

**PREMIER**  
**A Trial of Lifestyle Interventions for Blood Pressure Control**

**PROTOCOL**

**May 14, 2002**

## Summary of Edits

### Changes between Version 1.3 and 1.4

- Reformatted from double to single space
- Figure 1 – updated to show alcohol recommendation of  $\leq 1$ oz/day is specific to men (p.25 ver 1.3, p. 22 ver 1.4)
- The 7-Day Physical Activity Recall (Form #18) may be completed either during the interim period or at SV3. (p. 33 ver 1.3, p. 28 ver 1.4, and Table 4, p. 37 ver 1.3, p. 32 ver 1.4))
- Added collection of samples for analysis of carotenoids, folate, and B-12 for cohorts 2-4 (p. 33 ver 1.3, p. 28, ver 1.4, and pgs.44-45 ver 1.3, pgs. 37-38 ver 1.4).
- Corrected duration of fast for fasting bloods from 8 hours to 12 hours (p.44 ver 1.3, p. 37 ver 1.4).
- Intervention Contact Schedule (Table 6, p.52 ver 1.3, p. 45 ver 1.4) updated and retitled *Approximate* Intervention Contact Schedule
- AE definition expanded: physical related injuries become AEs only when resulting in a medical visit (p.69 ver 1.3, p. 56 ver 1.4)

### Changes between Version 1.4 and 1.5

- Modified Safety Monitoring section to reflect new definition of AEs.
- Modified the description of the primary outcome measures to further clarify the imputation procedure and to discuss sensitivity analyses.
- Local review of laboratory values happens in two stages (“extreme” values are reviewed immediately); participants receive copies of all clinically relevant results.
- Deleted the word “clinician” for CC AE review.
- Stopping guidelines added to Sample Size/Statistical Power section.
- Language added per NHLBI guidelines stating that DSMB reviews of outcomes and AEs across all centers will be reported to all IRBs associated with the trial.
- Homocysteine will be done at baseline and 6 months, but not at 18 months.

### Changes between Version 1.5 and 1.6

- Corrects AE definitions to remove hyperlipidemia, gallbladder disease, diabetes, and cancer from list of AEs. However, these continue to be separately tracked and reported.
- Reduces the number of blood pressure measurements taken at 6 and 18 months from four sets of two measurements to three sets of two measurements.

### Changes between Version 1.6 and 1.7

- Added referral to physician for further evaluation within two months for BP  $\geq 140/90$  to escape level 1 at the 12-month visit.

### Changes between Version 1.7 and 1.8

- Added Appendix 2: Local BP referral procedures from all four sites

# PREMIER Protocol

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# PROTOCOL

## 1. Overview

PREMIER is a randomized clinical trial that will determine the effects of two multicomponent lifestyle interventions, relative to an advice-only control condition, on blood pressure (BP). Although numerous organizations recommend several lifestyle changes to control BP and potentially prevent hypertension, comprehensive strategies that simultaneously implement all lifestyle recommendations have yet to be developed and tested.

The two lifestyle interventions tested in PREMIER are a “comprehensive” intervention implementing the longstanding lifestyle recommendations for BP control (reduced salt intake; increased physical activity; limited intake of alcohol; and weight loss, if overweight), and a “comprehensive plus DASH” intervention implementing the longstanding lifestyle recommendations plus the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (rich in fruits, vegetables, and low-fat dairy products, and reduced in saturated fat, total fat, and cholesterol). Study participants (n=800) are 25 years of age or older, with systolic blood pressure (SBP) of 120-159 mmHg and diastolic blood pressure (DBP) of 80-95 mmHg. Half of the participants are expected to be female, 40 percent African American, and 30 percent hypertensive. After an initial screening period, participants are randomly assigned to one of two lifestyle interventions or to an “advice-only” control group. Follow-up lasts 18 months after randomization. The primary outcome is the change in SBP at six months, with change in SBP at 18 months and change in DBP at six and 18 months as secondary outcomes. Additional outcome variables include fasting lipids, glucose, insulin, and homocysteine levels.

The trial hypotheses are examined in all participants as well as separately in non-hypertensive and hypertensive subgroups. Results from PREMIER should provide the scientific rationale for routinely implementing combined lifestyle intervention programs to control BP and ultimately prevent BP-related cardiovascular disease.

## 2. Aims and Objectives

PREMIER will determine the blood-pressure-lowering effects of two multicomponent lifestyle intervention programs in persons at risk for hypertension (SBP of 120-139 and DBP of 80-89) and in those with stage 1 hypertension (SBP of 140-159 and/or DBP of 90-95). In this clinical trial, participants are randomly assigned to one of three groups:

1. The **“advice-only”** control arm, in which participants receive information on how to reduce salt intake, increase physical activity, reduce alcohol intake, and lose weight if overweight. The information provided to participants is similar to that in the information-oriented programs that are sometimes provided as part of routine medical care.
2. The **“comprehensive lifestyle intervention,”** in which participants receive a behavioral intervention program designed to accomplish longstanding recommendations for BP control (reduced salt intake, increased physical activity, reduced alcohol intake, and weight loss if overweight).
3. The **“comprehensive plus DASH lifestyle intervention,”** in which participants receive a behavioral intervention program designed to promote the DASH dietary pattern (increased intake of fruits, vegetables, and low-fat dairy products, and reduced intake of saturated fat and total fat) in addition to the longstanding recommendations for BP control (reduced salt intake, increased physical activity, reduced alcohol intake, and weight loss if overweight).

### *Primary Specific Aims*

1. Test the effects on SBP of the “comprehensive plus DASH” intervention in comparison to the “advice-only” control group at six months.
2. Test the effects on SBP of the “comprehensive” lifestyle intervention program in comparison to the “advice-only” control group at six months.
3. Test the difference in SBP between the “comprehensive plus DASH” intervention and the “comprehensive” intervention at six months.

The *a priori* hypothesis corresponding to these aims is that the comprehensive plus DASH lifestyle intervention will reduce blood pressure more than the comprehensive lifestyle intervention, which in turn will reduce blood pressure more than the advice-only intervention. This hypothesis is tested by comparing change in SBP from baseline to the six-month assessment among participants in the three treatment groups.

### *Secondary Specific Aims*

4. Test the effects on SBP at 18 months, and the effects on DBP at six and 18 months, of the comprehensive plus DASH intervention in comparison to the advice-only control group.
5. Test the effects on SBP at 18 months, and the effects on DBP at six and 18 months, of the comprehensive intervention in comparison to the advice-only control group.
6. Test the effects on SBP at 18 months, and the effects on DBP at six and 18 months, of the “comprehensive plus DASH” intervention in comparison to the comprehensive intervention.

The *a priori* hypotheses corresponding to these aims parallel those for the primary specific aims and are tested in an analogous manner. Although the primary aims all focus on six-month outcomes, the longer-term perspective embodied in these secondary aims is a critical part of the design of PREMIER. Previous trials have clearly shown that intensive lifestyle interventions achieve their greatest effects on blood pressure early on and that these effects then tend to diminish over time. Hence, evaluation of the interventions at six months provides an estimate of efficacy. From a public health perspective, however, it is also important to demonstrate reductions in blood pressure over a longer timeframe.

### ***Other Aims***

7. Test the effects of the PREMIER interventions (specific aims 1-6 above) in normotensive and hypertensive participants separately.
8. Estimate the effects of the PREMIER interventions on hypertension status (SBP  $\geq$  140, DBP  $\geq$  90, or treatment with antihypertensive medications) at six and 18 months in participants who were normotensive at baseline.
9. Estimate the effects of the PREMIER interventions on hypertension status (SBP  $\geq$  140, DBP  $\geq$  90, or treatment with antihypertensive medications) at six and 18 months post-randomization for those who were hypertensive at baseline and in the entire study population.
10. Estimate the effects of the PREMIER interventions in subgroups defined by race, sex, obesity status, and age.
11. Estimate the effects of the PREMIER interventions on fasting lipids, glucose, insulin, and homocysteine.
12. Estimate adherence to, and impact of, the PREMIER interventions as indicated by changes in: a) body weight, b) 24-hour urinary excretion of sodium, potassium, phosphorus and urea nitrogen, c) estimated energy expenditure, d) cardiorespiratory fitness, e) number of daily servings of fruits, vegetables, and dairy products, f) intake of total energy and percent of energy from total fat and saturated fat, and g) intake of alcohol.
13. Estimate the effect of the interventions on hypothesized psychosocial mediators and outcomes, effect of the interventions in subgroups defined by potential psychosocial effect modifiers, and relationships between the interventions, psychosocial mediators, and behavioral outcomes (diet, physical activity, weight).

### 3. Background and Rationale

Elevated BP is among the most common and important risk factors for atherosclerotic cardiovascular disease (ASCVD). Results from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that approximately 24 percent of the population, or almost 50 million persons in the United States, have hypertension, defined as an SBP  $\geq$  140 mmHg, a DBP  $\geq$  90 mmHg, and/or current use of antihypertensive medication (Burt *et al.*, 1995). Only 47 percent of adults have optimal BP defined as a systolic BP  $<$  120 mmHg and DBP  $<$  80 mmHg (see appendix). As age increases, the prevalence of hypertension rises progressively, such that  $<$  20 percent of adults ages 70 and older have an optimal BP.

Adverse patterns of BP disproportionately affect certain groups. In particular, African Americans have a higher prevalence and greater severity of hypertension than other minorities (e.g., Mexican Americans) and European Americans (Burt *et al.*, 1995). As well, women aged 60 and older tend to have higher prevalence of hypertension than men of similar age, while the reverse is true at younger ages. In certain groups, the prevalence of hypertension is almost ubiquitous; for example, nearly 80 percent of black women ages 60 and older have hypertension.

Efforts to control the epidemic of BP-related ASCVD have largely focused on implementation of pharmacologic therapy in persons with hypertension. Such efforts reflect a compelling body of evidence that drug therapy is an effective means to prevent stroke and coronary heart disease. A typical DBP reduction of 5 mmHg from drug treatment has been estimated to reduce the incidence of coronary heart disease events by 15 percent and cerebrovascular disease by 45 percent (Collins *et al.*, 1990).

Nonetheless, reliance on drug therapy is an incomplete and unsatisfactory solution to the problem of adverse BP patterns in the US. First, the risk of cardiovascular disease increases progressively throughout the range of BP, including ranges of BP considered normal (MacMahon *et al.*, 1990). Furthermore, a substantial fraction of adults have a BP in the above-optimal range, a level below which traditional drug treatment is initiated, but that nonetheless places them at increased risk of vascular disease. Stamler *et al.* (1993) estimated that 32 percent of BP-related deaths from coronary heart disease occur in individuals with a SBP between 110 and 139 mmHg. Second, reliance on drug therapy requires an endless cycle of detection, treatment, and maintenance. Hence, problems such as lack of awareness (present in nearly one third of hypertensives in NHANES III) and non-universal access to health care mitigate the potential effectiveness of drug therapy. Third, drug therapy can be expensive and can cause side effects and adverse biochemical changes. Some classes of antihypertensive agents—specifically, short-acting calcium channel blockers—may even increase the risk of myocardial infarction (Psaty *et al.*, 1995). Fourth, there is general concern about the appropriateness, not to mention aggregate costs, of placing nearly 25 percent of the US adult population on medication when effective non-drug therapies are available. Fifth, and perhaps most important, drug therapy does not address the major underlying and potentially reversible causes of elevated BP—that is, adverse lifestyles associated with suboptimal dietary habits and low levels of physical activity.

