP curriculum to be completed for the next visit. Participants will receive enough food and activity records to last until their next visit. Participants will have a window of ± 2 weeks to complete all sessions. Visits that cannot be completed on-site (because of illness, travel, etc.) may be completed by phone.

During the second year, participants will have 12 (i.e., approximately monthly) lifestyle counseling sessions. At least six will be scheduled in-person visits, with the option of conducting others by phone. Visits during the second year will follow the same structure as those during the first. In addition to these scheduled meetings over the 2 years, all participants in this condition will have the opportunity to "drop in" at their clinic to measure their weight. For example, a clinic might designate Thursday from 5 to 6 PM as the drop-in time at which participants could stop by to measure their weight.

Dietary goals. Dietary goals for this condition are the same as those described for the Usual Care condition (based on the DPP). The principal difference between the Usual Care and Brief Lifestyle Interventions conditions is that participants in the latter group will be instructed, for at least the first 6 months, to record daily all foods and beverages consumed. This will begin at the first meeting with the Lifestyle Coach (at week 0). At the second meeting (Week 2), participants will be instructed to record their calorie intake with the assistance of the calorie guide provided (e.g., Calorie King). Food records will be reviewed at each meeting to determine participants' success in meeting calorie goals, and problem solving will be used to facilitate adherence. Over time, participants also will monitor the times, places, and activities associated with their eating. The Lifestyle Coach also will help participants develop an eating plan in which they consume breakfast, lunch, and dinner, with snacks as needed. Snacks will include fruits and vegetables to meet the goals described previously. Participants also will be provided meal plans (from the DPP) that suggest choices for breakfast, lunch, dinner, and snacks.

Participants' calorie goals will be evaluated after the first 6 months and adjusted appropriately based on an individual's desire to remain weight stable or to lose more weight. After month 6, participants also will be permitted to decrease the frequency of their record keeping (e.g., to only 3 days a week). This reduced schedule recognizes that even the most motivated participants have difficulty keeping weekly records after the first 6 months.

Physical activity goals. Participants in the Brief Lifestyle Counseling intervention will have the same activity prescription as those in Usual Care (i.e., increasing their activity to ≥ 180 minutes per week during the first 6 months). The principal difference between these two groups is that, at each visit, those in Brief Lifestyle Counseling group will be instructed to engage in aerobic activity (e.g., walking) for a specific number of minutes each day, building to ≥ 30 minutes/day, 6 days a week. Participants will be instructed to exercise at a moderate intensity so that they could talk comfortably with a partner while walking. They will record daily their type and duration of activity, including only bouts in which they have been active for ≥ 10 minutes (as used in Look AHEAD). Lifestyle coaches will review physical activity records with participants and provide suggestions for improving adherence.

Participants' activity goals will be re-evaluated after the first 6 months. Those who have met the 180 minute/week goal will be encouraged to increase to ≥ 200 minutes/week. Problem solving will be used to improve adherence in those who have not met the initial goal. These participants also will receive their pedometers at approximately month 6 and will be given the same step goals as persons in Usual Care. However, participants in the Brief Lifestyle Counseling condition will be given monthly step targets to help them reach 10,000 steps a day (by month 12). They will be instructed to keep daily records of their steps (and minutes of activity) from months 7 to 12. After this time, those who wish may decrease their recording (e.g. to 3 days a week, as discussed previously). Participants in this group also will receive the handouts that illustrate methods to increase strength/resistance training at home.

Lifestyle modification goals. The adapted DPP intervention will include other traditional lifestyle modification topics (e.g., challenging negative thoughts, obtaining social support), most of which will be accompanied by a homework assignment to be completed before the next visit with the Lifestyle Coach. An important behavior will be having participants weigh themselves at least once a week and record their weight. Regular self monitoring of weight appears to be critical in long-term weight management.^{31,63} Participants who do not have access to a scale for weekly weigh-ins will be provided an inexpensive bathroom scale.

These participants also will receive the Community Resource Guide, previously described, as well as the home strength training program. The home strength training program covers activities intended to help participants increase muscular strength and endurance and promote weight loss. It is a stand alone program that requires no further instruction.

Assessment of participants' adherence to Brief Lifestyle Counseling. Participants' adherence to this treatment condition will be assessed principally by tracking (i.e., recording) their attendance of scheduled visits with their PCP, as well as all sessions with their Lifestyle Coach. Drop-in visits, as well as sick visits, also will be recorded.

These participants will be informed of the need to keep food and activity records during the 2-year program. Participants who wish to do so will be given the opportunity to keep records prior to beginning the study to determine if they are acceptable to them. Adherence to the dietary goals can be broadly assessed during the first 6 months by counting the number of days each week that participants complete a food record. (This would be a tertiary analysis.) Records can be scored dichotomously (i.e., 0 or 1) to indicate whether the participant completed a record for the day in question. At least two meals must be recorded to receive credit for the day. (Our research team used this method in several previous

studies and found that the total number of days recorded correlated positively with weight loss.⁹¹) Food records kept after month 6 will be used principally for clinical purposes. Adherence to physical activity can be assessed during the first 6 months by counting the number of minutes of aerobic exercise per week that participants report in their activity diaries. Minutes can be summed for all aerobic activities (with equal weightings) to obtain a weekly value. During months 7 to 12, we can continue to count minutes of physical activity per week, as well as the total number of steps walked per day. Strength training will be counted separately from aerobic activity for participants who report it. Activity records after month 12 will be used principally for clinical purposes.

Enhanced Brief Lifestyle Counseling Intervention

Goals. The goals of this intervention are to induce a loss of 7% or more of initial weight, to increase participants' physical activity to ≥ 180 minutes or more per week, and to maintain these improvements over 24 months. These goals will be achieved by the provision of the same program of lifestyle modification, described in the previous section, which will be enhanced by the participants' use of either meal replacements or weight loss medications. This intervention provides a higher intensity of treatment, as proposed by the NHLBI's algorithm for the management of obesity.

Description and delivery of the intervention. Participants in this condition will have the same schedule of PCP visits and receive the same program of lifestyle modification as individuals in the Brief Lifestyle Counseling condition. These participants, however, will have been informed, as part of the consent process, of the use of meal replacements and weight loss medications. At the time of randomization, the research assistant will again review this information and answer any questions participants may have. At their first study visit with their PCP (i.e., week 0), physicians will again describe these two options, noting the potential benefits and risks of both meal replacements and weight loss medications. PCPs will discuss both sibutramine and orlistat, note any medical conditions that participants have that might contraindicate the use of either medication, and then answer any questions participants have. The PCP will ask participants to choose which approach they prefer (i.e., meal replacements vs. medications). Physicians will help participants make this choice by clarifying potential concerns about either approach and by offering an opinion if the participant asks for one. In either case, participants will not be scheduled to begin their adjunctive treatment until the third visit with their lifestyle Coach (at month 1) and, thus, they will have more time to consider their choice.

Participants who select meal replacements will be instructed by the PCP (at the week 0 visit) that they should replace two meals and one snack each day with portion- and calorie-controlled products (i.e., shakes and bars) for an initial period of 4 months, and one meal and one snack each day thereafter for the remainder of the 2-year study. This prescription is consistent with the lifestyle intervention in the Look AHEAD study. Participants will be provided written instructions on how and when to use meal replacements and will develop a daily schedule for consuming them. Additionally, at their week 2 visit with their Lifestyle Coach, they will be provided a sampler package that contains a variety of meal replacement products with 180-220 kcal per serving (e.g., Slim-Fast shakes, and Slim-fast meal bars) so that they can select products they will use regularly. At month 1, participants will inform their Lifestyle Coach of their chosen products and the products will be provided directly to them (at the clinic site or by shipping product to their home). A new supply of product will be provided every month.

Participants who choose the pharmacotherapy option will select from weight loss medications currently approved by the FDA for long-term use. These include sibutramine (Meridia™), orlistat (Xenical™), and Alli™, an over-the-counter version of orlistat that provides a 60 mg dose, rather than the 120 mg dose contained in Xenical™. All patients who elect to take sibutramine will be scheduled for an ECG prior to beginning the medication (at week 4) to ensure that they do not have arrhythmias or occult heart disease that could be exacerbated by the medication. These participants also must have blood

pressure \leq 140/90 mm Hg (including controlled on medication). Resting heart rate must be \leq 85 beats per minute (BPM). In addition, PCPs will have the opportunity to meet with these participants at week 4 to review again the use of sibutramine and ensure that participants are medically appropriate for the medication. Participants will be provided a prescription for 10 mg/d of sibutramine to be taken in the morning for year one of treatment intervention. After the first year, participants may be switched to the 15 mg dose if the PCP and participant wish to induce further weight loss (which typically plateaus by this time) or if participants are experiencing weight regain (of any magnitude). The prescription will be filled by the pharmacy at the Hospital of the University of Pennsylvania and mailed directly to participants. The Lifestyle Coach (i.e., medical assistant) will measure blood pressure and pulse on all sibutramine-treated patients at all subsequent counseling visits and inform PCPs of any occasions on which blood pressure has risen (\geq 10 mm Hg systolic or \geq 5 mm Hg diastolic) or pulse has increased (by 15% above baseline). PCPs will schedule additional visits with these patients, as needed, and will use dose reduction and stopping rules for medication developed by Dr. Robert Berkowitz, a co-investigator on the study who has extensive expertise in the pharmacologic treatment of obesity.

Participants who select orlistat will be instructed by PCPs at the week 4 visit to begin taking the medication 2 or 3 times per day with meals. (Patients who do not eat breakfast will not take the medication in the morning.) Participants will be started on the 60 mg dose to reduce the risk of adverse gastrointestinal side effects. After the first 6 months, participants may be switched to the 120 mg dose if the PCP and participant wish to induce further weight loss (which typically plateaus at this time). Participants will be encouraged to take a multivitamin approximately 2 hours after their evening dose of the medication. Orlistat will be prescribed for patients who select pharmacotherapy but whose blood pressure is greater than 140/90 mg Hg or whose pulse is greater than 85 BPM. Orlistat does not affect these parameters and, thus, orlistat-treated patients will not be required to have an ECG prior to treatment or undergo vigorous blood pressure monitoring. Lifestyle Coaches will review with these participants, at week 2, the need to reduce fat intake to no more than 20 grams per meal (60 grams per day) in order to prevent adverse gastrointestinal events (i.e., oily stools, flatulence, etc). In addition, participants who take either orlistat or sibutramine will be asked to keep a daily medication log. Patients on either medication will be provided monthly refills by the Hospital of the University of Pennsylvania. Use of all medications (including dates of initiation and discontinuation, as well as dose changes and adverse events) will be monitored throughout the 2-year intervention.

With the agreement of the PCP and Lifestyle Coach, during the trial, participants in the Enhanced Brief Lifestyle Counseling condition may switch between the meal replacement and pharmacotherapy options or may select different products within each category. Participants will not be provided more than one medication at a time or be provided meal replacements and medication simultaneously. A toolbox fund of \$1000/participant/year should be sufficient to cover the cost of either adjunctive therapy.

Frequency, duration, and format of intervention contacts. Participants in the Enhanced Brief Lifestyle Counseling intervention will have the same schedule of quarterly PCP visits as persons in the two other treatment conditions. Participants who elect to use orlistat or sibutramine will have an additional visit with their PCP at week 4 to review the use of the medication. Participants in this condition also will have the same schedule and type of sessions with a Lifestyle Coach as persons in the Brief Lifestyle Counseling group (i.e., at months 0, 0.5, 1, 2, 3, etc). At each visit, participants will review their success in meeting their diet and activity goals. In addition, those who take orlistat or sibutramine will keep a medication log and review their adherence with their Lifestyle Coach. The use of meal replacements will be recorded and reviewed in a similar manner. As noted, meal replacements and medications will be introduced at week 4, after participants have become accustomed to keeping food records, counting calories, and increasing their physical activity.

Dietary goals. Dietary goals for these participants are the same as those for persons in the Brief

Lifestyle Counseling condition, described previously. Participants who elect to use meal replacements will be instructed to replace two meals (typically breakfast and lunch) with a shake and replace one snack with a shake or meal bar. They will be encouraged to consume an evening meal of conventional foods and to add fruits and vegetables to their diet until they reach their daily calorie goal. All participants in this group will be provided the DPP meal plans to facilitate the selection of conventional foods. They will record all foods and beverages consumed, including their use of meal replacements, and calculate their daily calorie intake in the same manner as participants in the Brief Lifestyle Counseling intervention. Participants who elect to use orlistat or sibutramine will consume a diet of self-selected conventional foods, following the same methods as individuals in the Brief Lifestyle Counseling condition. Those who use orlistat will be counseled by the PCP and the Lifestyle Coach about the need to restrict their fat intake to no more than 20 grams per meal, to avoid the gastrointestinal symptoms associated with the medication.