In view of these issues, national policy-making bodies recommend certain lifestyle, or non-drug, therapies as initial treatment of stage 1 hypertension, as an adjunct to drug therapy, and, most recently, as means to prevent hypertension (see appendix). Such an approach, particularly efforts

to prevent hypertension and to control stage 1 hypertension without medication, should have enormous societal benefits (e.g., preventing BP-related ASCVD events and potentially reducing the costs of pharmacologic management). Furthermore, a desirable BP achieved without drug therapy carries substantially less risk of cardiovascular disease than a similar BP level achieved through medication (Coresh *et al.*, 1993). Hence, implementation of lifestyle modification should be a high national priority.

### ***Established Recommendations for Lifestyle Modifications***

The Fifth Report of the Joint National Committee on the Detection, Evaluation and Treatment of High BP (JNC V) and the Working Group Report on Primary Prevention of Hypertension recommended four “lifestyle modifications” to reduce BP: 1) reduced sodium intake, 2) weight loss, 3) reduced alcohol consumption, and 4) increased physical activity (JNC V, 1993; Working Group, 1993). Based on the results of the DASH clinical trial, the Sixth Report of the Joint National Committee also recommends a diet rich in fruits, vegetables, and low-fat dairy products and reduced in saturated fat, total fat, and cholesterol (JNC VI, 1997).

#### ***Reduced Sodium Intake***

Inter-population and intra-population observational studies have documented a positive, direct relationship between sodium intake and BP (INTERSALT, 1988; Elliott *et al.*, 1996; Law *et al.*, 1991; Frost *et al.*, 1991), and experimental studies confirm this relationship. In a recent, comprehensive overview of randomized clinical trials (n=32 trials, total of 2635 participants), assignment to a reduced-sodium-intake treatment group was associated with 4.8/2.5 mmHg reductions in SBP/DBP in hypertensives and 1.9/1.1 mmHg reductions in normotensives (Cutler *et al.*, 1997). These BP reductions occurred from an average net reduction in sodium intake of approximately 77 mmol/24hr. Furthermore, there is no convincing evidence that a reduced sodium intake poses any health hazard. An observational study reporting an increased risk of myocardial infarction in men with low urinary sodium excretion (Alderman *et al.*, 1995) has been criticized on several grounds, including the lack of internal consistency (opposite trends in women), and insufficient control of potential confounders. Another observational study demonstrated an inverse relationship between salt intake and mortality; however, additional analyses that adjusted for calorie intake showed that the relationship was direct (Alderman *et al.*, 1998).

Because most adult Americans consume well over the maximum recommended daily intake of 100 mmol of sodium, virtually all Americans are candidates for reducing sodium intake. Recent trials show that behavior change interventions can reduce daily intake by approximately 30-50 mmol. In TOHP1 (Trials of Hypertension Prevention), participants assigned to the sodium intervention lowered sodium intake by 44 mmol/d (28 percent) from a baseline of 155 mmol/d (TOHP1, 1992). In TOHP2, sodium excretion fell by 33 mol/d (18 percent) from a baseline of approximately 180 mmol/d (TOHP2, 1997). In TONE (Trial of Nonpharmacologic Interventions in the Elderly), sodium intake fell by 40 mmol/d (28 percent) from a baseline of 144 mmol/d (Appel *et al.*, 1997a, Whelton, 1998). Results tend to differ by race-ethnicity and to a lesser extent by gender, such that sodium reduction is less in African Americans than in European Americans and less in women than in men; the latter is largely explained by lower baseline intakes of sodium. Additional analyses of data from TOHP1 and TONE indicate a dose response relationship between sodium reduction and the extent of BP reduction (Kumanyika *et al.*, 1993)

and hypertension control (Appel *et al.*, 1997a). These trials also document that a reduced sodium intake, once achieved, tends to be well maintained.

### *Weight Loss*

A strong and persuasive body of evidence from both observational and experimental studies indicates that weight is positively (directly) associated with BP and hypertension (Stamler J., 1991; NHLBI, 1998). The relationship is present in both genders and in most ethnic-racial groups. The importance of this relationship is reinforced by the high and increasing prevalence of overweight in the United States (Kuczmarski *et al.*, 1994). In the NHANES III survey, 55 percent of adult Americans were overweight, defined as a BMI  $\geq 25$  (NHLBI, 1998). Furthermore, overweight was highly prevalent in all surveyed race-gender groups.

Virtually every major trial that has examined the influence of weight loss on BP has documented a substantial and significant relationship between change in weight and change in BP. Reductions in BP occur even before (and without) attainment of desirable body weight. In one study that aggregated results across 11 weight loss trials, the average SBP/DBP reduction per kg of weight loss was 1.6/1.1 mmHg (Staessen *et al.*, 1989). Recent lifestyle intervention trials have uniformly achieved short-term weight loss. In several instances (Neaton *et al.*, 1993; Whelton *et al.*, 1996; Whelton, 1998; TOHP2, 1997), substantial weight loss has also been sustained over the long term (three or more years). For instance, mean weight loss in participants assigned to a weight loss intervention was 2.0 kg at three years in TOHP2 and 3.9 kg at 2.5 years in TONE (each net of control); in TOMHS (Trials of Mild Hypertension Study), a study in which all participants received a multifactorial intervention including weight loss, mean weight loss was 2.6 kg at 4 years.

### *Regular Physical Activity*

Evidence from observational studies and experimental studies suggests that increased physical activity can lower BP. Numerous studies have found a negative correlation between habitual physical activity and the development of hypertension. An inverse relationship between physical activity and BP has been observed in both sexes, all age groups, and in both African American and European Americans (Ainsworth *et al.*, 1991; Reaven *et al.*, 1991; Tuomilehto *et al.*, 1987). In addition to the observational evidence, more than 30 experimental studies have evaluated the impact of physical activity on BP (Kelley, 1994; Kelley, 1995). Most of these studies used aerobic training protocols at vigorous intensities (i.e., 60% maximal oxygen uptake or 70% maximal heart rate or greater) (Kelley, 1995; Arroll & Beaglehole, 1992). Fewer trials have evaluated lower intensity of exercise for BP effects. Moderate-intensity activity has been shown to decrease BP to an extent similar to, if not greater than, higher-intensity exercise in normotensive (Braith *et al.*, 1994) and hypertensive individuals (Hagberg *et al.*, 1989; Roman *et al.*, 1981). The entirety of these studies indicates that regular, moderate to vigorous physical activity lowers BP by 10/8 mmHg in hypertensives and 2/3 mmHg in normotensives. Even though most of these trials have at least one major design limitation (Arroll & Beaglehole, 1992), the better designed studies have resulted in an average reduction of 7/5 mmHg (Fagard 1993; Fagard, 1995). Policy-making bodies deem the evidence sufficient to advocate regular aerobic physical activity as a means to reduce BP (JNC VI, 1997; Working Group, 1993).

### *Limitation of Alcohol Intake*

The relationship between high alcohol intake (typically three or more drinks per day) and elevated BP has been reported in a large number of observational studies (MacMahon, 1987; Klatsky *et al.*, 1977). In the Prevention and Treatment of Hypertension Study (PATHS), a reduction in alcohol intake among moderate drinkers also reduced BP to a small, albeit non-significant, extent (Cushman *et al.*, 1998). A few trials have also demonstrated that reductions in alcohol intake among heavy drinkers can lower BP in normotensive and hypertensive men (Puddey *et al.*, 1985; Puddey *et al.*, 1987).

### *Dietary Patterns and BP*

Results from the Dietary Approaches to Stop Hypertension (DASH) clinical trial, in conjunction with previous studies of vegetarian diets, provide strong and persuasive evidence that modification of dietary patterns can have a profound influence on BP (Appel *et al.*, 1997b). DASH was a randomized, controlled feeding study testing the impact of three dietary patterns on BP in 459 individuals with a DBP of 80-95 mmHg and SBP < 160 mmHg (Sacks *et al.*, 1995). The three dietary patterns were 1) a control diet low in fruits, vegetables, and dairy products, with fat content typical of US consumption; 2) a diet rich in fruits and vegetables but otherwise similar to the control diet; and 3) a “combination” diet rich in fruits, vegetables, and low-fat dairy products, and reduced in saturated fat, total fat, and cholesterol. The nutrient profiles and dietary patterns used in DASH are shown in Table 1. In PREMIER, we use the term “DASH dietary pattern” to refer to the DASH combination diet.

The DASH dietary patterns were tested in a highly controlled, eight-week feeding study in which sodium intake and weight were held constant across the three diet arms. Participants were encouraged to keep physical activity levels constant throughout the study and were advised to limit alcohol intake to no more than two alcoholic beverages/day. Participants were asked to eat only food provided to them in the trial and nothing else.

**Table 1. Dietary Patterns\***

	<b>Control Diet Nutrient Target</b>	<b>Fruits and Vegetables Diet Nutrient Target</b>	<b>Combination Diet Nutrient Target</b>
<b>Nutrients</b>			
Total fat (percent of total Kcal)	37	37	27
Saturated fat (% Kcal)	16	16	6
Monounsaturated fat (% Kcal)	13	13	13
Polyunsaturated fat (% Kcal)	8	8	8
Carbohydrates (% Kcal)	48	48	55
Protein (% Kcal)	15	15	18
Cholesterol (mg/day)	300	300	150
Fiber (g/day)	9	31	31
Potassium (mg/day)	1700	4700	4700
Magnesium (mg/day)	165	500	500
Calcium (mg/day)	450	450	1240
Sodium (mg/day)	3000	3000	3000
<b>Food Groups (no. of servings/day)</b>			
Fruits and juices	1.6	5.2	5.2
Vegetables	2.0	3.3	4.4
Grains	8.2	6.9	7.5
Low-fat dairy	0.1	0.0	2.0
Regular-fat dairy	0.4	0.3	0.7
Nuts, seeds, and legumes	0.0	0.6	0.7
Beef, pork, and ham	1.5	1.8	0.5
Poultry	0.8	0.4	0.6
Fish	0.2	0.3	0.5
Fats, oils, and salad dressing	5.8	5.3	2.5
Snacks and sweets	4.1	1.4	0.7

\* Values are for 2100-kcal diets.

The fruits and vegetables and combination diets were designed to provide clusters of nutrients postulated to reduce BP (increased potassium, magnesium, and fiber in the fruits and vegetables diet, and increased calcium, potassium, magnesium, fiber, and protein, and reduced saturated fat, total fat, and cholesterol in the combination diet). Sodium and weight were held constant in order to test the effects of the diets rather than known determinants of blood pressure. Compared to control, the combination diet reduced SBP and DBP by 5.5 and 3.0 mmHg (each  $P < 0.001$ ); the fruits and vegetables diet also reduced BP, but to a lesser extent. Among the 133 hypertensive participants (SBP: 140-159 mmHg, and/or DBP: 90-95 mmHg), the combination diet reduced systolic and diastolic BP by 11.4 and 5.5 mmHg (each  $P < 0.001$ ); in 326 non-hypertensive participants, corresponding reductions were 3.5 mmHg ( $P < 0.001$ ) and 2.1 mmHg ( $P = 0.003$ ). Additional analyses indicate that the DASH combination diet was more effective in minorities, particularly African Americans, compared to non-minorities (SBP/DBP reduction of 6.8/3.5 versus 3.0/2.0, respectively) (Svetkey *et al.*, 1999).