Participants' calorie goals will be evaluated after the first 6 months and adjusted appropriately, as described previously. Individuals using meal replacements will be encouraged to replace one meal and one snack a day with meal replacement products for the remainder of the 2-year trial, to facilitate the maintenance of lost weight. Those who wish to lose additional weight, or to reverse small weight gains, will be allowed to periodically replace two meals and one snack with shakes and bars.

Physical activity goals. These participants will have the same physical activity goals and will be helped to achieve them in the same manner as persons in the Brief Lifestyle Counseling condition (as described previously).

Lifestyle modification goals. Participants in this condition will receive the same curriculum of lifestyle modification, Community Resource Guide, and home-strength-training program as those in the Brief Lifestyle Counseling intervention. As with the Brief Lifestyle Counseling group, participants will be instructed to weigh themselves at least weekly and to record their weight. Those without access to a scale will be provided one, as previously described.

Assessment of participants' adherence to Enhanced Brief Lifestyle Counseling. Participants will be informed of the need to keep food and activity records during the 2-year study. Participants who wish to do so will be given the opportunity to keep records prior to beginning the study to determine if they are acceptable to them. Diet and activity adherence in this condition can be assessed by the same methods used in the Brief Lifestyle Counseling intervention. In addition, adherence to meal replacements or medications will be assessed for at least the first 6 months.

DELIVERING THE INTERVENTIONS: QUALITY ASSURANCE AND CONTROL

Standardizing Delivery of the Interventions

The three interventions will be delivered following detailed protocols. For each participant visit, the protocol will instruct the PCPs and Lifestyle Coaches on the topics they are to cover with participants and the manner in which they are to do so. Participants in all three interventions will receive handouts at each visit, and providers will complete a checklist indicating they have provided the handout and followed other directions included in the protocol. Prior to initiating the study and delivering the intervention, all PCPs and Lifestyle Coaches will have completed an extensive training program, provided by staff at the Center for Weight and Eating Disorders. The training, in most cases, will be provided on site at each of the 6 participating practices.

Initial certification of PCPs. PCPs will be trained in delivering the protocol by the Supervising Physicians (or the PI) from the Center for Weight and Eating Disorders. Supervising Physicians will address topics that include how to broach the topic of obesity with patients and how to present and

explain the handouts that will be provided to all participants during their quarterly visits with their PCPs. Extensive attention will be devoted to educating PCPs about the use of orlistat and sibutramine. Prior to treating study participants, all PCPs will have been certified in delivering the interventions. Initial certification will be conducted by the Supervising Physicians who will observe each PCP providing sessions from the Usual Care and Enhanced Brief Lifestyle Counseling conditions to a confederate (i.e., University of Pennsylvania study staff) during a simulated treatment session (i.e., role play). Supervising Physicians will use a checklist (adapted from the Look AHEAD study) to assess PCPs' adherence to the protocol. PCPs will be certified when their performance meets criterion for each of at least two simulated sessions in each treatment condition. Feedback will be provided after each simulation, and additional certification sessions will be scheduled, if needed, until PCPs perform to criterion.

Ongoing monitoring and certification of PCPs. Throughout the first two years of the trial, PCPs will meet at least once a month (by phone or on site) with their Supervising Physician to review their adherence to the Usual Care and Enhanced Brief Lifestyle Counseling protocols. After the first two years of the trial, these training meetings will continue to take place on a regularly scheduled basis. Supervising Physicians will continually remind PCPs not to prescribe medications or meal replacements for participants in the Usual Care condition.

PCPs will be re-certified by the Supervising Physicians every 6 months. On each occasion, the Physician will observe (or listen to audiotapes of) two randomly selected sessions with patients from the Usual Care condition and two with patients from the Enhanced Brief Lifestyle Counseling condition. Supervising Physicians will rate the PCPs' adherence to the treatment protocol using a checklist (adapted from the Look AHEAD study). Detailed feedback will be provided to PCPs. The PCP must obtain acceptable ratings on each of the observations in each condition to be recertified in that condition.

Initial certification of Lifestyle Coaches. Lifestyle Coaches will be selected from among each practice's existing medical assistants, based on their warmth, strong interpersonal skills, and interest in weight management. The Lifestyle Coaches will receive an intensive program of training that, in most cases, will be provided on site by Lifestyle Coach Supervisors from the Center for Weight and Eating Disorders. Prior to reviewing the implementation of the protocol per se, Lifestyle Coaches will be provided background information on the causes and consequences of obesity, the prejudice and discrimination to which obese individuals are subjected, and empirically supported diet and exercise interventions for obesity. The training will then focus on how the Lifestyle Coaches will deliver the lessons contained in the curriculum adapted from the DPP. This will include training in developing a prescription for behavior change (i.e., what behavior is to be adopted and when, where, and how will it be practiced), as well as in using problem solving skills (to help participants when they encounter barriers to change).

Before treating study participants, Lifestyle Coaches will have been certified following the same methods used with the PCPs. For the Brief Lifestyle Counseling condition, Lifestyle Coach Supervisors will observe each Lifestyle Coach conducting the initial treatment session with a confederate (i.e., University of Pennsylvania study staff). For the Enhanced Brief Lifestyle Counseling condition, Lifestyle Coach Supervisors will observe each Lifestyle Coach conducting the third treatment session when meal replacements, orlistat, or sibutramine are introduced to the patient. Using a checklist (adapted from the Look AHEAD study), the Lifestyle Coach Supervisor will assess adherence to the protocol, as well as the Lifestyle Coach's interpersonal skills (e.g., communication style, rapport, empathic listening). Extensive feedback will be provided after each simulated session. Lifestyle Coaches will be certified in each intervention when they have a satisfactory rating on each of the treatment sessions.

Ongoing monitoring and certification of Lifestyle Coaches. Throughout the 2-year trial, Lifestyle Coaches will meet at least once a month (on site or by phone) with their Lifestyle Coach

Supervisor to review the protocol for the upcoming month and to discuss any clinical issues concerning participants. Supervisors will continually reiterate the importance of strictly adhering to the protocol and not introducing the use of meal replacements or medications with participants in the Brief Lifestyle Counseling group. Lifestyle Coaches will be recertified every 6 months for the duration of the study. On each occasion Supervisors will observe (or review audiotapes of) two randomly selected sessions from each of the two interventions (i.e., Brief Lifestyle Counseling and Enhanced Brief Lifestyle Counseling). Lifestyle Coaches must receive acceptable ratings on both tapes from each intervention to be recertified. Additional sessions and instructions will be added to train Lifestyle Coaches to criterion, if necessary.

Retention of Study Participants in the Intervention

All study visits, with both PCPs and Lifestyle Coaches, will be entered into the automated-scheduling system at each of the 6 practice sites. This will be done by office staff, in conjunction with the part-time research assistant at each practice site (who will be responsible for monitoring participants' visit attendance). The scheduling system will automatically prompt office staff to call patients to remind them of upcoming visits. In addition, it will track their completion of visits. In the event that a participant misses a visit, he or she will be contacted within 24 hours by the Lifestyle Coach or research assistant, and the visit will be rescheduled (preferably in the same week or the following week).

Retention will be further facilitated by the medical assistant and research assistant reviewing, on a weekly basis, all completed and upcoming visits. The research assistant will share the results of this meeting with study staff during a weekly administrative meeting at the Center for Weight and Eating Disorders.

We will employ a number of retention strategies that have been used successfully in previous long-term trials. Research and clinical staff at all sites will be instructed in methods of establishing a strong therapeutic relationship with participants. As an example, staff will send birthday and holiday cards to participants or small "weight loss milestone" gifts (e.g., University of Pennsylvania mugs or t-shirts). In addition, parking costs will be covered at all sites at which it is not free of charge. Finally, participants will be given a \$50 honorarium (i.e., in the form of a gift card or check) to cover the costs of time and travel required to complete outcomes assessments at baseline and months 6, 12, and 24 and a \$25 honorarium for the 18 month visits. Additionally, participants will receive \$25 if they are required to return to their PCP's office to repeat any part of a research visit if there is a problem with their lab draw, questionnaires or physical measures, and the research team needs to repeat any test to gather this missing information. In the event that a participant stopped attending treatment visits with the Lifestyle Coach, we still should be able to collect much of the outcome data during the participant's routine visits with his or her PCP.

9. DATA COLLECTION

MEASUREMENTS AND METHODS

Complete outcome data will be collected at two screening visits (SV1 and SV2), at a randomization visit (RV), and at follow-up visits at months 6, 12, and 24 (V6, V12, and V24). At the 18 month visit, physical measures will be assessed and medication usage will be updated, adverse events will be recorded and the participant will complete a participant cost follow-up questionnaire. The variables to be assessed and the measurements taken are described below.

Physical Measurements

Standardized equipment and protocols will be used to obtain physical measurements.

Weight. Weight is the primary outcome for this study and will be measured to the nearest 0.1 lb, in duplicate, at each assessment visit. Participants will be dressed in light indoor clothes without shoes. Each primary care clinic will be provided a Tanita BWB 800 digital scale, which will be calibrated monthly by the research assistant using standard weights, following the procedure defined in the Look AHEAD protocol. The participant will be instructed to stand still in the middle of the scale platform with head erect and eyes looking straight ahead. When the scale's display indicates that it has "locked" on a reading to the nearest 0.1 lb, the participant will be instructed to step off the scale. The research assistant will set the scale to zero, then repeat and record the weight measurement. If the two readings are discrepant, the above procedure will be repeated until two consecutive identical readings are obtained. Weight also will be measured at month 18.

Height. Height will be measured and recorded in cm at SV1 or SV2 and at V24 using a wall-mounted stadiometer. Body mass index will be calculated as kg/m^2 to verify eligibility. A Seca 202 wall-mounted stadiometer graduated in centimeters or millimeters, with a horizontal measuring block, will be provided to each clinical site. The participant will stand erect on the platform without shoes and with his/her back parallel to the vertical mounted measure scale (but not touching the wall). The participant will look straight ahead with feet flat on the floor and his/her head in the Frankfort horizontal plane [the horizontal plane is defined by the lower margin of the bony orbit (the bony socket containing the eye) and the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear)]. The horizontal measuring block will be brought down snugly, but not tightly, on the top of the head. The participant's height will be recorded to the nearest 0.5 cm (or 50 mm). The research assistant will instruct the participant to step away. The measuring block will be raised and the participant asked to return and repeat the measurement. Measurement of height will be repeated until two consecutive identical values are obtained.

Waist Circumference. A Gulick II Tape Measure (model 67020) will be used to obtain duplicate waist girth measurements to the nearest 0.1 cm at each assessment visit. This is a non-metallic, no-stretch, self-calibrating device that applies a known amount of tension (four ounces) to the measuring tape. A tension indicator minimizes subjective and measurement error. Participants will be standing with feet together and the measure will be taken around the abdomen horizontally at midpoint between highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line. The midpoint will be marked on both sides using a washable marker. (Participants may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position.) The tape will be aligned with the markings and positioned in the horizontal plane at the correct height. The research assistant will then mark the position of the tape on the participant's back in order to ensure proper placement for the second reading. The participant will be instructed to keep arms relaxed at the sides, breathe naturally, and, after breathing in and out, hold at the end of a normal exhalation. Appropriate tension will be ensured by

pulling on the end of the tensioning mechanism until the calibration point is just seen. The measurement will be taken from the tape's "zero line." Circumference will be recorded to the nearest 0.1 cm. The tape will be removed and the procedure repeated until two consecutive measurements within 0.5 cm are obtained.

Blood Pressure and Pulse. Blood pressure and pulse will be measured in triplicate at each assessment visit using the Omron HEM-907-XL automated sphygmomanometer. This study will use the same equipment and procedures for measuring blood pressure and pulse as were used in the OMNI-Heart study. Measurements will be taken at least 30 minutes after last consumption of caffeine or nicotine. Arm circumference will be measured on the bare upper arm (preferably the right arm), with participants standing and holding their arm parallel to the floor. First, length will be measured from the acromion (bony protuberance at the shoulder) to the olecranon (tip of the elbow), using a metric tape and the midpoint will be marked on the dorsal surface of the arm. Participants will then relax their arm along side of the body and a measuring tape (the same model used to measure waist circumference) will be drawn around the arm at the midpoint. Each site will have four cuff sizes available and a chart that indicates the appropriate cuff sizes for arm circumference. The chart will be attached to the sphygmomanometer for easy reference: small (arm circumference of 17-22 cm), medium (22-32 cm), large (32-42 cm), and extra large (> 42 cm). The participant will be seated in a quiet room with back supported, legs uncrossed, and the elbow and forearm resting comfortably on the table with palm turned upward. The brachial artery will be located by palpation and the skin marked with a felt-tipped marker. The cuff will be placed around the upper right arm (the left may be used if the right is compromised) with the midpoint of the length of the bladder positioned over the brachial artery. The mid-height of the cuff will be at heart level and the cuff should be tight enough that only one finger can be inserted between the cuff and arm. After the participant has sat quietly for 5 minutes, the sphygmomanometer will be set to take three readings, separated by 30-second intervals. Blood pressure and pulse, for a given visit, will be recorded as the mean of the three measurements. Blood pressure and pulse also will be measured at month 18.

Biochemical Measurements. Nine-hour fasting blood samples will be obtained at SV1 or SV2 and all subsequent assessment visits. Specimens will be processed and sent to a central laboratory for analysis of the following: comprehensive metabolic panel, complete blood count (at SV1 or SV2 only); lipid levels and lipoproteins (triglycerides, LDL-C, HDL-C, and total cholesterol); glucose; insulin; and high sensitivity C-reactive protein. Insulin sensitivity will be determined using the homeostasis model assessment (HOMA).

Metabolic Syndrome. The presence of metabolic syndrome (and whether participants meet threshold values for its individual components) will be assessed at screening (using values obtained at SV1 and SV2) and all subsequent assessment visits. The methods for obtaining these measures have been described previously. ATP-III guidelines will be used to determine whether participants meet criteria for metabolic syndrome and its individual components (i.e., waist circumference > 102 cm for men or > 88 cm for women; triglycerides \geq 150 mg/dL; HDL-C < 40 for men or < 50 for women; blood pressure \geq 130/85 mmHg; and fasting glucose \geq 110 mg/dL). The exception to this is fasting glucose, where we will accept a glucose \geq 100, following the most recent guidelines from the American Diabetes Association for impaired fasting glucose. A participant must meet at least two components of the metabolic syndrome to be eligible for the study (and three components must be present to meet criteria for the metabolic syndrome).

Questionnaires/Chart Abstraction

Demographics. A self-report demographic questionnaire will be administered at baseline to assess patient characteristics that include age, race/ethnicity, socioeconomic status (employment, education, and income), internet usage, health status, and health insurance status.

Medical History and Medication Usage. Participants will report medical conditions and medications at RV and all subsequent assessment visits to monitor any adverse events and changes, particularly in antihypertensive, antidiabetic, and lipid-lowering medications. Patients' medical charts will be reviewed periodically to ensure completeness of their reports.

Dietary Intake. Self-report measures of fruit, vegetable, and dietary fat intake will be administered at each assessment visit. The fruit and vegetable screener that will be used in this study was developed for the Eating at America's Table Study and assesses the frequency, variety, and portions of participants' fruit and vegetable intake in the past month. The fat screener was developed by the National Cancer Institute's Risk Factor Monitoring and Methods staff. It assesses the approximate percentage of energy from fat by asking participants to report the frequency with which specified high-fat foods were consumed in the past 12 months.

Appetite and eating behavior. Participants will use visual analogue scales to rate their hunger, fullness, cravings and related dimensions of appetite. The Eating Inventory will be used to assess cognitive restraint, disinhibition, and hunger.¹⁰⁵ These instruments will be administered at each visit.

Physical Activity. Physical activity will be measured at each visit using three questions from the College Alumnus survey (commonly known as the Paffenbarger Survey), which allow for calculation of self-reported leisure time, physical activity and kilocalorie expenditure per week.¹⁰⁶ Additionally, a five-part item from the Harvard Medical School Nurses' Health Study will be administered at each visit to assess the number of hours per week spent sitting or standing in various activities. This measure includes assessment of "monitor time" (e.g., time spent watching television/videos).¹⁰⁶

Mood. The Patient Health Questionnaire-8 will be used to measure symptoms of depression at SV2 for screening purposes and at all subsequent visits to assess changes from baseline. This is a shortened version of the PRIME-MD PHQ, which focuses exclusively on symptoms of depression.¹⁰⁷

Quality of Life. Quality of life will be measured at RV and all subsequent assessment visits with the Medical Outcomes Study Short Form 12 (SF-12) and the Impact of Weight on Quality of Life-Lite (IWQoL-Lite). The SF-12 (a shorter version of its parent instrument, the SF-36) measures overall health-related quality of life related to physical and mental health (e.g., mobility, activities of daily living, pain, mood), while the IWQoL-Lite is the short form of an obesity-specific measure of quality of life.^{108, 109} Both instruments will be used to measure changes in quality of life during the trial.

Sleep Quality. The Pittsburgh Sleep Quality Index will be used to measure sleep quality and the frequency of sleep disturbance over the past month.¹¹⁰ This self-report instrument will be administered at baseline and all subsequent assessment visits.

Sexual Function. Males and females will complete the International Index of Erectile Function and Female Sexual Function Inventory, respectively.^{111, 112} These widely used self-report measures will be completed at RV and all subsequent assessment visits.

Weight Terms Questionnaire. This questionnaire will be administered at RV only. It measures participants' preferred terms for describing their obesity.¹¹⁴

Economic Analysis. A one-page questionnaire will be administered to participants at RV and all subsequent assessment visits. This instrument will inquire about time spent to attend study visits, which will be converted to a per-hour cost based on the individual's occupation. The questionnaire also will ask about changes in costs for food and for physical activity (e.g., exercise equipment). The items for this

instrument are based on those used in the Diabetes Prevention Program. The EuroQoL-5D (EQ-5D) also will be given at all assessment visits, beginning with RV. The EQ-5D is a “health states preference” measure that estimates quality-adjusted life years (QALYs) and will be used to measure cost per QALY for the economic analysis.¹¹³

SCHEDULE

In addition to the study assessment visits (i.e., SV1, SV2, RV, V6, V12, V18 and V24), weight will be measured for clinical purposes at each treatment visit. Blood pressure also will be monitored at each treatment visit for participants in the Enhanced Brief Lifestyle Counseling group who take sibutramine. During V24, participants will be given the opportunity to sign an addendum to the consent form which offers participants the possibility of participating in a 36 month follow-up visit if study funds become available. This visit will follow the same format as the 24 month assessment visit.

SV1 will be conducted immediately after patients see their PCP for a routine clinical visit. The PCP will review patients’ medical histories and medications for inclusion/exclusion criteria (aided by a checklist), briefly assess patients’ interest in participating in the study, and refer patients to the on-site research assistant who will review eligibility and obtain informed consent. Consenting individuals will be scheduled for SV2, at which a fasting blood sample will be drawn. Screening weight, height, waist circumference and blood pressure may be measured at SV1 or SV2. Patients who remain eligible will be scheduled for the RV within 6 weeks. At the RV, participants will receive their group assignment and begin treatment. Given the proximity of the SV2 to RV, screening blood test results will serve as baseline values. Additionally, the screening height value will serve as the baseline value. Baseline values for weight, waist circumference, and blood pressure will be taken at RV. Table 2 below summarizes the data collection items and schedule.

Table 2. Study Visits and Measurements

Visit	SV1	SV2	RV	V6	V12	V18	V24
Month	-6 to -1 week	-6 to -1 week	0	6	12	18	24
Eligibility	X						
Physical Measurements*	X		X	X	X	X	X
Consent Addendum for 36 month visit							X
Demographics 1. Baseline Information 2. Weight Terms Questionnaire	X X						
Medical History	X						
Concomitant Medications	X		X	X	X	X	X
Adverse Events 1. Adverse Events Form 2. Interim Events Form 3. Serious AE Form				X	X	X	X
NCI Fat Screener			X	X	X		X
NCI Fruit & Veg Screener			X	X	X		X
Paffenbarger			X	X	X		X
PHQ-8 (Mood)		X	X	X	X		X
SF-12 (Quality of Life)			X	X	X		X
IWQoL-Lite			X	X	X		X
Eating Behaviors (EBQ)			X	X	X		X
Eating Inventory			X	X	X		X
Pittsburgh Sleep Quality Index (Sleep Quality)			X	X	X		X
EuroQol-5D			X	X	X		X
Patient Cost Baseline			X				
Patient Cost Follow-Up				X	X	X	X
Provider Baseline	X						
Practice Manager Baseline	X						
Cost of Intervention	To be administered monthly to study staff						
Erectile Function (EF)			X	X	X		X

Female Sexual Function Index (FSFI)			X	X	X		X
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* Physical measurements: Height (at SV1 or SV2 and V24), Weight, Waist Circumference, Blood Pressure and Heart Rate.

10. QUALITY ASSURANCE AND QUALITY CONTROL

Quality Assurance (QA) pertains to activities that promote collection of high quality data, while Quality Control (QC) pertains to activities that detect emerging issues. Our basic approach to QA is as follows:

- prepare a well-documented manual of operations
- implement a master-trainer model to train and certify other staff
- train and certify all primary data collectors, with special emphasis on procedures related to trial outcomes
- recertify data collectors at least annually
- establish proficiency requirements before initial certification of technicians
- routinely observe technicians
- routinely calibrate equipment
- pilot test new questionnaires and data collection procedures (particularly web-based data collection)
- develop individualized reports of completed tasks by visit, and
- maintain logs of certified staff and calibrated equipment

(Note that QA and QC procedures for the interventions are covered separately in the Intervention section.)

To identify problems with sufficient time to institute appropriate corrective actions and to quantify the quality of data collected during the trial, we intend to perform the following QC activities:

- monitor counts of completed visits and key data collection items
- monitor distributions of trial outcomes, overall, by technician and practice
- assess reproducibility of laboratory studies
- record lag time in data entry
- review quality of web-based data entry
- review types and distribution of data entry errors and
- prepare QC reports for staff, investigators, and oversight bodies (NHLBI and DSMB)

Certification and Recertification

The Penn research assistants responsible for data collection will be trained in study procedures for measuring weight, height, waist circumference, blood pressure and pulse, as well as procedures for ensuring eligibility and abstracting relevant data from participants' medical charts. Standardized procedures, manuals and educational materials will be developed. Research staff, Lifestyle Coaches, and Primary Care Providers will be certified and recertified in the use of study materials. Further details concerning quality assurance and quality control are provided in the Data Management section of the protocol and in Appendix 3.

In order to be certified in the measurement of weight, height, waist circumference, blood pressure and pulse, each Penn research assistant must obtain these measurements, using the procedures described above, for at least three non-participants (e.g., clinical site staff, study personnel, other volunteers). The master trainer or project manager will observe these measurements to certify the research assistants. Research assistants may not obtain these measurements for actual study participants until they have been certified in each procedure. Recertification of the master trainer will occur yearly and recertification of the research assistants will be required at 6-month intervals for the duration of the study. As with original certification, recertification of the research assistants will require observation by the study coordinator. However, measurement procedures only need be performed on two individuals and those individuals may be actual study participants.

Certification in chart abstraction methods also will be supervised by the project manager, who will select the medical charts of three participants and review the charts for inclusion and exclusion criteria, as well as medical history and medication usage. The initial review by the project manager will be guided by a form that queries for medical history (including diagnoses and treatments), medication changes, and the reasons for and outcomes of each contact with the health care system in the previous 6 months. The research assistant must review the same charts, using the same forms. Certification will be granted when research assistants have reviewed at least three charts, with 100% agreement with the study coordinator for at least two consecutive charts (additional charts will be reviewed if necessary to obtain perfect agreement). Research assistants will be recertified at 6-month intervals for the duration of the study. To be recertified, research assistants must obtain 100% agreement with the study coordinator for at least two consecutive, randomly selected, participant charts.

Certification in the completion of study source documents (e.g. adverse event forms, questionnaires, physical measurement forms) will be supervised by the project manager. Certification will be granted when research assistants have successfully administered, completed and reviewed the study documents for three “test” participants. Research assistants will be recertified through a random, 100% source document review, of three enrolled participants at 6-month intervals for the duration of the study.

Research assistants who fail certification or recertification on a given procedure will receive corrective feedback by the certifying observer and will not be permitted to obtain the corresponding measurements until certification or recertification criteria have been met.

11. SAFETY AND SAFETY MONITORING

Overview

The study will monitor the medical safety of participants. One aspect of this monitoring is to evaluate potential volunteers at screening to determine whether it is safe for them to participate in the planned intervention. Since this is an effectiveness trial conducted within primary care offices, safety evaluation will be done in close collaboration with the participant's PCP. PCPs in the study will be active members of the treatment team. They will be very familiar with the intervention that their patients are receiving.