The rationale for the DASH trial evolved from the results of many studies. Epidemiological studies have demonstrated significant inverse associations between blood pressure and micronutrients: potassium, calcium, magnesium, and fiber (Working Group, 1993). In clinical trials, supplementation of diet with potassium has significantly reduced blood pressure (Whelton, 1997); corresponding evidence for calcium and magnesium supplements is inconsistent. Specific foods and dietary patterns also have been inversely associated with BP—notably, vegetarian diets, plant foods, fruits, and vegetables. Furthermore, higher intakes of fruits and vegetables and potassium have been inversely associated with the incidence of stroke (Gillman *et al.*, 1995; Ascherio *et al.*, 1998; Khaw & Barrett-Connor, 1987).

Despite observational evidence regarding the beneficial effects of fruits, vegetables, and dietary patterns on BP and other diseases, few trials have been undertaken to evaluate the effects of fruits, vegetables, and dietary patterns. Results of the DASH trial as well as general interest in fruits and vegetables for the prevention of cancer, diabetes, and other chronic diseases (Steinmetz & Potter, 1996) provide a strong rationale for the evaluation of the combination dietary pattern in the context of other diet and lifestyle recommendations in free living individuals selecting their own food.

### ***The Impact of Multicomponent Interventions on BP***

Despite the potential for substantial reductions in BP from multicomponent lifestyle intervention programs, few trials have examined the combined impact of simultaneously implementing two or more lifestyle interventions. To our knowledge, only five large-scale trials have tested interventions with two or more components: the Primary Prevention of Hypertension (PPH) Trial, the Hypertension Control Program (HCP), the Trials of Mild Hypertension Study (TOMHS), the Trials of Hypertension Prevention, Phase II (TOHP2), and the Trial of Nonpharmacologic Intervention in the Elderly (TONE). Each of these trials is described below. While each trial has provided valuable information, several issues hinder their generalizability. First, the effects of multicomponent interventions in hypertensive individuals is uncertain, one trial enrolled medication-controlled hypertensives, and just one trial enrolled persons with non-medicated hypertension (TOMHS) (Neaton *et al.*, 1993). Because all groups in TOMHS received the lifestyle intervention, the actual extent of BP reduction from this program is not clear. Second, despite the high prevalence of hypertension in African Americans and the potential benefits of non-drug therapies in this population, less than 25 percent of participants in each study were African American. Third, the study populations were often skewed in other respects (e.g., 86 percent men, all < 45 years old in the Primary Prevention of Hypertension Trial). Fourth, only one trial (TOMHS) included enhanced physical activity as part of its intervention, and no trial implemented the current recommendation for regular physical activity on most days of the week (USDHHS, 1996). Finally, none of the five trials included modification of dietary patterns similar to the DASH combination diet.

The **Primary Prevention of Hypertension (PPH)** trial was a five-year trial that tested the impact of a multicomponent intervention (weight loss, reduced sodium intake, reduced alcohol intake, and increased physical activity) on incident hypertension in 201 persons (87 percent men, 82 percent white, age < 45) with above-optimal BP (122/82 mmHg) at baseline (Stamler R. *et al.*, 1989). In comparison to the control group, the multicomponent intervention significantly reduced the risk of hypertension (RR=0.46, p=0.027). Although the risk reduction observed in

this trial is impressive, the number of events was small, and the homogeneity of the study population hinders its generalizability.

The **Hypertension Control Program (HCP)** was a four-year trial testing whether hypertensive individuals would become non-hypertensive after gradual withdrawal of antihypertensive medications by following a multicomponent nutritional intervention (weight loss, reduced sodium intake, and limitation of alcohol intake) compared to individuals who were withdrawn from medication and did not participate in the nutritional intervention (Stamler, *et al.*, 1987). The population sample included 189 persons on antihypertensive drug therapy with DBP <90, age  $\geq 35$  (mean age 56) years, 65% male, and 85% white. At 4 years, 39% of those in the nutrition intervention group remained normotensive without drug therapy compared with 5% who were withdrawn from drug therapy but did not follow the nutritional intervention (Chi-square = 16.2,  $P < .001$ ). Similar to the PPH trial, the HCP sample size was small, and the homogeneity of the study population hinders its generalizability. In addition, physical activity was not emphasized in the intervention.

The **Trials of Mild Hypertension Study (TOMHS)** was a four-year trial that tested the effects on blood pressure of five classes of antihypertensive medication. All groups, including a placebo group, received a multifactorial intervention: weight loss, sodium reduction, physical activity, and reduced alcohol intake (Neaton *et al.*, 1993; Elmer *et al.*, 1995a). Study participants were 902 individuals (62 percent men, 80 percent non-Black, mean age of 55 years) with a DBP of 85-99 mmHg (mean SBP/DBP=140.4/90.5). In the placebo group that received just the lifestyle intervention, average within-group BP changes were a 10.6 mmHg reduction in SBP and a 8.1 reduction in DBP. While these reductions are impressive, the actual extent of BP reduction from the lifestyle intervention is unclear in this trial, because TOMHS did not have a “no intervention” control group. Thus, reductions in blood pressure could have been attributed to causes other than the lifestyle intervention, such as regression to the mean, and habituation to blood pressure measurements.

The **Trials of Hypertension Prevention-Phase II (TOHP2)** was a 2x2 factorial, multicenter trial testing the long-term effects of weight loss and/or a reduced salt intake on incident hypertension in 2383 overweight middle-aged adults (66 percent men, 82 percent non-Black, mean age of 44 years) with a DBP of 83 to 89 mmHg and a SBP < 140 mmHg (TOHP2, 1997). At six months, the height of intervention adherence, the incidence of hypertension was lowest in the combined weight loss/reduced sodium group (2.7 percent), intermediate in the weight loss (4.2 percent) and sodium reduction (4.5 percent) groups, and highest in the usual care group (7.3 percent). At 18 months, this pattern persisted. Across the entire 36-48 months of possible follow-up, however, the incidence of hypertension was significantly less in each lifestyle intervention group than in the usual care group but not different from each other. Although interpretation of TOHP2 is complex, the pattern of incident hypertension at six and 18 months suggests that the effects of the weight loss and reduced sodium intake interventions, under optimal conditions of adherence, may be additive.

The **Trial of Nonpharmacologic Interventions in the Elderly (TONE)** tested the effects of reduced sodium intake and weight loss, alone and combined, on BP control after withdrawal of antihypertensive therapy. Trial participants were 975 hypertensives (52 percent men, 77 percent non-Black), ages 60-80 years, with a baseline BP < 145/85 mmHg (Appel *et al.*, 1995; Whelton *et al.*, 1996). In a 2x2 factorial design, overweight participants were assigned to usual care, sodium reduction alone, weight loss alone, or a combined intervention. Three months after the

start of intervention, withdrawal of medication was attempted. Participants were then followed for a median of 25.3 months. The primary outcome was a composite endpoint defined by the occurrence of an average BP > 150/90 mmHg, resumption of BP medication, or an ASCVD clinical event. In obese participants, the hazard ratios for the three active interventions (relative to usual care) were 0.64 for weight loss, 0.60 for sodium reduction, and 0.47 for the combined intervention (each  $p < 0.01$ ) (Whelton *et al.*, 1998). In the context of an older population with high adherence, these results indicate that weight loss and sodium reduction, together, have substantially greater effects than either intervention alone.

In addition to these four lifestyle intervention trials, the **Dietary Approaches to Stop Hypertension 2 Study (DASH 2)** is an ongoing NHLBI-sponsored feeding study designed to determine the main and interactive effects of three levels of sodium intake and two dietary patterns on BP among 400 participants (50 percent African American, 50 percent women) with above-optimal BP or stage I hypertension. The two dietary patterns are the DASH control diet and the DASH combination diet. The three sodium levels are: 1) a “higher” sodium level (150 mmol), reflecting current US consumption; 2) an “intermediate” sodium level (100 mmol), reflecting the upper limit of current US recommendations for sodium; and 3) a “lower” sodium level (50 mmol), reflecting potentially optimal sodium levels for lowering BP. This trial, which is a controlled feeding study, not a behavioral intervention trial, will be completed by the end of 1999.

### ***Rationale for Other CV Outcome Measures***

Besides reducing blood pressure, the components of the PREMIER interventions should have beneficial impacts on other ASCVD risk factors. In addition to blood pressure, other outcome measurements to be obtained at baseline and follow-up are fasting lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), fasting glucose and insulin (indices of insulin resistance), and fasting homocysteine (a putative, modifiable ASCVD risk factor).

### ***Rationale for PREMIER***

Results from DASH have stimulated considerable interest in dietary patterns as nonpharmacologic therapies for reducing BP. As documented above, surprisingly little is known about the effects of simultaneously implementing longstanding recommendations for nonpharmacologic lifestyle interventions, much less the effect of adding the DASH combination dietary pattern to these recommendations. Furthermore, because most recent trials have studied the impact of nonpharmacologic interventions in persons with a normal but above-optimal BP, even less is known about the effects of multicomponent interventions in hypertensives. The importance of enrolling hypertensives in such studies is well demonstrated by the DASH trial, which included persons with above-optimal BP as well as persons with stage 1 hypertension. In DASH, the impressive BP reductions observed in hypertensives magnified the potential importance of the trial by demonstrating reductions with obvious clinical significance. Thus, the DASH study has created new impetus for lifestyle modification to prevent and treat hypertension.

Adherence to multicomponent nonpharmacological interventions, such as those to be delivered in PREMIER, has not been well investigated. Several studies have used multicomponent interventions for blood pressure and other risk factor reduction (Stamler R.

*et al.*, 1987; Stamler R. *et al.*, 1989; Elmer *et al.*, 1995a; Van Horn *et al.*, 1997), but the number of components addressed in those studies is fewer than what will be delivered in PREMIER. The PREMIER intervention addresses several complex lifestyle behaviors: dietary change covering a broad array of nutrients and food groups related to blood pressure reduction; increased physical activity, which receives a major emphasis in PREMIER; and counseling on alcohol intake. Through process measures related to intervention attendance and self-monitoring records, and through impact measures such as weight loss, urinary excretion of minerals and urea nitrogen, 24-hour dietary recalls, seven-day physical activity recalls, and cardiorespiratory fitness, PREMIER will be able to assess whether different components of the intervention had better adherence than others.

The current model for implementing lifestyle modification involves advice from the physician and, in some cases, referral to a dietitian or health educator. Dietary counseling typically involves one or two individual counseling sessions, in which a diet history is obtained, followed by provision of educational materials and advice on how to reduce salt and, to a more variable extent, reduce calorie and alcohol intake. Unfortunately, the relatively low frequency and intensity of contact are insufficient to effect much change (Solberg *et al.*, 1996; Ammerman *et al.*, 1994).

Contemporary health care systems may limit the physician's ability to provide lifestyle intervention, but they also offer an opportunity for the development of specialized health education and prevention programs. Indeed, some lifestyle change interventions have become part of routine care in most HMOs, and there is a trend toward adding more (Budd & Gruman, 1995). A few examples of such programs include a behavioral pain management program that requires more than 100 hours of patient contact time (Tulkin, 1995); a six-session program designed to help patients with stress-related illness (Burnes, 1995); a six-session arthritis self-help course (Lorig, 1995; Lorig *et al.*, 1993); a wide variety of smoking cessation programs, some of which include 10-15 group sessions (Zapka *et al.*, 1997; McAfee *et al.*, 1995); and a nurse-case manager directed, home-based risk factor management program for individuals with documented coronary heart diseases (Miller *et al.*, 1996).

Other multi-session, behavioral intervention programs for diabetic care, cardiac rehabilitation, weight loss, etc., are in use in contemporary health care systems. Such programs show that the model we propose for PREMIER (comprehensive behavior change intervention with frequent sessions, patient and family involvement, and extended maintenance contacts) is a practical and desirable model for treating elevated blood pressure. Results from the PREMIER study will provide objective evidence on the extent of blood pressure reduction from a behavioral intervention program that could be implemented as part of routine health care.

In PREMIER, participants are randomly assigned to one of three groups (advice-only control, comprehensive, and comprehensive plus DASH). Each of the three possible pairwise comparisons has substantial scientific and public health significance. The comparison of the comprehensive plus DASH arm to advice only determines the maximal extent of BP reduction achievable from nonpharmacologic therapy, combining all longstanding recommendations along with the DASH dietary pattern, in free-living individuals. The comparison of the comprehensive (without DASH) arm to advice only determines the extent of BP reduction from a program designed to accomplish longstanding recommendations. The comparison of the comprehensive plus DASH arm to the comprehensive arm determines the additional value of the DASH combination diet beyond longstanding recommendations.

## 4. Study Design

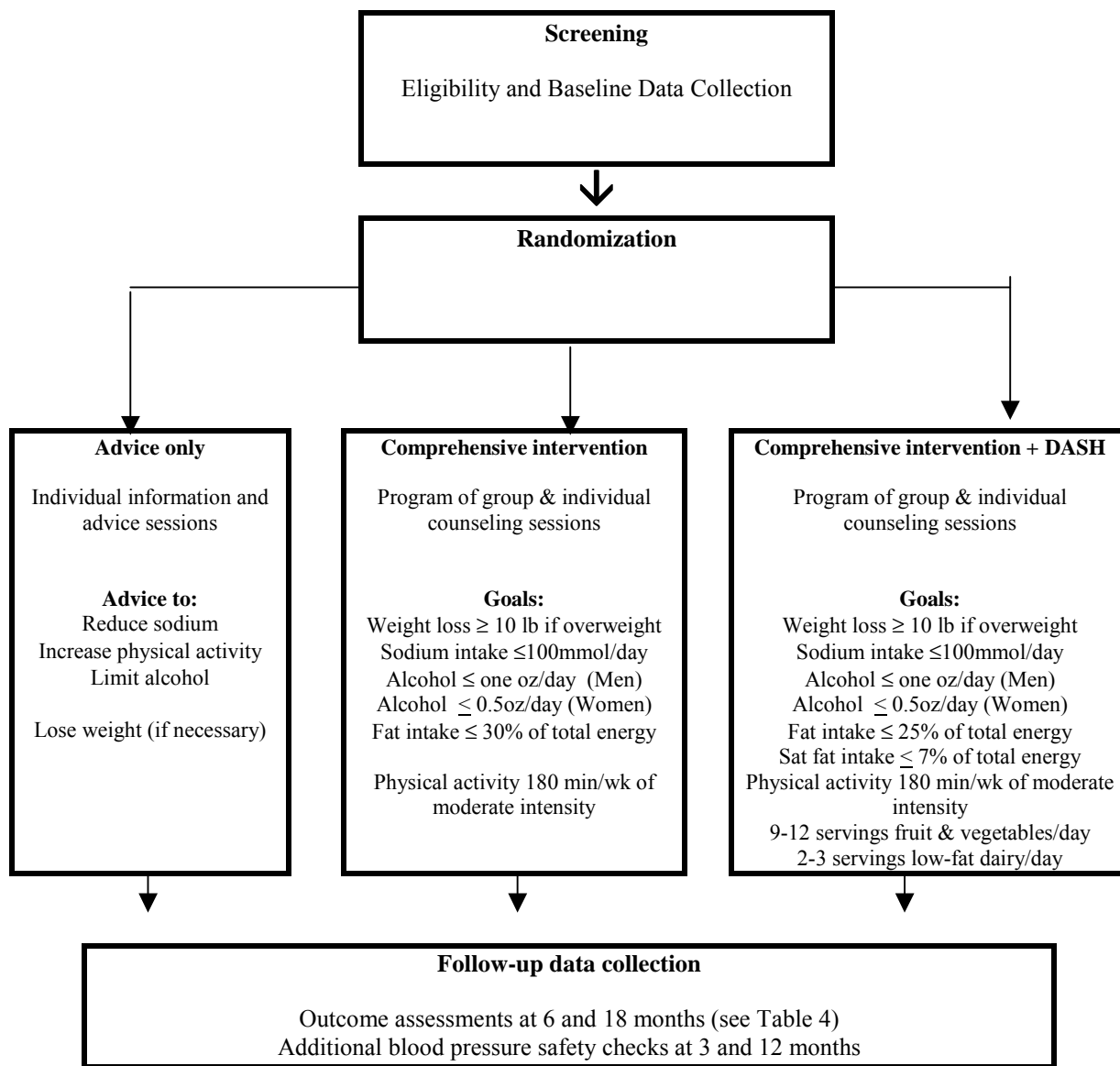
### *Overview*

PREMIER is a randomized clinical trial with three arms: an advice-only control group and two lifestyle change groups (see Figure 1). Participants are 800 adults, aged 25 years or older, with above-optimal blood pressure or stage 1 hypertension who are not taking anti-hypertensive medications. Approximately 40% of participants are expected to be African Americans and one-half women. After screening for eligibility, participants are randomly assigned to one of three groups: an advice-only control condition, a comprehensive lifestyle intervention program that includes reduced sodium intake, increased physical activity, limited intake of alcohol, and weight loss if overweight; and a comprehensive plus DASH intervention including all of the elements of the comprehensive lifestyle intervention plus the DASH dietary plan (rich in fruits, vegetables, low-fat dairy products, and reduced in saturated fat, total fat, and cholesterol). Follow-up data collection and safety monitoring occurs frequently over the year and a half of participation. The primary outcome variable is SBP measured at six months after randomization. Other outcomes include DBP, measures of dietary intake, physical activity, cardiorespiratory fitness, hypertension status, and biochemical markers.

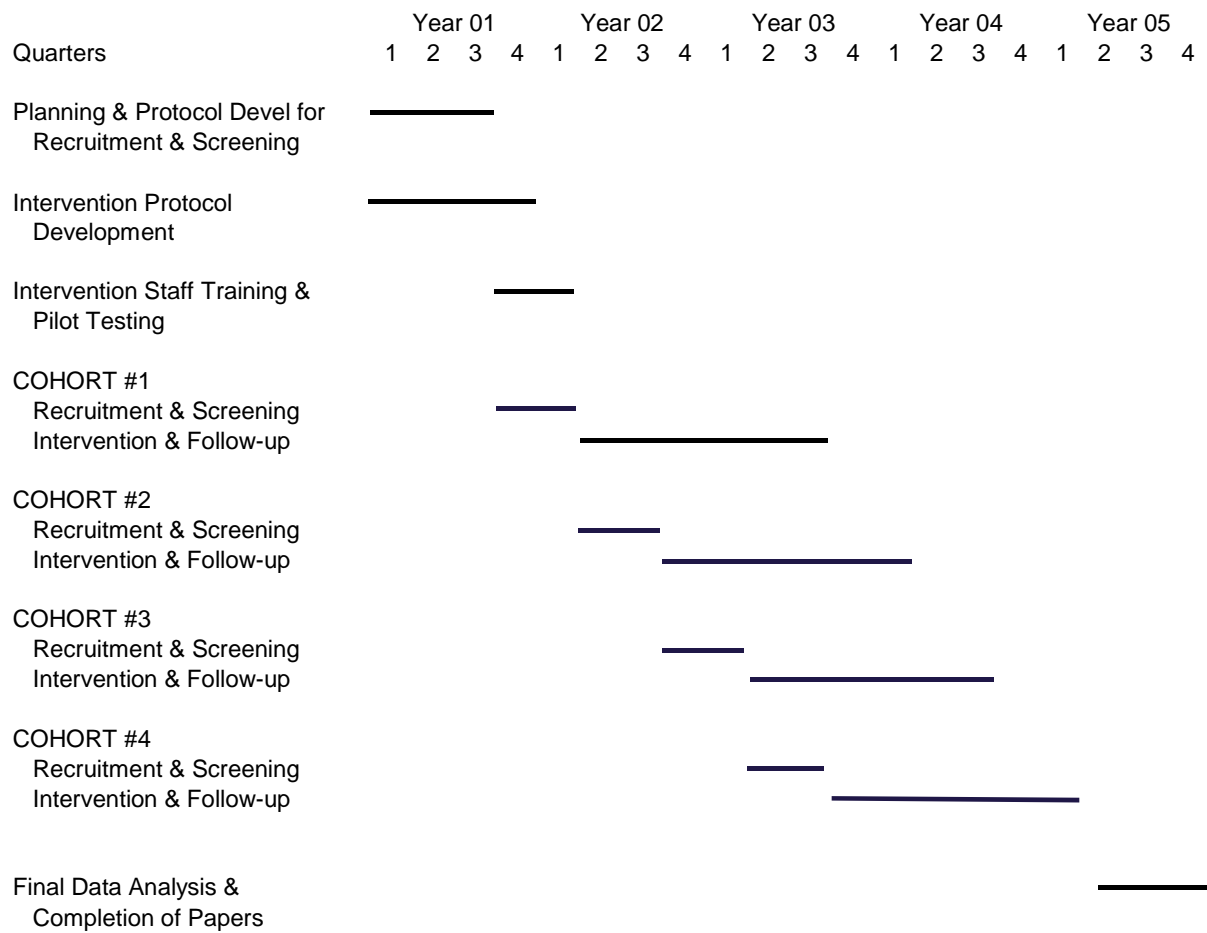
### *Workplan and Timeline*

The workplan and study timeline are shown in Figure 2. Activities in the first year include final development of the protocol, development of a detailed manual of procedures, staff training, development of the trial's data management system, and implementation of the trial-wide communications system. Recruitment of the first cohort of participants begins in year 01. Total sample size for this study is 800, recruited in three to five cohorts. Each of the four clinical centers in this collaborative project recruits an equal number of participants during a two-year period. Recruitment for the last cohort is completed at about the end of year 03, and follow-up data collection for the final cohort is completed in year 05. Final data analyses and paper writing are done in year 05.

**Figure 1. PREMIER Design Overview**



**Figure 2. Example of Four-Cohort Timeline and Workplan**



## 5. Eligibility

### *Study Sample*

Trial participants are 800 community-dwelling persons, ages 25 and older, with a systolic BP of 120-159 mmHg and diastolic BP of 80-95 mmHg. The rationale for choosing this BP range is to enroll persons who are candidates for non-drug intervention programs designed to reduce BP. This group includes individuals with normal but above-optimal BP and those with stage 1 hypertension. The Working Group Report on the Primary Prevention of Hypertension (1993) specifically designates persons with above-optimal BP as a group at high risk for hypertension, justifying special attempts to lower BP. Similarly, the JNC VI recommends non-drug therapy as initial treatment for stage 1 (class A and B) hypertension (see appendix). Using recruitment procedures similar to DASH and DASH2, 50 percent of trial participants are anticipated to be women and approximately 30 percent to have hypertension. Because of the disproportionate burden of hypertension in African Americans and because of the possibility that several intervention components (reduced salt intake and the DASH dietary pattern) may reduce BP to a greater extent in African Americans than in other groups (Whelton *et al.*, 1996; Svetkey *et al.*, 1999), we set 40 percent as the trial recruitment goal for African Americans. Duke, Johns Hopkins, and Pennington each recruit 50 percent African Americans, while the CHR recruits 10 percent African Americans.