Another aspect of safety is monitoring the safety of participants enrolled in trial. If a volunteer has a medical or surgical illness, the safety of continuing or resuming participation in interventions will be ascertained by the participant's PCP. Finally, surveillance for serious adverse events and other relevant clinical events will occur by interview at regularly scheduled intervals.

Potential Risks

The following sections describe potential risks associated with the study, along with procedures to minimize risk.

Physical activity. We recognize the need to minimize the potential risks of physical activity in previously sedentary individuals with CVD risk factors. In this study, the responsibility must be met in the context of a lifestyle modification intervention in which 1) primary care is provided 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 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 with their PCP if a participant wishes to progress to vigorous physical activity (as they would do in routine clinical care).

Nutrient intake. Calorie restriction can potentially lead to inadequate nutrition. To minimize this risk, participants will be encouraged to eat a variety of foods from all food groups and to maintain a moderate degree of calorie restriction (500-1000 calories/day) during the period of active weight loss. If severe caloric restriction is suspected (as noted by marked and prolonged weight loss) and is unresponsive to advice from the Lifestyle Coaches, the intervention will be suspended and the participant will be referred to the PCP. Patients will be advised that the consequences of marked and sustained caloric restriction include serious health risks, such as gallstones and/or cholecystitis.

Hypoglycemia related to exercise and lifestyle interventions. For participants who may be susceptible to hypoglycemia due to use of anti-diabetic medications, weight loss interventions have the potential to increase the risk of hypoglycemia, especially during the time when diet and/or physical activity interventions are implemented. Participants with diabetes will require approval from their PCP prior to enrolling. PCPs will be provided with an algorithm from the multi-center Look AHEAD trial for reducing medications prior to starting or during the study. The algorithm will be strongly emphasized among participants in the Enhanced Brief Lifestyle Counseling group who use meal replacements, as this group seems to have a higher risk of hypoglycemia. (This is not thought to be due to the composition of the meal replacements themselves, but rather because persons using meal replacements achieve a greater calorie deficit.) In addition, participants with diabetes will be educated about symptoms of hypoglycemia and instructed to self-monitor glucose levels more frequently during active weight loss. They will be urged to contact their PCP if they have symptoms or blood glucose values suggestive of hypoglycemia. Changes in diabetic regimens and overall management of diabetes will remain under the control of the participant's PCP.

Symptomatic hypotension related to exercise and lifestyle interventions. For participants who may be susceptible to hypotension because they are using medications that lower blood pressure, weight

loss interventions have the potential to increase the risk of hypotension, especially during the time when diet and/or physical activity interventions are implemented. Participants will be educated about symptoms of hypotension and urged to contact their PCP if they have symptoms suggestive of hypotension. In addition, research staff will contact the PCP for any participants receiving medication for blood pressure control, who develop symptomatic hypotension, to discuss adjustment or discontinuation of these medications. Changes in blood pressure regimens and overall management of hypertension remain under the control of the participant's PCP.

Pharmacotherapy. Participants assigned to Enhanced Brief Lifestyle Counseling will choose between meal replacements (e.g., Slim-Fast) or weight loss medication (orlistat, taken with meals, or sibutramine, 10 mg taken once daily during the first year, with the option of 15mg/day in the second year). Orlistat does not affect the central nervous system. Persons taking this drug, however, have a $\geq 10\%$ risk of experiencing the following side effects: headache; oily spotting (of stools); abdominal pain or discomfort; flatus with discharge; fecal urgency; fatty/oily stool; increased defecation; back pain; and upper respiratory infection. Participants who choose orlistat have a rare chance of severe liver injury. Participants should stop taking the medication and immediately report any signs and symptoms of severe liver injury include itching, yellow eyes or skin, fever, weakness, vomiting, fatigue, dark urine, light-colored stools, or loss of appetite to their primary care provider and research staff. Participants who have gastrointestinal side effects will be instructed to eat fewer than 20 grams of fat at each meal to avoid these symptoms. All participants taking orlistat will be instructed to take a multivitamin at night (separated by at least 2 hours from the dinnertime dose of the drug) to avoid the possibility of fat-soluble vitamin deficiency (Vitamins A, D, E, and K).

Participants who choose sibutramine are at a $\geq 10\%$ risk of experiencing the following side effects: headache; insomnia; dry mouth; anorexia; and constipation. However, the most clinically significant side effects of the drug are increases in blood pressure and pulse. All persons taking this drug will have blood pressure and pulse checked at least monthly during the first 3 months and at least quarterly thereafter. At each monthly visit, the Lifestyle Coach will report participants' blood pressure and pulse to the PCP. Patients who have sustained increases in blood pressure (≥ 10 mm Hg systolic or ≥ 5 mm Hg diastolic) or pulse rate ($\geq 15\%$) *after the first 3 months* will either be titrated down (from 10 mg daily to 5 mg daily) or, if necessary, be discontinued from drug. During the first 3 months, increases in blood pressure (up to 20 mm Hg systolic and up to 10 mm Hg diastolic) and pulse (up to a 20% increase) will be tolerated, as these often improve with time. These parameters for monitoring participants' vitals signs while on drug are based on four published studies of sibutramine conducted by the Penn investigative team, two trials in adolescents and two in adults.^{55, 90, 91, 101} However, PCPs will have ultimate discretion over the use of weight loss medications based on the participant's medical status.

Using the lower doses (5 mg or 10 mg) of sibutramine in the first year should limit the number of patients who experience significant increases in blood pressure or pulse. In addition, all participants using sibutramine will be carefully screened to ensure that they meet all of the following criteria:

- Blood pressure must be at goal on ≤ 3 anti-hypertensives
 - $< 140/90$ mm HG for general population
 - at goal for specific risk groups ($< 130/80$ mm Hg for diabetes or renal insufficiency)
- No history of CHD, CVD, PVD or CHF with the exception of diabetes
 - No evidence of prior MI on ECG, stress test, or echocardiogram
- No concomitant use of SSRI anti-depressants, stimulant agents (e.g., modafinil, methylphenidate), OTC weight loss medication/supplements, triptans for migraine, or lithium
- No ongoing arrhythmia that is clinically significant (e.g., atrial fibrillation)

Cardiovascular events. All participants with ASCVD will require approval from their PCP prior to enrolling. In addition, participants will be educated about CHD and CVD symptoms and urged to contact their PCP if they have a change in their symptoms. Overall, ASCVD management remains under the control of the participant's PCP.

Cardiovascular events also will be assessed as part of a standardized assessment for adverse events (AEs), conducted at months 6, 12, 18, and 24. When research staff learns that a cardiovascular event (including a procedure) has occurred, the intervention will be suspended, and the PCP will be contacted. The intervention may be resumed after approval from the participant's PCP.

Results of routine clinical labs and physical measures obtained as part of study visits will be provided to the participant and PCP, typically within 1 month. In addition, items meeting the criteria for "Alert Values" will be communicated more rapidly, as described in the table on the next page. Abnormal laboratory values not meeting alert value criteria will be handled as routine or more urgent, based on the opinion of study physicians and collaborating PCPs.

A study physician (or physician and nurse practitioner working together), with appropriate expertise, will be designated as the "Safety Officer(s)" and will review medical eligibility criteria, clinical measures, and laboratory reports. This individual also will serve as the primary contact for staff, participants, and their PCPs regarding medical issues. The Safety Officer also will be responsible for reviewing and reporting SAEs for the site, as detailed elsewhere. This person (or persons) will have appropriate back-up during vacations or other absences to provide continuous medical safety coverage for the duration of the study.

The Safety Officer will provide an additional layer of medical supervision, beyond that already provided by participants' own PCPs. Given that all three treatment interventions will be delivered by participants' PCPs (rather than by study personnel), PCPs will be very familiar with participants' medical status and will have the opportunity to learn from participants directly of any changes in health that occur as a result of the treatment provided. PCPs also will receive copies of all laboratory reports at the same time study staff receive them.

Research staff, as well as Medical Assistants (Lifestyle Coaches), also will be informed of "alert" values (for blood pressure and other conditions) that will require them to notify participants (and potentially PCPs and the Safety Officer) for intervention. These alert values are shown in the table below. Because all study outcome measures will be obtained at the participants' primary care practice, immediate medical attention should be available for level-1 blood pressure readings (> 180/110 mm Hg), significant symptoms of depression, or other concerning events. The Safety Officer will be informed of all events listed on the right-hand side of the table and will confer with appropriate PCPs to determine the resolution of the events.

<u>Alert Values</u>			
Measure	Alert Value	Notify Participant	Notify PCP/Safety Officer

Blood Pressure (Avg.)	Level 1 SBP \geq 180 mm/Hg OR DBP \geq 110 mm/Hg	In clinic. Advise to follow-up with PCP within 1 week.	Within 1 week. <u>IF symptomatic</u> (e.g. chest pain, headache, short of breath), notify safety officer and/or PCP immediately.
	Level 2 SBP \geq 160 mm/Hg OR DBP \geq 100 mm/Hg (and not Level 1 BP)	In clinic. Advise to follow-up with PCP within 1 month.	Within 1 week. <u>IF symptomatic</u> (e.g. chest pain, headache, short of breath), notify safety officer and/or PCP immediately.
	Level 3 SBP \geq 140 mm/Hg OR DBP \geq 90 mm/Hg (and not Levels 1 or 2)	In clinic. Advise to follow-up with PCP within 2 months.	Per routine reporting. <u>IF symptomatic</u> (e.g. chest pain, headache, short of breath), notify safety officer and/or PCP immediately.
	SBP \leq 90 mm/Hg OR DBP \leq 50 mm/Hg	In clinic. Advise to follow-up with PCP within 1 week.	Within 1 week. <u>IF symptomatic</u> (lightheaded, feels faint), notify safety officer and/or PCP immediately.
PHQ-8 (Depression Questionnaire)	Total Score \geq 15 and < 20	In clinic. Advise to follow-up with PCP or mental health care provider within 1 month.	None.
	Total Score \geq 20	In clinic. Advise to follow-up with PCP or mental health care provider within 1 week.	Notify PCP OR participant's mental health provider within 1 week.
<u>Laboratory tests*</u>			
Blood glucose	< 50 mg/dl OR > 400 mg/dl	Within 1 week or sooner as indicated by exact value and clinician judgment.	Within 1 week or sooner as indicated by exact value and clinician judgment.
Triglycerides	TG \geq 1000 mg/dl	Within 1 week or sooner as indicated by exact value and clinician judgment.	Within 1 week or sooner as indicated by exact value and clinician judgment.

* The exact alert levels for glucose and triglycerides will be defined by the laboratory performing the assay and may change slightly over time. Other laboratory tests may be obtained (e.g. serum potassium and other measurements as part of chemistry panel. For these tests, we will also use the alert levels of the laboratory and will notify participants and PCP within one week or sooner, depending on the value and on clinical judgment.)

Serious adverse events (SAE) surveillance. As defined by the Food and Drug Administration, serious adverse events are defined by one of the following:

- death
- life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Important medical events that do not result in death or require hospitalization may be considered serious adverse events if they jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes in the definition.

Surveillance for SAEs and other relevant clinical events that may be associated with study participation will occur at 6 months, 12 months, 18 months, and 24 months. This will be done using an open-ended questionnaire which asks about new symptoms, urgent/unplanned medical care, and hospitalizations. In addition to the fixed time points, participants in the Brief Lifestyle Counseling and Enhanced Brief Lifestyle Counseling conditions may report adverse events during their monthly visits with the Lifestyle Coach. Lifestyle Coaches (e.g., medical assistants) will be trained to recognize the symptoms that might be expected from weight loss or from either of the two drugs. Medical assistants will inform the PCP of all new symptoms or events reported by participants, including any changes from previous visits. Research assistants (who will be reviewing the charts of patients to assess attendance) will follow up with PCPs to formalize reporting of these events. The study Safety Officer will review all completed AE forms, will classify the event according to several dimensions (expectedness, relatedness, and type) and will take appropriate action. Safety-related events will be reported in a timely fashion as required by the Data and Safety Monitoring Board, the local IRB, and the NHLBI.

Expected events. Over the two-year duration of the study, a number of medical events may be expected to occur in obese adults, including routine surgeries and procedures, the development of cancer or chronic conditions, new or increased symptoms from a chronic condition, musculoskeletal problems, and motor vehicle or other accidents (e.g., falls).