### *Eligibility Criteria*

The eligibility criteria for this trial (see Table 2) have been selected to yield a reasonably representative sample of adults with above-optimal BP or stage 1 hypertension. Most of these criteria exclude individuals for whom the interventions would be inappropriate, who have health problems requiring immediate attention, or who are candidates for aggressive antihypertensive drug therapy. For example, we screen out heavy drinkers of alcohol and those who consume 6 or more drinks on one occasion twice or more per week, because they are more likely to benefit from an alcohol treatment program than from the lifestyle interventions in PREMIER.

We have set a lower age limit at 25 years to ensure that the participants in the lifestyle intervention programs are comfortable in mixed-age groups. Our experience in group-based weight-loss programs for a general population has shown that very young adults do not adapt well to mixed-age social support programs (Stevens *et al.*, 1989).

The body mass index (BMI) eligibility criteria (18.5-45 kg/m<sup>2</sup>) were selected to exclude those who are underweight (NLHBI, 1998), because they may not respond well to the dietary change interventions and may be at risk for eating disorders, and those who are massively obese, for whom different weight loss strategies than those to be provided by the PREMIER lifestyle interventions may be more appropriate (NHLBI, 1998).

Persons with diabetes (current use of insulin or oral hypoglycemic agents *or* a non-fasting blood glucose level of  $\geq 160$  mg/dl *or* a fasting blood glucose level  $\geq 126$  mg/dl), are excluded, since national guidelines suggest pharmacologic antihypertensive therapy is appropriate for them.

Participants who are positive on either the Rose angina questionnaire or the Rose claudication questionnaire (Rose *et al.*, 1977) are referred to their personal physician for further evaluation



and may only participate with the approval of both that provider and a PREMIER clinician. Participants with a positive Rose angina questionnaire at baseline must have all three of the following in order to remain eligible: approval of the participant's personal physician, a negative stress test within the past six months, and approval by the PREMIER clinician.

Finally, persons with evidence of recent therapy for serious psychiatric disorders are also excluded.

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**Table 2. Eligibility Criteria**

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**Inclusion Criteria**

Baseline SBP 120-159 mmHg and DBP 80-95 mmHg  
Age 25 or older as of the PSV visit  
Willing and able to participate fully in all aspects of the intervention  
Provide informed consent  
BMI 18.5-45 kg/m<sup>2</sup>  
Access to telephone

**Medication Exclusions**

Regular use of anti-hypertensive drugs or other drugs that raise or lower BP  
(any in previous three months prior to SV1)  
Current use of insulin or oral hypoglycemic agents  
Use of oral corticosteroids >5 days/month on average  
Current use of medications for treatment of psychosis or manic-depressive illness  
Use of oral breathing medications other than inhalers > 5 days/month on average  
Use of weight-loss medications in the 3 months prior to SV1

**Medical History Exclusions**

Cardiovascular event (stroke, MI, PTCA, CABG, or ASCVD-related therapeutic procedure)  
Congestive heart failure  
Current symptoms of angina or peripheral vascular disease by Rose Questionnaire (Rose *et al.*, 1977), unless approved by both participant's personal physician and a PREMIER clinician. For angina symptoms, participant also must have a negative stress test within the past 6 months. If no personal physician, must be referred.  
Cancer diagnosis (except for non-melanoma skin cancer) or treatment in past two years  
Renal insufficiency (GFR<60 ml/min as estimated using Cockcroft-Gault formula)  
Random glucose  $\geq$  160 mg/dL or FBS  $\geq$  126 mg/dl  
Psychiatric hospitalization within the last 2 years

**Other Exclusions**

Unable to provide acceptable BP measurements  
Consumption of more than 21 alcoholic drinks per week  
Consumption of 6 or more drinks on one occasion twice or more per week  
Planning to leave the area prior to the anticipated end of participation  
Body weight change > 15 pounds in the 3 months prior to SV1  
Pregnant, breast feeding, or planning pregnancy prior to the end of participation  
Current participation in another clinical trial  
Investigator discretion for safety or adherence reasons  
Household member of another PREMIER participant or of a PREMIER staff member

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## **6. Recruitment and Screening**

### ***Recruitment***

In our collective experience conducting similar studies, the combination of mass mailing, community-based screening, and mass-media announcements has been extremely effective for recruiting participants with above-optimal BP or stage 1 hypertension. Of these, mass mailing serves as the principal recruitment strategy for PREMIER. Each clinical center has access to computer tapes of age-eligible licensed drivers and/or registered voters, and each has successfully implemented large-scale mass mailings. Each of the four clinical centers also has well-established links with large employers that have facilitated work-site-based recruitment efforts in previous studies. Finally, each center also has considerable experience using mass media (e.g., radio advertisements, public service announcements, newspaper articles) recruitment methods.

Each clinical center also implements targeted strategies to increase minority enrollment. Examples of strategies to enhance minority enrollment include a) mass mailings targeted to certain zip codes and b) special community-based screening events. Advertisements, articles, and public service announcements on radio stations and in newspapers that reach minority populations are also used.

### ***Screening***

Participant eligibility for PREMIER is determined in a series of three formal screening visits, each of which includes questionnaires and clinical measurements to determine eligibility. Data collected in the screening visits also provide baseline levels for later analyses of treatment effects. Whereas the recruitment and pre-screening strategies vary depending on local conditions, the protocols for the formal screening visits are the same at all centers. In order to efficiently screen participants while minimizing misclassification, BP eligibility is assessed at each screening visit using successively narrower eligibility ranges (see Table 3).

While all participants need to provide written informed consent prior to participating in the formal screening visits, the manner in which this consent is obtained is determined locally by each clinical center in conjunction with its own Institutional Review Board (IRB). At a minimum, clinical centers obtain separate consents to cover the screening phase of the trial and the post-randomization phase. The Coordinating Center (CC) is responsible for documenting the informed consent processes used at each site independent of any local IRB documentation that may be required.

**Table 3. PREMIER Blood Pressure Eligibility Criteria and Screening Visit Windows**

Visit	Measure	Eligible Range (mm/Hg)	Visit Window
PSV	SBP	118-179 <sup>1</sup>	
	DBP	78-109 <sup>1</sup>	
SV1	SBP	118-170 <sup>2</sup>	≤4 months after PSV
	DBP	78-100 <sup>2</sup>	
SV2	SBP	119-165 <sup>2</sup>	≥7 days after SV1
	DBP	79-98 <sup>2</sup>	
SV3	SBP	120-159 <sup>2</sup>	≥7 days after SV2
	DBP	80-95 <sup>2</sup>	
R/I <sup>3</sup>	SBP	NA	≤6 months after SV1
	DBP		

<sup>1</sup> PSV blood pressure is optional, and these are suggested ranges, which can be modified by individual clinical centers.

<sup>2</sup> based on cumulative average of all SV measurements (except PSV) to date

<sup>3</sup>This BP may be done at any time after SV3 and prior to randomization. It is not used for eligibility, but only in calculating baseline BP

### *Pre-Screening Visit (PSV)*

Each clinical center conducts a brief, preliminary evaluation of eligibility, either in person or by telephone. This pre-screen is a fast, inexpensive means to identify ineligible volunteers prior to scheduling a formal screening visit. The pre-screen includes a brief questionnaire regarding major exclusions and collection of some key demographic variables, including age, height, and weight. As part of the pre-screen, clinical centers may elect to gather a single, exclusionary BP measurement using any type of BP measuring device they wish. This latter measurement may be taken at any time prior to beginning the SV1 visit and need not coincide with completion of the pre-screen questionnaire. Eligibility ranges for this optional BP measurement are determined locally (see Table 3).

Individuals who complete pre-screening are either excluded from further participation or are scheduled for the SV1 visit.

### *Screening Visit 1 (SV1)*

SV1 occurs no more than four months after the PSV (which may occur simultaneously with SV1) and no more than six months prior to randomization. If more than four months have elapsed since the PSV, the PSV must be repeated. In this case, the repeat PSV may be combined with the SV1. The SV1 is intended to provide general information about the study and identify major exclusionary criteria at minimal expense. This 20-30 minute visit includes two random zero (RZ) BP measurements, measurement of height and weight, review of general dietary and behavioral information pertinent to the interventions, and a review of medical eligibility factors.

The BP eligibility cutpoints at SV1 are listed in Table 3 and are based on the average of the SV1 BP measurements. In addition to these *eligibility ranges*, *BP safety thresholds* are described in the Safety Monitoring section.

Participants who are eligible to continue on the basis of SV1 are scheduled for the second screening visit (SV2). Ineligible participants are thanked for their cooperation and, if necessary, referred to their personal physician for further evaluation.

#### *Screening Visit 2 (SV2)*

SV2 occurs at least seven days after SV1. It includes BP measurement, complete review of medication use, a nonfasting blood sample for eligibility (creatinine, glucose), instructions and supplies for completing a food record and a 24-hour urine collection, and completion/review of additional eligibility and non-eligibility baseline questionnaires.

The BP eligibility cutpoints at SV2 are listed in Table 3 and are based on the cumulative average of the SV1 and SV2 blood pressure measurements. In addition to these BP eligibility ranges, BP safety thresholds are described in the Safety Monitoring section of this protocol.

Participants who are eligible to continue on the basis of SV2 are scheduled for the third screening visit (SV3). Ineligible participants are thanked for their cooperation and, if necessary, referred to their personal physician for further evaluation.

#### *Screening Visit 3 (SV3)*

SV3 occurs at least seven days after SV2. It includes BP measurement, a fasting blood draw (analyzed centrally for total cholesterol, LDL-C, HDL-C, triglycerides, insulin, glucose, and homocysteine, and additionally in cohorts 2-4 for carotenoids, folate, and vitamin B-12), processing of the 24-hour urine specimen (analyzed centrally for Na, K, phosphorus, and nitrogen), the physical activity recall, and completion/review of additional eligibility and non-eligibility questionnaires. The physical activity recall may alternatively be completed in the interim period after SV3, prior to randomization.

The BP eligibility cutpoints for SV3 are listed in Table 3 and are based on the cumulative average of the SV1, SV2, and SV3 blood pressure measurements. In addition to these BP eligibility ranges, BP safety thresholds are described in the Safety Monitoring section. Although listed as part of SV3, the fasting blood draw may be completed at any time between SV2 and randomization. Similarly the 24-hour urine may be collected and processed at any time between SV2 and randomization.

To assure that participants fully understand the demands and nature of the study before they enroll, at SV3 an interventionist again reviews study requirements with the participants and obtains dietary information pertinent to the intervention. In addition, the interventionist assesses the participants' motivation and willingness to participate in the study using the Diet and Physical Activity Questionnaire and any other available subjective or objective information, and may exclude participants on the basis of this assessment.