Pregnancy and other exclusions. If a participant becomes pregnant during the study, she will be excluded immediately from further participation in all study activities, and outcome data will be censored as of the estimated date of conception. If she has not yet seen a physician, she will be immediately referred for standard prenatal care. If a participant develops any other exclusionary condition (e.g., cancer) following randomization, further participation will be determined by the Safety Officer in conjunction with the participant's PCP.

Data Safety Monitoring Plan. A Data Safety and Monitoring Board will monitor the progress of the trial, including safety-related matters. DSMB members have access to unmasked 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.

12. POWER AND SAMPLE SIZE

The trial has sufficient resources to enroll 390 participants who will be randomly allocated in equal numbers to each of the 3 groups:

Group A: Usual Care

Group B: Brief Lifestyle Counseling

Group C: Enhanced Brief Lifestyle Counseling

The primary contrasts are (C vs. A) and (B vs. A). The (C vs. B) contrast is secondary and is not considered in computing power.

To determine study power, we set the type I error at 0.05. Other determinants of power include the inherent standard deviation of a single observation (σ) in the study population and the correlation between the baseline and 24 month measurements (ρ). We use $\sigma = 17.0$ kg and $\rho = 0.85$, based on results from previous studies. Data from the PREMIER trial, among those whose baseline BMI ≥ 30 kg/m², showed a baseline weight of 103.8 kg and an 18 month treatment effect of -3.4 kg for EST+DASH intervention group relative to the control group. In this study the estimated $\sigma = 16.5$ kg and $\rho=0.85$ (correlation between baseline and 18m). The estimated value for σ is 17.3 from the Penn database and 20.5 from Harvard, each based on previous studies among participants with BMI ≥ 30 kg/m². Estimated values for ρ for previous studies were all close to 0.85. Note that the longitudinal correlation of 0.85 has high leverage on sample size in that relatively small changes in the assumed value can have a big impact on sample size. We assume an attrition rate of 20%, which is incorporated into our estimate of the minimal detectable difference (MDD), based on preliminary data.

The adjustment procedure to be used for controlling Type I error also affects study power. As described in the Analysis section, we intend to use the Holm procedure as our approach for controlling Type I error.¹¹⁵ According to this procedure, the smaller of the two P-values resulting from analyses of our 2 primary aims will be compared to 0.025 and if significant the other contrast will be evaluated at 0.05. Consistent with this form of Type I error control, our primary approach for estimating study is “the probability of at least one significant contrast” (column 1 in Table VI). Columns 2 and 3, which provide study power for a single test at $\alpha=0.025$ and 0.05, respectively, are provided for reference.

To estimate power, we used a basic model for an analysis that compares (24-month - baseline) differences among treatment groups. The variance of these differences is $2\sigma^2(1-\rho)$, where ρ is the 24-month correlation. Note that the adjusted differences (24-month - $\rho \times$ baseline) with appropriate adjustment of the mean model are “optimal.” However, with ρ near 1, the unadjusted differences are nearly optimal and more straightforward. Table V displays study power.

Table VI: Study power (1 – β) to detect treatment effects for n=390 (130/group)

Net tx effect in Kg	$\alpha=0.025^A$ (at least 1 of 2 significant)	$\alpha=0.025^B$ (1 of 1 significant)	$\alpha=0.05^C$ (1 of 1 significant)
2.00	0.52	0.31	0.41
2.50	0.72	0.47	0.58
2.75	0.80	0.56	0.66
3.00	0.87	0.64	0.74
3.25	0.92	0.72	0.80
3.50	0.95	0.78	0.86
4.00	0.99	0.89	0.93
4.50	1.00	0.95	0.97

^APower if either of 2 independent tests is positive at $\alpha=0.05/2$; ^BPower for single test at $\alpha=0.05/2$; ^CPower for single test at $\alpha=0.05$.

The trial has 80% power to detect a treatment effect of 2.75 kg for the “at least 1 of 2 tests” each with size 0.025 (column A); a treatment effect of 3.60 kg for the “1 of 1 test” with size 0.025 (column B); and a treatment effect of 3.25 kg for the “1 of 1 test” with size 0.05 (column C). Hence, based on column A, the trial has at least 80% power to detect a net treatment difference in weight of 2.75 kg relative to the projected Usual Care mean weight reduction of 0.5 kg. This minimally detectable weight reduction of 2.75 kg is achievable given treatment differences from preliminary data, even when the projected net treatment differences are reduced to account for non-adherence and a drop-out rate of 20%. These projected net mean differences are 3.3 kg and 7.0 kg, for Brief Lifestyle Counseling and Enhanced Brief Lifestyle Counseling, respectively, based upon our previous studies of 6 to 12 months detection.⁹⁸ Hence, we anticipate little or no weight reduction in our comparison group and a net effect size of ~ 3 kg or more. Other behavioral intervention studies have achieved or exceeded this level of weight loss. Mean net weight loss was 5.5 kg in the DPP.

13. ECONOMIC ANALYSIS

The proposed study is not adequately powered for a “gold-standard” economic analysis. Such an analysis would require a trial of several thousand participants, as well as the allocation of resources to collect detailed health care utilization data. However, a cost-effectiveness analysis can be conducted, using inputs derived from study staff, as well as participants. The outcome of the economic sub-study will be cost per quality-adjusted life year (QALY) during the two year time horizon of each individual’s participation in the study. The use of cost per QALY will allow a comparison of cost-effectiveness between treatment of obesity and other health interventions.¹⁰⁴ Cost per pound of weight lost also will be calculated for each of the three treatment arms.^{116,117} The perspective for this analysis will be that of the payer.

The estimation of costs will consist mainly of brief questionnaires administered to study staff and to participants. These instruments will be administered monthly to study staff. The questionnaires have been developed to estimate the costs of treating study participants. This is in contrast to the costs of developing/planning the treatment. We do not seek to estimate development costs, as the intervention would not have to be re-developed in order to be implemented in a community setting. For example, within the category of participant recruitment, we intend to include the costs of assessing eligibility for treatment but not to include the costs of conducting study-related assessments (e.g., research questionnaires) at the time of enrollment. We will estimate the cost of treatment for each group, as well as the incremental cost and incremental cost-effectiveness ratio (in dollars per QALY) of Brief Lifestyle Counseling and of Enhanced Brief Lifestyle Counseling compared to Usual Care. The EuroQoL-5D will be used to estimate QALYs.

Staff costs will be divided into several categories. These are: 1) recruitment/enrollment; 2) materials development; 3) counseling visits (including preparation for visits, counseling time, documentation, and safety monitoring); 4) outcomes assessment; and 5) team meetings to discuss patient care. Separate instruments have been developed for each category of personnel who will be involved in treating study participants (lifestyle coaches; physicians/nurses; research assistants/coordinators; and investigators). These questionnaires are based on those used in the Diabetes Prevention Program, as well as those used previously by investigators from this group for prospective capture of resource use.^{107,108} The questionnaires will provide estimates of the time spent by each staff member on the study. Time spent will be multiplied by a standard hourly rate for each type of provider, taken from the Bureau of Labor and Statistics (www.bls.gov). The “toolbox” funds provided to patients in the Enhanced Brief Lifestyle Counseling group for use of meal replacements or medication also will be tracked.

Given the limited duration of post-intervention follow-up and the moderate weight losses expected, we do not anticipate observing cost offsets associated with reductions in health care resources use attributable to the intervention. Thus, we will not collect detailed health care utilization data. However, as a part of bi-annual follow-up visits, study participants will provide a list of medications. We will calculate drug costs from the “Red Book”, which provides Average Wholesale Price for medications. Based on prior research, we believe that the cost of medications for diabetes, hypertension, and hyperlipidemia may be sensitive to change.¹²⁰

Participants’ costs will be assessed on a bi-annual basis (at the time of study outcomes visits). The main cost to participants is the time they lose from work or other activities to attend study visits. Examples of other costs to be assessed include changes in spending on food and leisure-time physical activity.

We also will develop a Markov simulation model to estimate the lifetime cost-effectiveness of the intervention, as was done with the Diabetes Prevention Program.¹²¹ For this analysis, the perspective will

be societal. We will use the intervention costs (both payer and patient perspective) and changes in weight, blood pressure, and quality of life attributable to the intervention, in combination with published data associated with life expectancy, health related quality-of-life, changes in cardiovascular risk, and direct and indirect medical costs of associated with obesity and hypertension to estimate the total cost per QALY for the each of the two intervention conditions relative to Usual Care and for Enhanced Brief Lifestyle Counseling relative to Brief Lifestyle Counseling.¹²²⁻¹³⁰ Uncertainty surrounding cost and risk estimates from the model will be explored using cost-effectiveness acceptability curves, derived from Monte Carlo analyses making 10,000 evaluations of each model. The use of a Markov model also allows for sensitivity analyses, in which the effect of varying the discount rate, the change in weight or in QALYs, or the cost of different types of providers can be tested.

14. DISSEMINATION

The interventions tested in this trial are designed for implementation in routine medical practice. If either the Brief Lifestyle Counseling or the Enhanced Brief Lifestyle Counseling intervention is found to be effective, the ultimate public health impact will be determined by the ability to disseminate it. Therefore, the dissemination component of the study includes identifying patient and practice characteristics that will affect acceptance and success of the programs. The RE-AIM (Reach, Efficacy/Effectiveness, Adoption, Implementation, and Maintenance) framework provides useful guidance for identifying and documenting dissemination issues (see www.re-aim.org). In this framework, optimal dissemination requires an intervention that has been found effective in a representative group of individuals (representative of the community or clinical population served (i.e. individual-level impact)). The ability to translate the intervention into a usual practice setting (institutional impact) derives from the feasibility and cost of the program, the degree and quality of adoption, implementation, and sustainability of the program within the setting.

With this in mind, the primary objectives of our dissemination activities will be to: 1) collect quantitative and qualitative data related to dissemination issues; 2) determine an appropriate approach to disseminating components of the intervention that are found effective; and 3) implement and document dissemination activities. Plans for each type of activity are summarized below.

Collect Quantitative and Qualitative Data Related to Potential Dissemination Issues

To estimate the representativeness of study participants compared to the overall practice, we will use administrative data. We will be unable to collect individual-level information of those invited but not enrolled. Potentially available data at the neighborhood level include age, gender, ethnicity, BMI, insurance status, and prevalence of co-morbid conditions. To describe practice characteristics, we will collect data on size (average caseload, average number of encounters per week), number and types of providers (i.e., physicians, nurses, and medical assistants), use of electronic medical records, available weight loss programs and resources, and census tract descriptors of the area where the practice is located. To estimate the representativeness of participating clinicians, we will quantify the number invited, the number who declined or were excluded by the investigator or the practice, reasons for declinations or exclusions, demographic information, and physician characteristics (e.g. years at site, specialty, type of provider). Finally, among participating practices and clinicians, we will collect qualitative data about feasibility issues, unanticipated costs attributed to delivering the intervention, and perceptions of the feasibility, logistical and cost issues potentially associated with continuing the program once the study has ended. Formal process data (e.g., on attendance, adherence, fidelity in delivery of the protocol) will provide insights on quality of the intervention and dose delivered.

Determine an Appropriate Approach to Disseminating Components of the Intervention that are Found Effective

Quantitative and qualitative variables described above will be analyzed in conjunction with the effects of the active intervention arms on study outcomes to characterize the dissemination potential of the program, including considerations that may apply to effective implementation at the individual and practice levels. The final program content, requirements, and recommended approach for implementation will be packaged for dissemination.

Implement and Document Dissemination

Activities will be undertaken to market the program. Our primary focus will be health care providers and third-party payers, although activities might also be directed towards patients. These activities will be tracked. The success of dissemination, however, (as characterized in the RE-AIM framework) cannot be determined within the time frame of this grant.

Health care providers. In addition to publishing study results in peer-reviewed journals, we will send provider-focused descriptions of the study and its results to medical trade publications (e.g., American Medical News, American Nurse, and American College of Physicians Observer). Training workshops and symposia will be offered at appropriate professional meetings, or through other mechanisms, to increase the potential for dissemination. We will also post intervention materials and guidelines directly on the websites of relevant professional and scientific organizations (e.g., American Medical Association, American Heart Association, NHLBI, NAASO/The Obesity Society).

Third Party Payers. We plan to disseminate results of this study widely to organizations that might implement or promote the interventions. Information on effectiveness, feasibility, and cost of the interventions will be provided. The targeted audience includes directors of managed care organizations, health maintenance organizations, state Medicare and Medicaid programs, and disease management companies.