### *Fourth Baseline Blood Pressure*

Sometime after SV3 and prior to randomization, participants complete a fourth blood pressure assessment. This may happen either during an interim visit between SV3 and randomization or as part of the randomization visit. While not used to determine eligibility, this BP is used, along with those from SV1-SV3, to calculate the baseline blood pressure against which change is measured. There is not a minimum time interval between the SV3 visit and the measurement of the fourth baseline blood pressure.

### *24-Hour Diet Recalls*

Two unannounced 24-hour diet recalls are conducted between SV3 and the randomization visit to provide baseline dietary intake data. The recalls, which are conducted by telephone from the Diet Assessment Center of Pennsylvania State University, occur within three weeks of each other and on non-consecutive days. More than 90 percent of the eligible participants are expected to complete the two 24-hour recalls and be randomized into the trial. Completion of these two recalls is a requirement for randomization.

### *Cardiorespiratory Fitness*

A submaximal treadmill exercise test is conducted between SV3 and the randomization visit to provide information regarding baseline fitness. Moderate-intensity physical activity improves fitness in individuals who have previously been sedentary, and vigorous activity improves fitness in individuals who have previously been participating in moderate activity and who adopt higher-intensity activity. Completion of the exercise test is a requirement for randomization.

## **7. Randomization**

Following screening, and no more than six months after SV1, participants attend a separate Randomization/Intervention visit during which additional baseline measurements are collected, eligibility is confirmed, randomization occurs, and intervention begins.

### ***Additional Baseline Measurements***

Prior to randomization, staff measure weight (which serves as the baseline weight against which change is assessed) and waist circumference. Baseline waist circumference may be measured in the interim period *or* at the R/I visit. Additional non-eligibility baseline data, if not previously gathered, are collected at this time. A review of major medical eligibility criteria must also have been completed within 30 days of randomization in the event that more than 30 days would have elapsed between SV1 and randomization.

If informed consent has not previously been obtained, staff next ask the participant to provide written informed consent for the intervention phase of the trial. After providing informed consent, participants receive a randomization assignment and are officially enrolled in the intervention phase of the trial.

### ***Randomization***

Randomization assignments are generated on site using software developed by the Coordinating Center. These assignments are stratified by clinic and baseline BP categories (normotensive vs. hypertensive) and within these categories are blocked to provide a balance in treatment assignments over time. As part of the randomization process, the computer verifies eligibility and the completeness of baseline data entry. Individuals lacking proper documentation of eligibility or key baseline data elements are not randomized. Participants learn their treatment assignment from a staff member who is not involved in follow-up data collection.

### ***Blinding***

PREMIER study participants know their intervention assignments, as do clinical center staff who are involved in delivering the interventions. However, all clinical center staff involved in follow-up data collection are kept blinded to participant treatment assignments, and all intervention staff are kept blinded to participant blood pressure data. Participants are told their baseline blood pressure measurements and also receive a summary of their six-month blood pressure measurements. Provision of such information is appropriate in view of the fact that many participants will have stage 1 hypertension. Participants also receive a complete set of blood pressure results, along with a summary of their laboratory measurements, at the conclusion of intervention (see Participant Closeout, Section 11).

## **8. Baseline and Follow-Up Measures and Data Collection**

This section describes the measurements collected during screening and follow-up, and the schedule for data collection (see Table 4). Protocols for assessing these measurements are also summarized. In addition to the screening activities described previously, safety monitoring is conducted at three, six, 12, and 18 months following randomization, and formal clinic visits for primary outcome assessments are conducted at six and 18 months after randomization.

### ***Primary Outcome Measures***

All BP measurements (with the exception of the PSV BP) are performed using a random zero sphygmomanometer (Wright & Dore, 1970) following the same procedures used in SHEP (SHEP Group, 1991), TOHP (Satterfield *et al.*, 1991), and DASH (Sacks *et al.*, 1995). These measurements are taken with participants in a seated position, using the right arm (unless the right arm is missing or unsuitable for use, in which case the left arm is used). Participants refrain from eating or smoking for at least 30 minutes prior to BP measurements and sit quietly for five minutes before the first measurement. At each clinic visit two BP measurements are obtained with at least 30 seconds between measurements. Systolic BP is defined as Korotkoff I (appearance of the first sound), and diastolic pressure is Korotkoff V (disappearance), with all measurements rounded to the nearest 2 mmHg. All staff collecting blood pressure data are trained and certified in the use of a standard protocol and are kept blinded to participant treatment assignments.

At each of the primary (six-month) and secondary (18-month) assessment points, three sets of BP measurements are taken over a three-month interval. A single set of BP measurements is obtained at the three- and twelve-month visits.

**Table 4. Data Collection Schedule**

	PSV	SV1	SV2	SV3	Interim	R/I	3	6	12	18
Demographics/Eligibility	X									
Informed consent		X			Rand. Consent					
Height		X								
Weight		X				X	X	X	X	X
Blood pressure		X	X	X	X		X	X <sup>1</sup>	X	X <sup>1</sup>
Diet/phys act checklist		X								
Eligibility questionnaire		X								
Rose angina questionnaire		X					X	X	X	X
Rose PVD questionnaire		X								
Fasting or Nonfasting blood for elig			X							
Instr for doing 24-hr urine			X					X		X
Instr for doing food record			X							
Current medication use			X <sup>2</sup>				X	X <sup>2</sup>	X	X <sup>2</sup>
Instr for doing 24-hr recall				X						
Meeting w/ interventionist				X						
Symptoms/side effects ques				X			X	X	X	X
Diet/phys act questionnaire				X						
7-day phys activity recall					X			X		X
24-hr diet recalls (x2)					X			X		X
Submaximal treadmill test					X			X		X
Waist circumference						X		X		X
Confirm elig & randomize						X				
Eligibility review ques					Within 30 days of RV, if needed					
Patient history ques					Prior to randomization					
Process 24-hour urine					Prior to randomization			X		X
Fasting blood					Prior to randomization			X		X
Alcohol intake ques					Prior to randomization			X		X
Psychosocial measurements					Prior to randomization			X		X
Adverse events							as needed			

<sup>1</sup> Three sets of blood pressure measurements are taken over a three-month period (6-8 months and 16-18 months)

<sup>2</sup> All medications must be brought into the clinic for review by clinic staff at baseline, 6 months, and 18 months. At all other times participants are only asked about use of eligibility meds.

Baseline BP is defined as the average of the four sets of blood pressures collected prior to randomization. The PSV blood pressures are not included in this calculation. Blood pressure at six months is defined as the average of all available sets of BPs measured at the six-month follow-up visit. Blood pressure at 18 months is defined similarly. In the event that three days of measurements are not available, the outcome measure is defined as the mean of the available BP measures at that point. If no BP measurements are available at the 6 or 18 month point for an individual, then they will be imputed by the “hot deck” procedure of Solas: Missing Data Analysis (Statistical Solutions, Boston, MA). Specifically, control participants with complete data will be used to develop a model to predict final (six or 18 month) BP on the basis of: clinical center, age, sex, race, baseline and post randomization blood pressures, and body mass index. The standardized regression coefficients from this model will then be used to weight the



predictor variables for matching purposes. For each individual with missing endpoints, the imputed blood pressure will be chosen at random from among the five control participants with the “closest” set of weighted predictor variables. The same usual care individual will not be matched more than once. The use of prior blood pressures will allow us to account not only for the absolute level of the most recent blood pressure measurements, but also for the trajectory of blood pressure change. This should therefore produce different imputation distributions for individuals with high but stable blood pressure versus those with escalating blood pressures. Nonetheless, this procedure may still systematically underestimate blood pressure for those individuals whose blood pressures are missing because they started on blood pressure medications. For these individuals we will also conduct and report on a sensitivity analysis in which their last (nonstudy) clinic blood pressures taken prior to the start of medication are used in place of their imputed measurements.

In the event that a participant starts on blood pressure medication and subsequently withdraws from the medication, a blinded clinical adjudication subcommittee reviews the study chart and determines if it is appropriate to use subsequent BP measurements as outcome data.

#### *Assignment of Hypertension Status*

A participant is declared hypertensive at the six- or 18-month cluster if any of the following conditions apply:

- SBP  $\geq$  140 (average of all available sets of BPs)
- DBP  $\geq$  90 (average of all available sets of BPs)
- Taking antihypertensive medication daily

#### *Adjudication of Study Outcomes*

It is inevitable that during the course of the study some participants will reach study endpoints that may require an individual decision about censoring of outcome data or designation of hypertensive status. It is impossible to anticipate all scenarios. Therefore, the PREMIER investigators will designate an adjudication committee to be composed of study personnel (including at least one clinician) who are blinded to treatment assignment. This committee will review individual cases when predetermined criteria for designation of hypertension status are not clearly met.

#### *Other Study Measures*

##### *Physical Measures*

Height, without shoes, is measured once at baseline using a wall-mounted stadiometer.

Weight, in light indoor clothes without shoes, is measured at baseline and at three, six, 12, and 18 months post randomization using either a balance beam scale or a high-quality digital scale. All scales are calibrated annually by the Bureau of Weights and Standards and quarterly by trained study personnel using standard weights. Change in weight serves as an indicator of intervention effectiveness, since one of the goals of both lifestyle interventions for those who are overweight is to reduce weight. Body mass index is calculated as the Quetelet index ( $\text{kg/m}^2$ ).

Waist circumference is measured using a tape, according to a standardized protocol, at baseline, six months, and 18 months.

### *Symptom Monitoring*

As part of routine safety monitoring, symptoms suggestive of possible side effects of the interventions (e.g., musculoskeletal or gastrointestinal complaints) are assessed via self-reported questionnaire data at three, six, 12, and 18 months post randomization. This information is also gathered during screening to serve as a baseline against which to compare the post-randomization data.

The Rose angina and peripheral vascular disease questionnaires (Rose *et al.*, 1977) are asked at baseline in order to exclude individuals with a recent history of angina pectoris and claudication. The angina questionnaire is repeated at three, six, 12, and 18 months post randomization to detect the incidence of new angina pectoris. A more complete description of participant safety monitoring is provided in the Safety Monitoring section.

### *Current Medication Use*

Current medication use is assessed during screening both to determine eligibility and to gather information on baseline patterns of use of selected medications not relevant to eligibility. The latter include lipid-lowering medications and hormone replacement therapy. A comprehensive assessment of current medication use is made again at the six- and 18-month post-randomization visits. In addition, participants are asked about the use of exclusionary medications at the three- and 12-month post-randomization visits.

### *24-Hour Diet Recalls*

Nutrient intake at each major assessment point (baseline, six months, and 18 months) is determined from two unannounced, non-consecutive 24-hour dietary recalls conducted by telephone. The recalls are performed by the Diet Assessment Center of Pennsylvania State University, under subcontract to the Coordinating Center, according to a standardized protocol. The use of telephone recalls conducted by a centralized facility with established protocols and trained staff should reduce the potential for participant reporting bias, facilitate data management, and enhance the overall quality control of these data. Similar procedures have been successfully used in African-American and European-American populations.

In order to ensure our ability to collect this information, participants must have access to a telephone and be willing to comply with the assessment procedure. Experience from previous clinical trials in populations served by the clinical centers suggests that virtually all screening volunteers have telephones or access to them.

The Nutrition Data System (NDS) developed and maintained by the Nutrition Coding Center of the University of Minnesota is used to generate the estimates of individual nutrient intake from the recalls.

**Food Groups:** The 24-hour recall subcontractor at Pennsylvania State University uses a combination of the USDA definitions of serving sizes and the Minnesota NCC output files to calculate food groups (including fruits, vegetables, and dairy). Their food group classification is

similar, but not identical to the USDA system. It has 32 food groups that can be combined into fewer groups to approximate the food pyramid guide.

### *Submaximal Treadmill Test*

A submaximal treadmill test administered at baseline, six months, and 18 months is used to estimate cardiorespiratory fitness. Cardiorespiratory fitness is expressed as the heart rate to a set workload. Change in heart rate response to a set workload is the measure for change in fitness. The treadmill protocol varies by sex and age categories so that a moderate intensity workload is not exceeded.

### *Physical Activity*

The 7-Day Physical Activity Recall (Blair *et al.*, 1986; Sallis *et al.*, 1985) is used to assess physical activity at baseline and again at six and 18 months post randomization. It has previously been used to assess the impact of physical activity on the development of cardiovascular disease risk factors in a large bi-racial sample (Sidney *et al.*, 1991) and also as a tool to assess the effect of community-based (Young *et al.*, 1996; Dunn *et al.*, 1997) and clinic-based (Blair *et al.*, 1998) interventions to increase physical activity. The 7-Day Physical Activity Recall has been tested for validity and reliability (Blair *et al.*, 1986; Sallis *et al.*, 1985) and it is responsive for assessing change in physical activity (Young *et al.*, 1996; Dunn *et al.*, 1997).

This interviewer-administered questionnaire takes about 20 minutes to complete and estimates total daily energy expenditure by asking participants to estimate the number of hours spent in sleep and in “moderate,” “hard,” and “very hard” activities during the previous seven days. Hours spent doing “light” activity are calculated as the remaining time. The amount of time spent in each category is multiplied by the average metabolic equivalent (METs, or kcal/kg/hr) of each category, and summed to calculate energy expenditure in terms of kcal/kg/day. Two-week test-retest reliability was 0.67 in a study by Sallis *et al.* (1985).

### *Psychosocial Measures*

Three main categories of psychosocial measures will be obtained: hypothesized mediators of the intervention effect, potential outcomes, and potential effect modifiers. The measures will be obtained by using existing self-administered psychosocial instruments at baseline, six months, and 18 months.

Based on the social cognitive theoretical underpinnings of the intervention, two main hypothesized mediators of the intervention are selected to be measured: self-efficacy and social support. The intervention is designed to increase self-efficacy and social support for both physical activity and dietary behaviors. The “Eating Habits Confidence Survey” and the “Exercise Confidence Survey” (Sallis *et al.*, 1988), and the “Social Support and Eating Habits Survey” and the “Social Support and Exercise Survey” (Sallis *et al.*, 1987), will be used. These instruments have been shown to be reliable and have high internal consistency (Sallis *et al.*, 1988, 1987) and are associated with other measures of physical activity and dietary behaviors (Sallis *et al.*, 1987; Sallis *et al.*, 1992). It is hypothesized that self-efficacy and social support will be increased in the two active intervention arms compared with advice only.

The primary potential psychosocial outcomes to be measured are quality of life (QOL) and perceived stress. QOL is assessed with the “Medical Outcomes Study Short Form Health Survey” (MOS SF-36) (Ware, 1993; Ware and Sherbourne, 1992). The SF-36 is a widely used quality of life instrument that measures eight health status domains: physical functioning, role functioning-physical, role functioning-emotional, bodily pain, general health, social function and psychological well-being/mental health, and vitality. These domains can be grouped into two global scales: physical health and mental health. This standardized instrument has been used in a variety of settings, including studies of anti-hypertension therapy, and has an extensive normative database. It is well validated and has good psychometric properties when self-administered (Gill & Feinstein, 1994). Several scales are hypothesized to be affected by lifestyle interventions such as those in PREMIER (Grimm, 1997). In addition to QOL, measures will be made of perceived stress. The 4-item “Perceived Stress Scale” (PSS) (a subset of the 14-item scale) (Cohen *et al.*, 1983; 1988) is used. The PSS measures the degree to which situations in one’s life are perceived as stressful. The interventions may decrease perceived stress by virtue of increasing physical activity levels and personal attention, but there is also a possibility that the interventions may increase perceived stress by having too many demands on the participants; either of these situations can be determined by comparing PSS measures across intervention study arms.

Perceived body image is measured as a potential effect modifier by using the Stunkard silhouettes, an instrument that consists of nine silhouettes of men and women ranging from “very thin to very fat” (Stunkard *et al.*, 1983). The participant is asked to select which silhouette reflects their current perceived body shape and also to select which silhouette reflects their ideal body shape. The difference between the perceived and ideal is a measure of body dissatisfaction. It is hypothesized that individuals with greater body dissatisfaction will have a greater response to the weight loss component of the PREMIER interventions.

For measurement in all three study arms, stage of change (Prochaska & DiClemente, 1983; Marcus *et al.*, 1992) will not be measured by a specific instrument, but stage will be inferred at different points in the followup. At baseline, all participants are assumed to be past the pre-contemplation stage and at least at the contemplation stage, because in giving consent to be in the study they have agreed to try and change their health behaviors. The action stage, i.e., having made behavior changes, will be determined by using the self-report adherence measures of diet (24-hour recall) and physical activity (7-day physical activity recall) as well as the objective urinary measures of dietary adherence and of submaximal cardiorespiratory fitness. Participants who have achieved the PREMIER behavioral goals at 6 months can be considered to be in the action stage, and those that maintain those goals until 24 months can be considered to be in the maintenance stage. For participants in the Comprehensive and Comprehensive plus DASH interventions, the interventionists will regularly monitor readiness to make additional behavior changes using motivational interviewing techniques and will match individualized interventions messages to the participant’s stage of readiness to change.

### *Alcohol Use*

In addition to the information on alcohol intake obtained from the 24-hour recalls, questions asking about usual alcohol intake over a week’s time and number of episodes of having 6 or more drinks on one occasion will be administered at baseline (during screening) and at six and 18 months. The question on frequency of 6 or more drinks on one occasion is adapted from a previously validated questionnaire (Bohn MJ *et al.*, 1995). Alcohol intake over a week’s time

will be used to assess whether participants achieved the goal of 2 or less (1 or less for women) drinks per day.

### *Urinary Measures*

Twenty-four-hour urinary excretions are collected at baseline and again at six and 18 months post randomization. Aliquots are sent to a central laboratory for assessment of urinary sodium, potassium, phosphorous, creatinine, and urea nitrogen. This information is used to estimate dietary intake of these micronutrients for purposes of assessing intervention effectiveness. Urinary phosphorus serves as a marker of dairy consumption, urinary urea nitrogen as a marker of protein consumption, and urinary potassium as a marker of fruit and vegetable consumption. All three rose significantly among participants who consumed the combination diet in DASH. Similarly, urinary sodium is known to be a good marker of dietary sodium intake.

### *Blood Measures*

Twelve-hour fasting blood samples are obtained at baseline and again at six and 18 months post randomization. These specimens are then processed and sent to a central laboratory for analysis of: serum lipid levels (triglycerides, LDL-C, HDL-C, and total cholesterol); fasting insulin and glucose. Homocysteine will be assessed at baseline and 6 months, but not at 18 months. These measures are expected to improve as a result of the PREMIER interventions, particularly, the comprehensive plus DASH intervention. Standardized procedures are established for the processing and storage of these specimens in order to ensure the integrity of the analyses.

Blood measures of serum carotenoids, folate, and vitamin B-12 are obtained for cohorts 2-4 at baseline, six months, and 18 months. An advantage of blood measures compared to urinary measures of adherence is that blood samples are straightforward to obtain, whereas the accuracy of the urinary estimates is highly dependent upon the completeness of the 24-hour urine collection. Serum carotenoids are highly reflective of fruit and vegetable intake and are generally accepted as a method to demonstrate adherence to dietary interventions that promote increases in fruit and vegetables. Serum folate and vitamin B-12 are collected because the comprehensive plus DASH intervention is hypothesized to lower homocysteine. The comprehensive plus DASH intervention promotes a diet high in fruits, vegetables, and dairy, and these foods are high in folate and vitamin B-12, which are primary nutritional (inverse) determinants of blood homocysteine. Because the PREMIER interventions should have a favorable impact on blood pressure, lipid profiles, and physical activity, which are also associated with homocysteine, it will be difficult to attribute changes in homocysteine to dietary factors unless blood levels of folate and vitamin B12 are measured. Standardized procedures are established for processing these serum specimens, which are sent separately to the laboratory at the Centers for Disease Control and Prevention (CDC), Atlanta, GA.

### *Adherence*

A number of measures described above assess the extent to which the interventions achieve their target goals and, in particular, the extent to which they achieve the intended separation between the comprehensive and comprehensive plus DASH interventions. The three main foci of the comprehensive intervention are dietary changes to achieve weight loss, sodium reduction, and increased physical activity. Dietary changes are assessed by actual weight loss; change in sodium intake is measured by 24-hour recalls and urinary excretion of sodium; and change in

physical activity and fitness is measured by the 7-Day Physical Activity Recall and submaximal treadmill test, respectively. Adherence to the comprehensive plus DASH intervention is assessed by weight loss; the 24-hour diet recalls for servings of fruits, vegetables, and dairy products; urinary excretion of sodium, potassium (fruits and vegetables), phosphorus (dairy), and urea nitrogen (protein); increases in serum carotenoids and folate; by reductions in blood lipids; and by change in physical activity and in fitness. The 24-hour diet recalls are used to characterize the nutrient and food group intake of each intervention group and to determine the difference between each group for these dietary parameters.

From the objective measures of adherence we hypothesize to find that, relative to the advice only group, the comprehensive group will have lower weight, lower urinary sodium excretion, and lower submaximal heart rate. The comprehensive + DASH group will similarly have, compared to the advice only group, lower weight, lower urinary sodium excretion, and lower submaximal heart rate. In addition, the comprehensive + DASH group will have higher 24-hour urinary potassium, phosphorus, and urea nitrogen excretion, higher serum carotenoids and folate, and lower blood LDL-C levels than the advice only and the comprehensive groups.

Based on adherence measures from self-report, we hypothesize that relative to the advice only group, the comprehensive and the comprehensive + DASH groups will have higher levels of physical activity as measured by the PAR. In addition, the comprehensive + DASH group will have more servings of fruits, vegetables, and low-fat dairy than either the comprehensive group or the advice only group, as measured by the 24-hour dietary recalls. Because alcohol intake is expected to be low, in part due to exclusionary criteria related to alcohol, we hypothesize that changes in alcohol will be small and similar in all three groups.

In addition, adherence to the overall intervention “process” is assessed by documenting attendance at group and individual sessions, completion of lifestyle-intervention-directed dietary records and self-monitoring checklists, completeness of data collection for individual participants, and dropout rates.

We will also collect and store lab specimens (urine and blood) in such a way that future analysis of markers of dietary adherence may be conducted.

#### *Storage of Biological Samples*

Numerous endogenous vasoactive substances and candidate genes related to blood pressure or cardiovascular risk may influence blood pressure response to the PREMIER interventions. To facilitate future investigation of biological variables (e.g., plasma renin and angiotensin), candidate genes (e.g., angiotensinogen), and to allow possible future analyses of dietary intake markers, extra specimens of plasma, serum, and 24-hour urine are collected and stored at baseline, six months and 18 months. Buffy coats for future DNA extraction are also stored, but are only collected at baseline.