15. DATA MANAGEMENT

Data Collection

This trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) as outlined in the International Conference on Harmonization (ICH) document “Good Clinical Practice: Consolidated Guideline” and the Declaration of Helsinki. Data collection procedures were previously described starting on page 27. Data will first be collected on original source documents (i.e., paper documents) by research personnel. All screening and assessment data, with results from laboratory analyses of blood, ECGs and questionnaires, will be filed in the patient’s research chart. Data will be transferred onto case report forms (CRFs) as instructed by internal standard operating procedures. Original source documents will be secured according to the same standard that patient’s charts are secured at the individual practice sites. CRFs, and other study documentation will be maintained in a locked file cabinet in the research coordinator’s office until archived.

Database

A web based system that utilizes Adobe Acrobat PDFs with a Microsoft SQL backend will be developed specifically for this study. The database will be password-protected user accounts with different levels of access and privileges. Only research personnel assigned to this study will have access to the data. Research staff will be trained in the use of data entry system. All hard copy data forms will undergo editing/checking by a second research assistant. Missing and questionable data will be followed-up and corrected. Data in the database will not include any information that may be used to identify participants. The data will be secured with SSL encryption and will be time-stamped with audit trails that will be available for review.

Database forms will be designed to serve as the CRFs data entry screens and will look like actual hard copies of source documents allowing for quicker and more accurate data entry. All data entered into the database will be incrementally backed up daily and fully backed up weekly. All data in the database will be 100% verified. Backups will be stored in a fireproof safe.

Verification and validation criteria for use in the study will be established by the study data manager. Procedures for management of data flow and data processing during the study will be established and research staff will be trained in these procedures.

Data Reporting

Four types of standardized reports will be produced on a regular basis: 1) participant recruitment and follow-up; 2) demographics; 3) data quality and monitoring reports; and 4) adverse events. All of these reports will be created combining the three treatment arms and presented both overall and by participating practice as appropriate. Reports will be provided to the Principal Investigator (PI) and Project Coordinator (PC) on a quarterly basis. Reports will be provided to the individual practices and the Data Safety and Monitoring Board (DSMB) approximately every six months or as requested for special circumstances.

Participant Recruitment and Follow-up

Under the direction of the study biostatistician, the study data manager will produce the following reports both overall and by participating practice:

- Number of participants randomized
- Number of participants randomized versus established accrual targets
- Number of participants who completed first year of treatment
- Number of participants who completed the second year of treatment
- Number of participants who withdrew from the study

Demographics

The study data manager will prepare reports summarizing the distributions of ethnicity, sex, and age for the entire study and each of the 6 participating practices.

Data Quality and Monitoring Reports

Under the direction of the study biostatistician, the study data manager will produce the following reports to monitor overall data quality. These reports will include, but are not limited to:

- Missing follow-up contacts
- Missing forms
- Missing values
- Query rates
- Timely entry and verification
- Untimely follow-up contacts
- Linkage of Patient Identifiers between forms

Additional monitoring reports that may be produced by the study data manager include laboratory data per participating practice, and query status updates. See Appendix 3 for a more detailed description of the data quality checks to be conducted.

Masking

Although no interim analyses are planned, descriptive analyses requested by the DSMB will be performed by the study data manager under the direction of the study biostatistician. The findings will be presented to the DSMB by the study biostatistician and data manager via meetings or conference calls. Neither the PI, nor any of the co-investigators, will be allowed to view these results.

All descriptive analyses provided to the DSMB will be provided by treatment but with the individual treatments identified only as A, B, or C. Such analyses will be of adverse events, withdrawal rates, and baseline characteristics, but not study outcomes. The treatments assigned to A, B, and C will be known only to the study statisticians. A sealed envelope providing the codes for the treatments will be provided to the chair of the DSMB to allow the board to identify the three treatments, if so desired. Although it may be possible to identify the individual treatments by comparison of results of the efficacy analyses, the same code will be used for each treatment throughout the report.

Adverse Events

Data on adverse events (AEs) and adverse drug reactions will be collected continuously throughout the study. In addition to the standard reporting outlined below, serious adverse events (SAEs) as defined in the protocol, will be reported to the PI, Penn IRB, Penn Project Coordinator, and the study data manager. If the participant is using a weight loss medication, the licensed product holder will also be notified who will, in turn, notify the Food and Drug Administration.

A list of all adverse events will be produced by the study data manager. This list will include the type and severity of the event, the relationship to any medication used, and other relevant information. The entries in the table will be sorted by patient and type of event. These reports will be generated as they occur, as well as described above.

In addition to the quarterly listings of AEs, the study data manager (using SAS) will produce summaries of the observed adverse events combined into categories based on baseline measures to detect any possible pattern with the associated AE. Confidence intervals will be generated for event rates if applicable. These reports will combine data across treatment conditions and participating practices. A sample is shown in Table 4. Events to be listed in these tables include:

- Number and percentage of AEs
- Number and percentage of SAEs

Analysis of the Primary Endpoint and Other Data

The primary outcome for the DSMB analyses will be the comparison of the change in weight between the treatment groups. The analysis of treatment differences for all primary and secondary outcomes at the repeated visits (baseline, 6, 12, and 24 months) in continuous outcomes (weight) and binary outcomes (metabolic syndrome data) under this design will be performed with nested random effects linear and logistic models with two levels of random effects for practice and patient.

Baseline data. Selected baseline factors will be summarized and compared between treatment groups and across practice to evaluate the adequacy of randomization and identify any imbalances that may affect treatment comparisons.

Withdrawal rates. Both withdrawal rates over time and reasons for withdrawal will be summarized and presented to the DSMB.

Primary and secondary endpoints. The primary measure and selected secondary measures will be compared between treatments cross sectionally and then longitudinally. Details of these analyses are given in the next section.

Final Data Analysis upon Completion of Trial

Upon completion of the trial, after all data have been entered in the database and query resolution is complete, the primary statistical analysis and description of the data will be performed by the SAS programmer and study biostatistician. They will produce a final report outlining all analyses and interpretation of the results. The report will be used as the basis of the primary manuscript to be prepared for publication. The analyses generating the final report are outlined below.

Examination of baseline characteristics. Standard descriptive statistics will be used to describe baseline characteristics, both overall and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, ethnicity, and other demographic

characteristics, and potential confounding factors. These factors will be examined both separately for each of the clinical sites and combined across practices. Summary statistics such as means, medians, and ranges will be produced for all measured variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods, including stem-and-leaf diagrams and boxplots, will be used to examine distributions, identify potential influential points, and guide the selection of transformations if warranted. The balance of baseline measures between the treatment groups will be compared using appropriate 3-sample tests including random effects ANCOVA and logistic models to adjust for practice clustering.

Analysis of Endpoints

Primary endpoint. The primary analyses for the primary and secondary aims will entail two pairwise intent-to-treat (ITT) comparisons of the three treatment arms: Enhanced Brief Lifestyle Counseling vs. Usual Care, and Brief Lifestyle Counseling versus Usual Care. These two comparisons will be made at the .025 alpha level for the continuous body weight variable. The nested random effects models used for these analyses will consist of two levels of random effects to adjust for individual patient and practice variability: random intercept and slopes for patient and random intercepts for practice (and if necessary, random slope for practice). In addition, these models will contain the following fixed effects: main effects for change from baseline to each follow-up visit, group differences (three treatment arms for intent-to-treat analyses or demographic groups), and interactions between the visit and group indicator variables. Tests of these interactions will correspond to tests of ITT differences among either the three treatment arms or demographic group differences with respect to changes from baseline to each of the follow-up visits. Estimates and confidence intervals for these group differences will be derived from interaction and main effects parameters of the

Confounders. Although we do not expect confounding of ITT effects because of the randomization of 390 patients, potential confounding of ITT effects among treatment arms or demographic groups (e.g., gender and ethnicity) will be assessed in a two step process: 1) analyzing the associations between potential baseline confounders (e.g., age, baseline weight, or metabolic syndrome) and treatment or demographic factor using multinomial logic regression models with either treatment or a demographic factor as the multinomial outcome and potential baseline confounders as covariates; 2) analyzing the associations between potential baseline confounders and either binary or continuous outcomes, using logistic or linear nested random effects models, respectively. If the associations involving the potential confounder in both steps are significant at the 0.20 level (we want to minimize the chances of not finding such a confounder), then we will include these confounders in the nested random effects models for the primary or secondary analyses. All other assessments of confounding variables will be for exploratory (i.e. hypothesis generating) purposes.

Secondary Endpoints. Continuous body weight is the outcome of secondary aims 3) and 4). The comparison of Enhanced Brief to Brief Lifestyle alone (secondary aim 3) will be assessed using the primary endpoint nested model. To test the hypothesis of secondary aim 4), a similar nested random effects model will be fit; however this model will include the group differences as a two level fixed effect (Brief Lifestyle Counseling + Enhanced Brief Lifestyle Counseling vs. Usual Care) and this group comparison will be made at the 0.05 alpha level. Other secondary outcomes include i) metabolic syndrome (and its individual components); ii) mood; iii) health-related quality of life; iv) sexual functioning; v) dietary intake; vi) appetite and eating behavior; vii) physical activity; and viii) cost-effectiveness. Although these measures are acquired annually, our analytic approach will parallel the approach of the primary outcomes; therefore, we will use either logistic or linear nested random effects models for binary or continuous outcomes, respectively. In addition, we will supplement these models with ANCOVA or logistic regression models at the year 1 and year 2 endpoint, co-varying baseline.

Analysis of Safety and Toxicity

Rates of adverse events by treatment arm will be presented (see Table 4, page 49). Serious adverse events will likewise be summarized. Frequency counts will be made according to the number of participants experiencing a particular adverse event during the study. These analyses will focus on those events considered possibly, probably, or definitely related to treatment, although all adverse event summaries will be provided. Participants experiencing multiple occurrences of the same event will be counted only once. In the case of multiple occurrences of the same event for a given participant, the highest grade of severity experienced by that participant will be used for tabulation by event severity.

Comparisons between treatment groups will use random effects ANCOVA and logistic models as appropriate to adjust for practice-level clustering.

Intent to Treat and Missing Data

All patients who have been randomized and have available data will be used for the primary comparison of treatments. The characteristics at time of randomization for those patients without complete follow-up will be examined; however, there will be limited statistical power to detect any major differences between these patients and those with complete follow-up. Any patient excluded from the intention-to-treat population and the reasons for exclusion will be listed.

Presentation and Format of Results

Examples of some of the tables described in the previous sections are given at the end of the Data Analysis and Monitoring Plan (DAMP). Additional tables, and appropriate figures, will be produced as needed. For general reporting, two decimal points for most efficacy and safety endpoints, p-values will be reported to two significant digits, and no rounding in any intermediate data steps or analysis steps (unless it is to the 10th decimal point for SAS computing reasons) will be used. All statistical programs will be developed using SAS and/or StatXact as described above.

Revisions to DAMP

An attempt has been made to anticipate possible data problems and to pre-specify handling conventions. However, it is recognized that this DAMP may not have covered all possible issues related to data analysis and reporting. Masked data reviews will be performed, and data problems found through such reviews will be handled according to the principles outlined in this DAMP and will be properly documented. Data problems found during final analysis (after unmasking) will be handled in the same manner and will be clearly noted in the study reports. Changes to data analysis and monitoring procedures which occur during the course of the study will be incorporated as amendments to the DAMP and included in the protocol if appropriate.

Table 4: Cumulative Adverse Events in Participants as of Date mm-dd-yyyy

	None	Mild	Moderate	Severe	Life-threatening	Fatal	Total AEs
Description	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1 - 5

Table 5: Summary of Representative Participant Characteristics by Treatment Group

	Treatment Group		
	A (N=)	B (N=)	C (N=)
Age	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.

	Median, range	Median, range	Median, range
Ethnicity			
Asian or Pacific Islander	N (%)	N (%)	N (%)
Black/African-American	N (%)	N (%)	N (%)
Latino/Hispanic/Mexican-American	N (%)	N (%)	N (%)
White/Caucasian	N (%)	N (%)	N (%)
Multi-ethnic	N (%)	N (%)	N (%)
Other	N (%)	N (%)	N (%)
Education			
Less than 9 th grade	N (%)	N (%)	N (%)
9 th to 12 th grade, no high school diploma	N (%)	N (%)	N (%)
High school diploma, G.E.D. or equivalent	N (%)	N (%)	N (%)
Some college, no college degree	N (%)	N (%)	N (%)
Associate's degree	N (%)	N (%)	N (%)
Bachelor's degree	N (%)	N (%)	N (%)
Graduate or professional degree	N (%)	N (%)	N (%)
Unknown	N (%)	N (%)	N (%)
Marital Status			
Married	N (%)	N (%)	N (%)
Not married, but long-term partner	N (%)	N (%)	N (%)
Single	N (%)	N (%)	N (%)
Separated or divorced	N (%)	N (%)	N (%)
Unknown	N (%)	N (%)	N (%)
Total number of persons in household	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Weight at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Height at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Body mass index at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Waist Circumference at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Gender			
Female	N (%)	N (%)	N (%)
Male	N (%)	N (%)	N (%)
Metabolic Syndrome at Randomization			
LDL-C at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
HDL-C at randomization	Mean ± s.d. Median, range	Mean ± s.d. Median, range	Mean ± s.d. Median, range
Blood pressure at randomization	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.

	Median, range	Median, range	Median, range
TG at randomization	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
	Median, range	Median, range	Median, range
Glucose at randomization	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
	Median, range	Median, range	Median, range
HOMA at randomization	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
	Median, range	Median, range	Median, range
hs-CRP at randomization	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
	Median, range	Median, range	Median, range

Table 6: Participant Accounting by Treatment Group

	Treatment Group		
	A (N=)	B (N=)	C (N=)
Entered	N (%)	N (%)	N (%)
Discontinued			
Violation of protocol	N (%)	N (%)	N (%)
Withdrawal of consent	N (%)	N (%)	N (%)
Administrative reason	N (%)	N (%)	N (%)
Physician recommended	N (%)	N (%)	N (%)
Adverse event	N (%)	N (%)	N (%)
Other	N (%)	N (%)	N (%)

Table 7: Clinical Adverse Event Summary

	Treatment Group		
	A (N=)	B (N=)	C (N=)
Participants without follow-up	N (%)	N (%)	N (%)
Participants with follow-up	N (%)	N (%)	N (%)
With no adverse events	N (%)	N (%)	N (%)
With one or more adverse event	N (%)	N (%)	N (%)
With serious adverse event	N (%)	N (%)	N (%)
Who died	N (%)	N (%)	N (%)
Discontinued due to adverse event	N (%)	N (%)	N (%)
Discontinued due to a serious adverse event	N (%)	N (%)	N (%)

Table 8: Summary of Primary Endpoint

	Treatment Group			p-value
	A (N=)	B (N=)	C (N=)	
WEIGHT (Month 0)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	

WEIGHT (Month 6)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
WEIGHT (Month 12)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
WEIGHT (Month 24)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.

Table 9: Secondary Measures Year 1

	Treatment Group			p-value
	A (N=)	B (N=)	C (N=)	
MetSyn (Month 0)	N (%)	N (%)	N (%)	
MetSyn (Month 6)	N (%)	N (%)	N (%)	
MetSyn (Month 12)	N (%)	N (%)	N (%)	
MetSyn (Month 24)	N (%)	N (%)	N (%)	
PHQ-8	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
SF-12 Mental Component	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
SF-12 Physical Component	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
IWQOL-Lite Total Score	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
PSQI	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
International Index of Erectile function (men)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
Female Sexual Function Inventory (women)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
NCI Fat Screener	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
NCI Fruit & Vegetable Screener	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
Eating Inventory	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
Eating Behavior Questionnaire	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
Paffenbarger Physical Activity Survey	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
EuroQol-5D	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	
Cost Surveys	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	

Table 10: Secondary Measures Year 2

	Treatment Group			p-value
	A (N=)	B (N=)	C (N=)	

MetSyn (Month 0)	N (%)	N (%)	N (%)
MetSyn (Month 6)	N (%)	N (%)	N (%)
MetSyn (Month 12)	N (%)	N (%)	N (%)
MetSyn (Month 24)	N (%)	N (%)	N (%)
PHQ-8	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
SF-12 Mental Component	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
SF-12 Physical Component	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
IWQOL-Lite Total Score	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
PSQI	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
International Index of Erectile function (men)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
Female Sexual Function Inventory (women)	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
NCI Fat Screener	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
NCI Fruit & Vegetable Screener	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
Eating Inventory	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
Eating Behavior Questionnaire	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
Paffenbarger Physical Activity Survey	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
EuroQol-5D	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
Cost Surveys	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.

16. TRIAL ORGANIZATION

Trial Governance

Practice-based Opportunities for Weight Reduction (POWER) Trials are three separate randomized clinical trials with common protocol elements sponsored by the National Heart, Lung and Blood Institute. The three participating sites include the University of Pennsylvania in Philadelphia, PA, Johns Hopkins University in Baltimore, MD, and Harvard University in Cambridge, MA. Johns Hopkins University (in Baltimore) is serving as the Resource Coordinating Unit (RCU). The overall structure of the trial is outlined in the cover letter to the three protocol written by Drs. Appel and Wells (from Johns Hopkins and the NHLBI, respectively).

Organizational Structure at the University of Pennsylvania

The Principal Investigator (PI) will have responsibility for all areas of the study. The Co-Principal Investigator will share in this responsibility, and will serve with the PI and other co-investigators and project manager as a member of the University of Pennsylvania's Steering Committee. This committee will meet monthly to oversee five cores which reflect the major aspects of the research study. These include Clinical Care Associates Core, Training and Intervention Materials Core, Assessment Core, Safety Core, and Data Management and Statistics Core. Each of these cores will provide regular, monthly reports to the Penn Steering Committee.

The Clinical Care Associates Core will ensure that the practices selected for the study remain appropriately staffed and equipped to complete the study. The Training and Intervention Core will actively participate in the training of the physicians and medical assistants and will be responsible for ensuring treatment fidelity across the 6 sites. This Core also will develop the intervention materials. The Assessment Core will work on assessment refinement and integrity throughout the study. The Statistics Core will work on issues related to data management and analysis. The Safety Core will be chaired by the Safety Officer. Membership will include the senior physician at each of the 6 primary care practices, as well as the PI and project manager. This core will monitor the participants' safety, including reviewing eligibility criteria, AEs and SAEs and related regulatory reports. The committee will meet approximately quarterly by teleconference.

The research team, including the PI, Co-PI, project manager, and research coordinators, will meet weekly for 60-90 minutes. Initially, the meetings will focus on issues related to the training. Once the training of primary care sites is complete, the focus of meetings will shift to issues related to participant recruitment, retention, and treatment implementation. In the last year of the grant, the focus of the weekly research team meetings will shift to issues of data analysis, manuscript preparation, and study dissemination.

17. TIMELINE

The trial consists of three phases: intervention refinement (Year 1), randomized trial (Years 2-4), and dissemination (Year 5). The intervention refinement phase started in October 2006. The intervention phase will be devoted to building strong collaborative relationships with the participating practices, and training practice staff. The randomized trial phase will begin in year two of the grant and will run for just over two years. The dissemination phase will take place during the final year of the award period. It will be dedicated to data analysis and dissemination of the study results and materials. Health care providers, patients, and third-party payers will be targeted for the dissemination of study results. A detailed timeline is provided as Appendix 1 to the protocol.

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19. APPENDICES

APPENDIX 2: PATIENT ELIGIBILITY CHECKLIST

Inclusion Criteria	Category	Specific Criteria
	*Age	21 years or older
	*Weight	Body Mass Index (BMI) between 30 to 50 kg/m ² and ≤ 400lbs
	Metabolic Syndrome	Must have 2 out of 5 components: check all that apply <input type="checkbox"/> Waist circumference: > 88 cm (women), > 102 cm (men) <input type="checkbox"/> SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg <input type="checkbox"/> Fasting glucose ≥ 100 mg/dl <input type="checkbox"/> Fasting triglycerides ≥ 150 mg/dl <input type="checkbox"/> HDL: < 40 mg/dl (men), < 50 mg/dl (women)
Exclusion Criteria	Category	Specific Criteria
	Blood Pressure	SBP ≥ 160 or DBP ≥ 100
	*Cardiovascular disease	Myocardial infarction, stroke, or TIA within the past 6 months
	*Prohibited Medication	Chronic use (at least 6 months) of medications likely to cause weight gain or prevent weight loss (e.g., corticosteroids, lithium, olanzapine, risperidone, clozapine)
	Psychiatric disease	Psychiatric diagnosis that would interfere with study adherence (e.g., schizophrenia), or psychiatric hospitalization in the past year
	Substance abuse	Self-report of substance abuse, including at-risk drinking (≥ 7 drinks per week for women, ≥ 14 drinks per week for men)
	Weight Change	≥ 5% loss within past 6 months
	Bariatric surgery	Prior or planned bariatric surgery
	Serious Medical Condition	Any serious medical condition likely to hinder accurate measurement of weight, or for which weight loss is contraindicated, or which would cause weight loss (e.g., end-stage renal disease on dialysis, cancer diagnosis or treatment within 2 years)
	Pregnant or Nursing	Pregnant or nursing within the last 6 months
	Plans to Relocate	Plans to relocate from the area within 2 years
	Living in household with a study participant or staff member	Another member of household is a study participant or staff in the trial
	Principle Investigator or PCP discretion	Principle Investigator or PCP deems an individual should not participate in the study

*Common eligibility criteria at University of Pennsylvania, Johns Hopkins University, and Harvard Medical School / Washington University

APPENDIX 3: QUALITY CONTROL CHECKS OF THE DATABASE

The following list a series of checks performed on the final data sets to ensure quality and accuracy of the double data entry. These listed items serve as the minimal quality control checks performed. Additional checks may be included based on issues by the investigator or CDM.

Check 1 - Comparison of Patient Header Information. Across all forms, we will compare the combination of Participating Practice indicator, Participant Initials, and Randomization Number. The three items (when all available) should be consistent across assessment points and forms.

Check 2 – Chronological Date Flow. Within form, we will investigate if the Date Flows across increasing Assessment points is increasing. As expected, later assessments should be acquired on later dates.

Check 3 – Completeness of Data – For each patient we will examine the completeness of the patient’s assessments.

Check 4 – Consistency of Dates between forms with common Assessment Points – We will examine if forms with Common Assessment points have the same assessment date, within the time frame of 1 month (different components of an assessment visit may happen on different days within a given month).

Check 5 – Gender Identification Items – We will examine the consistency between the Patient’s gender status, with gender specific items such as Pregnancy test questions, sexual functioning, contraceptives, etc....

Check 6 – Consistency between forms with common measures such as linking gender to the appropriate sexual functioning form delivered.

Check 7– Examine the occurrence of Adverse Events

Check 8 – Examination of Dates. Ensure dates are believable dates. Link to age of participant. Calendar date for the study.

Check 9. Examination of Range of Responses for all variables. Ensure all items meet their range restrictions.

Check 10. Logical checks of responses based on units specified (Height, Weight, etc...).

APPENDIX 4: MISSING AND INCOMPLETE DATA

Prevention of missing data is far superior to a statistical cure for incomplete data. Every effort will be made to collect outcome data on all randomized participants. For example, we will ask medical staff at the clinical practices to obtain weight measurements on individuals who have stopped participating in the trial. Due to the high longitudinal correlation, missed “interior” visits will not decrease information very much for a linear trend. However, they are needed to assess departures from a linear trend.

The underlying missing data process determines the biasing effects of missing data and structures valid analytic strategies.¹⁰³ Briefly, if data are missing completely at random (MCAR), then there is no induced bias and a complete case analysis, while inefficient, is valid. If data are missing at random (MAR), the probability of a potential observation being missing can depend on what has been observed, but not on what hasn't been observed. For example, MAR results when the probability of being missing depends on observed weight change (say, with a higher probability for those who gain weight), but not on the weight that would have been observed had the measurement been taken. In this situation either multiple imputation (MI) or development of a valid statistical model for the observed data (appropriate mean structure and correlation structure) will be valid. In this situation of MAR and a valid model for the observed data, the missing data process is “ignorable.” In a third situation, the probability of being missing depends on what would have been observed (e.g., the weight or BMI that would have been measured). In this case, neither MI nor developing a model for the observed data will completely eliminate bias.

Our analyses will assume MAR, but one can never empirically rule out the violation of this assumption. Robust statistical modeling coupled with sensitivity analysis can assess the stability of findings.

Administratively missing data (e.g., a person has been followed for 6 months and so doesn't have 12 month data) is not a concern with respect to potential biases. However, missed visits and dropouts need to be handled carefully. The missingness process is not likely to be MAR. Thus, aggressive sensitivity analyses will be needed around the imputation or other approaches, probably including some of the Sharfstein non-identifiable parameter approaches and/or other non-ignorable models such as shared parameter models. Last observation carried forward (LOCF) will be included in the set of approaches and comparisons, but if conclusions based on it differ from multiple imputation (MI) based on a prediction model, it will be discounted.

To use all participants when comparing treatments on the (24 month - baseline) weight change, we will take advantage of the statistical association between weights at 0, 12 and 24 months. We will build a longitudinal model and then use maximum likelihood estimation of the longitudinal random effects models (i.e., maximize the missing data likelihood and its curvature at the maximum). This approach will respect the inherent uncertainty in predicting the 24-month weights.

Another approach to dealing with missing 24-month weights is to conduct “liberal” and “conservative” analyses. One would assume that on average there is neither weight loss nor gain, $\{W_{24} - W_0 = 0\}$. Bernie Rosner analyzed Nurses Health Study data for those with BMI > 30, stratified on age, and generally there was a very slight weight loss and there were no strata with weight gains.

APPENDIX 5: ANALYTIC MODEL

Analysis is structured by a longitudinal model implemented via SAS PROC Mixed or GenMod. Initially, we present a model for weight, our primary endpoint. This model also applies to other continuous outcomes such as blood pressure and LDL-C. We then present a model for binary outcomes (e.g., HTN control). Lastly, we discuss missing data, censoring and on-treatment analyses.

1.1 Continuous Outcomes

The underlying, longitudinal model is as follows:

Model 1:

$$Y_{irt} = \text{visit}_t + \text{visit}_t \times I_{\{r=2\}} + \text{visit}_t \times I_{\{r=3\}} + \text{clinic}_{ir} + \text{gender}_{ir} + \text{race}_{ir} + \text{PHY}_{ir} + \text{PHY}_{ir} \times \text{visit}_t + e_{irt} \quad (1)$$

with,

- $t =$ visit indicator: $t = 0$ is randomization, $t = 1$ is the 6-month visit, $t = 2$ is the 24 month visit. (More visits can be added with different indexing).
- Y_{irt} = the measured dependent variable (e.g., weight) at visit t , for participant “ i ” in randomization group “ r ,” $r = 1, 2, 3$ (= A, B, C).
- visit is the visit-specific level for group $\{r = 1\}$ (group A), allowing for different expected values at each visit for the $r = 1$ group. This coding is equivalent to declaring visit a class variable in SAS.
- PHY_{ir} is a random physician effect.
- $I_{\{r=u\}}$ = the indicator of intervention group membership. These indicators multiplying the visit effects produce treatment group-specific offsets and so compute the (B vs. A) and (C vs. A) treatment effects as increments over the visit-specific level for group A. The (C vs. B) comparison is computed by taking the difference of the terms with $r = 3$ and $r = 2$. This coding is equivalent to declaring treatment group a class variable in SAS.
- The second line contains fixed effects for clinic, gender and race. The list of covariates can be expanded. The second line also contains a random physician effect PHY_{ir} . Note that PHY does not have a subscript “ t ” even though a participant may change physicians during the trial. The model with changing physicians is quite complicated. We will use the physician reported by the physician at the time of enrollment.
- The third line contains the interaction physician random effect with visit.
- e_{irt} = the “residual”, with an “unstructured” covariance matrix. Because follow-ups are at approximately constant times (0, 6, 12, 24 months) we can use the unstructured covariance. It eliminates the need to include (and the opportunity to include) a random intercept or other variance components.

Model (1) translates into a model for first-differences as follows.

Model 2:

$$\begin{aligned} (Y_{irt} - Y_{ir(t-1)}) &= (\text{visit}_t - \text{visit}_{t-1}) + (\text{visit}_t - \text{visit}_{t-1}) \times I_{\{r=2\}} + (\text{visit}_t - \text{visit}_{t-1}) \times I_{\{r=3\}} + \\ &\quad + (\text{visit}_t - \text{visit}_{t-1}) \times \text{PHY}_{ir} + (e_{irt} - e_{ir0}) \\ &= \text{inc}_t + \text{inc}_t \times I_{\{r=2\}} + \text{inc}_t \times I_{\{r=3\}} + \text{inc}_t \times \text{PHY}_{ir} + e_{irt}^* \end{aligned} \quad (2)$$

The covariance of the e_{irt}^* is inherited from the unstructured matrix in (1).

Notes on Model (2)

- The terms in the second row of Model 1 are no longer present in 2 because they are time-constant. This cancellation will occur for any time-constant covariates.
- The first three terms in Model 2 measure the treatment-specific changes in Y; the last two of these are the (B vs. A) and (C vs. A) treatment comparisons for the indicated increment.
- The next term allows for a physician effect on the increments and the last term is residual error.
- **Primary analyses:** The treatment comparisons for the primary aims are the 24 month to baseline differences for (B vs. A) and (C vs. A). These are computed by adding up the increments, which is equivalent (in all statistical aspects) to comparing the (24-month - baseline) differences. Similarly, the secondary aim comparing (C vs. B) will be addressed in this manner. These and other comparisons are implemented by computing contrasts (in SAS).
- Tests for the 2 primary aims will follow the Holm procedure, the smaller P-value will be compared to 0.025 and if significant the other comparison will be evaluated at 0.050.
- There is a Holm-induced joint confidence region for the pair of contrasts consisting of the pairs of treatment effects as the null hypothesis for which the Holm procedure would fail to reject. However, this region is difficult to communicate and we will use the individual 97.5% intervals. It is not optimal (there is a smaller region with the same coverage), but straightforward to communicate.
- Use of an unstructured covariance matrix eliminates the need (and the opportunity) to include a random intercept or other random effects.
- Irrespective of the structure for the longitudinal correlations (we are using unstructured), we will use robust standard errors.
- Model 2 can be generalized by including additive effects for clinic, gender and race. If included, they represent influences on the increments in weight and would appear as visit by covariate interactions in Model (1).

1.2 *Dichotomous outcomes (BP and HTN control)*

Using GenMod with the logit link, Bernoulli sampling distribution, an unstructured covariance working covariance and robust SEs, we will estimate,

Model 3:

$$\text{logit}\{E(Y_{irt})\} = \text{visit}_t + \text{visit}_t \times I_{\{r=2\}} + \text{visit}_t \times I_{\{r=3\}} + \text{clinic}_{ir} + \text{gender}_{ir} + \text{race}_{ir} \quad (3)$$

We have omitted the PHY_{ir} random effects. These could be included and the model run in GlimMix, but the population-level interpretation of the estimated odds ratios changes with the magnitude of the random effect. For ease of interpretation we use (3) estimated in GenMod.

Model 3 will support our principal analyses, but there is an attractive, transition model alternative.

Model 4: Unlike for measured outcomes, the first-difference model (Model 2) isn't available. However, a first-order, autoregressive transition model is a useful adjunct to (3). Note that for each participant the outcome is a binary time series that can be analyzed via a series of linked, 2×2 tables (rows are values at time (t-1), columns at time t with transitions modeled by logistic regression with treatment effects and, if desired, other covariates.

1.3 *Secondary Aims*

Adaptations of models (2) and (3) will be used as appropriate for our secondary aims. For example, we will investigate whether there is a gender, race or (gender) \times (race) effect on the increments by including the appropriate interaction terms.

1.4 *Missed Missing and incomplete data*

Prevention is far superior to a statistical cure, and every effort will be made to collect outcome data on all randomized participants. For example, we will ask medical staff at the clinical practices to obtain weight measurements on individuals who have stopped participating in the trial. Due to the high longitudinal correlation, missed “interior” visits won’t decrease information very much for a linear trend. However, they are needed to assess departures from a linear trend.

As detailed in Little and Rubin 2002{{1580 Little RJA, Rubin D 2002; }} and discussed by Mealli {{2184 Mealli,F. 2004; }}, the underlying missing data process determines the biasing effects of missing data and structures valid analytic strategies. If data are missing completely at random, then there is no induced bias and a complete case analysis, while inefficient, is valid. For example, administratively missing data (e.g., a person has been enrolled for only 6 months and so doesn’t have 12 month data) will not produce bias.

If the probability of a potential observation being missing depends on what has been observed, but not on what has not been observed, then estimates based on an appropriate analytic model (both the mean and error structure) for the observed data will not be biased. Use of a valid model for the observed data allows the missing data process to be ignored. For example, this situation occurs if the probability of missing a visit or dropping out depends on observed weight change (say, with a higher probability for those who gain weight), but not on the weight that would have been observed had the measurement been taken. In this situation either multiple imputation (MI) or development of a valid statistical model for the observed data (appropriate mean structure and correlation structure) will be valid.

Missed interior visits: We will assume that these are missing at random; that analysis of the observed data can be conducted with no adjustments other than those that account for the time interval between occasions when data are obtained.

Administrative Censoring and Dropouts

Our approach will use the weight increments that are available up to the censoring point coupled with a, possibly adjusted, predictive distribution for future increments.

For participants who are *Administratively Censored* (there hasn’t been time for more follow-up), we will assume that future increments are drawn from the predictive distribution of future increments based on the “representativeness” assumption. The approach builds up to a 24 month change by using each participant’s weight changes for the period of their follow-up. Consider the basic case wherein weights are determined at baseline, at 12 months and 24 months (Y_0, Y_{12}, Y_{24}). Our primary analysis has as its target ($Y_{24} - Y_0$). The “increments” approach writes: $(Y_{24} - Y_0) = (Y_{12} - Y_0) + (Y_{24} - Y_{12})$. The estimated 24-month change produced by appropriately summing all observed increments is equivalent to assuming that dropouts or those otherwise censored would have had future increments that are drawn from individually-tuned, predictive distributions computed using information from all participants as structured by model (2) (those who are censored are “representative”). Use of multiple-imputation or a Bayesian enhancement implemented by Markov Chain Monte Carlo methods, ensures that proper care is taken to account for uncertainty and not to “pretend” that the future increments were actually observed.

Explicit Dropouts, Losses to Follow-up and Medical Event Censoring: The foregoing relations allow use to employ a strategy that uses available increments up to the censoring point and then employ multiple imputation based on a predictive distribution for future increments with the mean adjusted to reflect likely non-representativeness. We can adjust the imputations to be “conservative” or “liberal” or reflect fine-grained dropout scenarios. To see the flexibility, consider the following approach:

Explicit Dropouts and Losses to Follow-up

- If the participant has lost weight during the observation period, adjust the predictive mean to produce an average 0 additional weight change. Of course, different future increment means can be used for explicit dropouts and losses to follow-up. (Professor Rosner with the Harvard group analyzed NHS data for those with BMI > 30, stratified on age. Generally, there was a very slight weight loss and there were no strata with weight gains).
- If the participant has gained weight during the observation period, adjust the predictive mean to produce future increments that continue at this individual's observed rate of weight gain.

Medical Event (including Death) Censoring

After a medical event (e.g., stroke, heart attack, pregnancy or death) a weight may not be available or subsequent weights may be strongly influenced by the condition (e.g., extreme weight gain from use of oral steroids). If subsequent weight changes are not available or should not be used, as for explicit dropouts and losses to follow-up, assumptions on the mean of the predictive distribution must be made. It may be reasonable to treat use no adjustment for stroke, heart attack and pregnancy, and for certain causes of death.

Sensitivity Analysis: Sensitivity analyses will be used to study stability of results from the primary analyses.

1.5 ***Outliers***

1.6 To ensure robustness of our primary analyses, potential outliers in the observed data will be explored using stem-and-leaf and box plots. Records of unusual data points identified will be examined for correctness. The remaining potential outliers will be identified using the extreme studentized deviate (ESD) approach {{Rosner, B. 1983;}} and decisions made on including them, adjusting them or setting them aside in the primary analysis.

1.7 ***On-treatment Analyses***

Primary analyses will be performed on an intention-to-treat basis. However, interpretation of weight loss trials is complicated because of drop-out from the intervention group and drop-in from the control group. Particularly common are early drop-outs, i.e. individuals randomized to intervention who attend only a few intervention sessions, sometimes none. Such persons are included in ITT analyses. In this setting, we will compute “on treatment” comparisons and variations on this approach that adjust such an analysis for differential correlates of adherence in the treatment groups.

Care is needed in answering such questions, and Bellamy et al, Mealli et al. {{2207 Bellamy,S.L. 2007; 2184 Mealli,F. 2004; }} provide a useful framework for such analyses. For a basic case, we consider how to handle participants who complete at most 2 intervention sessions. They will be included in the primary, as randomized, intent to treat analysis. A secondary question is, “how do the treatment groups compare for those who adhered to treatment?” A straightforward comparison of treatments based only on “compliers” is attractive, but is biased if the compliers differ among the treatment groups. A valid comparison depends on adjusting for these differences, being careful not to adjust away the treatment effect. Propensity score approaches using information available at randomization and up through the first session will adjust for this imbalance. More sophisticated approaches using time-varying propensities allow accommodating more complicated patterns of non-adherence.