## 9. Intervention Methods

### *Rationale*

The PREMIER trial is based on evolving health care delivery systems which 1) place more emphasis on patient self-care and lifestyle changes and 2) funnel patients from primary care clinics to specialized centers for specific medical needs (e.g., Tulkin, 1995; Harris *et al.*, 1996; Zapka *et al.*, 1997). Specialized educational centers and referral programs are being established with targeted follow-up contact methods and behavioral interventions to improve motivation and adherence.

The PREMIER interventions are comprehensive, multicomponent, lifestyle programs which recognize that achievement of meaningful lifestyle changes that affect BP and other cardiovascular disease risk factors require information, time, extended follow-up, educational materials, and provider resources (Budd & Gruman, 1995; Harris *et al.*, 1996; Mant, 1997; TACP, 1992). The PREMIER programs are designed to fit into this evolving health care model; if successful they could then be adapted to be intervention packages for a variety of these venues.

### *Intervention Overview*

At the randomization visit, participants are randomly assigned to one of three treatment conditions (see Figure 1): 1) a usual care advice-only control group; 2) a comprehensive lifestyle intervention implementing longstanding nonpharmacologic recommendations for BP control; and 3) the comprehensive lifestyle intervention program plus the DASH dietary recommendations.

#### *Advice-Only Control Condition*

Participants assigned to this condition receive advice to follow the guidelines established by the National High Blood Pressure Program (NHBPEP) (JNC VI, 1997), for patients with above-optimal blood pressure and stage 1 hypertension. These recommendations include: weight loss if overweight, limiting alcohol and dietary sodium intake, regular physical activity, and eating a healthful diet. Recommendations for general cardiovascular health include reducing dietary fat and cholesterol. These recommendations are provided at two individual visits which occur at the randomization visit and after data collection at the six-month time point. Printed educational materials are provided at these visits. At the end of the trial, the advice-only participants receive additional health education materials and advice. They are invited to a group meeting describing the use of these materials and information on community programs is provided. Unlike the other two treatment groups, no behavioral counseling is provided in the advice only control group.

#### *Comprehensive Lifestyle Intervention*

This multicomponent lifestyle intervention program is based on the current clinical practice guidelines for BP control and cardiovascular health, which recommend weight loss if overweight, limiting sodium and alcohol intake, regular physical activity, and eating a reduced fat diet. Table 5 provides an overview of selected aspects of this lifestyle intervention and the comprehensive plus DASH intervention.

The specific intervention goals are :

- reduce weight by 4.5 kg (10 lb.) or more if overweight
- limit daily sodium intake to 100 mmol or less
- limit fat intake to 30% or less of total Kcal
- engage in 180 minutes per week or equivalent of moderate physical activity
- alcohol intake of no more than one ounce of ethanol per day (men), or no more than 0.5 ounces of ethanol per day (women)

#### *Comprehensive Intervention plus DASH Diet*

This treatment group is also provided with a multicomponent lifestyle intervention program. The goals of this intervention include the same weight loss, sodium, physical activity and alcohol goals as the comprehensive lifestyle intervention, but this treatment arm also incorporates the DASH dietary pattern, which focuses on optimizing intakes of specific foods (fruits and vegetables and low-fat dairy) and nutrients (Ca, K, Mg, fiber, and reduced saturated fat and total fat). The specific intervention goals are :

- reduce weight by 4.5 kg (10 lb.) or more if overweight
- limit daily sodium intake to 100 mmol or less
- limit fat intake to 25 percent or less of total kcal, with an emphasis on reducing saturated fat to 7% or less of total Kcal
- engage in 180 minutes per week or equivalent of moderate physical activity to
- limit alcohol intake to no more than one ounce of ethanol per day (men), or no more than 0.5 ounces of ethanol per day (women)
- 9-12 servings of fruits and vegetables per day
- 2-3 servings of low-fat dairy products per day

The comprehensive and comprehensive plus DASH intervention programs differ in fundamental ways. First, the programs differ in the structure and presentation of the dietary intervention. The comprehensive plus DASH intervention program is built around the DASH dietary recommendations stemming from the DASH trial and focuses first on dietary patterns (Sacks *et al.*, 1995; Appel *et al.*, 1997b). Participants receiving the DASH dietary recommendations set specific fat-consumption ceilings and monitor their daily intake of fat as a technique for achieving this goal. In the comprehensive program, the weight-loss program focuses on reduction of total calorie intake by monitoring total food and calories only (see Table 5).

Whereas the comprehensive intervention recommends reducing intake of high-calorie foods, the DASH intervention encourages substituting fruits and vegetables for high-fat foods. The multiple health benefits of increasing fruit and vegetable consumption is emphasized in DASH intervention, and participants are helped to develop specific fruit and vegetable consumption goals (i.e., 9-12 servings per day depending on total energy consumption ) and keep dietary checklists to monitor fruit and vegetable consumption.

The treatment groups also differ in recommendations for dairy products. The DASH participants are encouraged to include at least two servings of low-fat or non-fat dairy products daily. To facilitate this change, they have this as an additional category in their food record checklist. By contrast, in the comprehensive intervention (without DASH) participants are not asked to set goals for dairy products. All three treatment groups will be given advice on smoking cessation,



using materials from the “Two-Three” initiative from the Agency for Health Care Policy and Research (AHCPR). Smoking behavior does not directly affect BP, but cessation is part of any lifestyle advice for decreasing CV disease risk, and all three treatment arms of PREMIER.

**Table 5. Aspects of the PREMIER Lifestyle Interventions**

	COMPREHENSIVE				COMPREHENSIVE + DASH			
	Recommend	Emphasis in Intervention	Self-Monitoring	Outcome Assessment	Recommend	Emphasis in Intervention	Self-Monitoring	Outcome Assessment
Physical Activity	180 min/wk	Yes	Yes	7 day activity recall, fitness test	180 min/wk	Yes	Yes	7-day activity recall, fitness test
Sodium	≤100 mmol/d	Yes	Yes	24-hr urine Na 24-hr recall	≤100 mmol/d	Yes	Yes	24-hr urine Na 24-hr recall
Alcohol	≤1 oz/d (♂) ≤0.5oz/d (♀)	Yes	No	Alcohol questionnaire	≤1 oz/d (♂) ≤0.5oz/d (♀)	Yes	No	Alcohol questionnaire
Weight*	≥10 lb loss at 18 months	Yes	Yes	Weight at 18 months	≥10 lb loss at 18 months	Yes	Yes	Weight at 18 months
Total Calorie	Individualized	Yes	Yes	24-hr diet recall	Individualized	Yes	Yes	24-hr diet recall
%Kcal Fat	≤ 30%	Yes	No	24-hr diet recall	≤ 25%	Yes	Yes	24-hr diet recall
%Kcal Sat Fat	≤ 10%	No	No	24-hr diet recall	≤ 7%	Yes	No	24-hr diet recall
Fruits + Veggies	Not specified	No	No	Food groups from 24-hr recalls 24-hr urine K	9-12 servings†	Yes	Yes	Food groups from 24-hr recalls 24-hr urine K
Dairy	Not specified	No	No	Food groups from 24-hr recalls 24-hr urine phosphorus	2-3 servings†	Yes	Yes	Food groups from 24-hr recalls 24-hr urine phosphorus

\* Weight loss recommended only for those with BMI ≥ 25

† Daily number of servings adjusted for individual caloric intake

## ***Description of the Lifestyle Intervention: Format, Structure, and Content***

### ***Format***

Using the lifestyle-change intervention methods developed in our earlier studies (Whelton *et al.*, 1998; Young *et al.*, 1996; Elmer *et al.*, 1995a; Elmer *et al.*, 1995b; Blair *et al.*, 1998; Stevens *et al.*, 1993; Lasser *et al.*, 1995), this program employs a series of group and individual sessions to help participants make appropriate lifestyle changes and develop the skills to maintain these changes over the long term.

The basic format of the two lifestyle interventions is the same. Both use the same schedule of group and individual visits (see Table 6), with the primary difference being the dietary recommendations—the comprehensive group does not receive instruction and behavioral counseling in adopting the DASH dietary recommendations, whereas the comprehensive plus DASH group does receive this instruction and counseling (see Table 5). During the initial 14 weeks, intervention sessions will occur weekly, except for two two-week breaks; the total number of group and individual sessions will be eight and three, respectively. During the next 14 weeks, group sessions will occur every other week (total of six sessions); a single individual session also occurs during this period. Thereafter, monthly group meetings and three quarterly individual meetings take place.

**Table 6. Approximate Intervention Contact Schedule**

*Note:*

- I2 has been moved to follow G4. Otherwise the sequence of visits is the same as that in protocol version 1.3
- The window between R/I and G1 is now 3-4 weeks
- The weeks have been renumbered so that week 1 starts with G1.
- Local clinics have the option to make minor scheduling changes to accommodate holidays, weather problems, or other special circumstances

Tx Group																										
A	Week																									
	Group																									
	Individual	R/																								
		Single intervention contact; printed materials only																								
B	Week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Group		G1	G2	G3	G4			G5	G6	G7	G8			G9		G10		G11			G12		G13		G14
	Individual	R/					I2						I3						I4							
		R/I window 3 to 4 weeks. Intervention contact weekly with 2 week breaks: 8 group meetings, 3 individual meetings												Intervention contact every other week: 6 group meetings, one individual meeting												
C	Week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Group		G1	G2	G3	G4			G5	G6	G7	G8			G9		G10		G11			G12		G13		G14
	Individual	R/					I2						I3						I4							
		R/I window 3 to 4 weeks Intervention contact weekly with 2 week breaks: 8 group meetings 3 individual meetings												Intervention contact every other week: 6 group meetings, one individual meeting												

Tx Group																									
A	Month	M6																							
	Group																								
	Individual	I-2																							
		Single intervention contact; printed materials only																							
B	Month		M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18											
	Group		G15	G16	G17	G18	G19	G20	G21	G22	G23	G24	G25	G26											
	Individual			I-5				I-6				I-7													
		Intervention contact monthly: 12 group meetings, 3 quarterly individual meetings																							
C	Month		M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18											
	Group		G15	G16	G17	G18	G19	G20	G21	G22	G23	G24	G25	G26											
	Individual			I-5				I-6				I-7													
		Intervention contact monthly: 12 group meetings, 3 quarterly individual meetings																							

Rev: 12/01/99

## *Theoretical Background, Structure, Content, and Delivery*

The PREMIER interventions have been derived from social cognitive theory (Bandura, 1986), self-applied behavior modification techniques—behavioral self-management—(Watson & Tharp, 1989), and the relapse prevention model (Marlatt & Gordon, 1985), and have been constructed with use of the transtheoretical, or stages-of-change model (Prochaska & DiClemente, 1983; Marcus *et al.*, 1992). Both social cognitive and behavioral self-management approaches stress the importance of an individual's ability to regulate his/her behavior by setting goals, monitoring progress towards the goals, and using modeling and observational learning to attain skills necessary to reach goals. Self-efficacy, or one's confidence in performing a given behavior, and one's outcome expectancies from the behavior are critical mediators in determining which behaviors are attempted and the amount of effort placed in adopting a new behavior. Relapse-prevention training provides specific skills to decrease the risk of slips turning into relapse when acquiring and maintaining a new behavior. The transtheoretical model recognizes that behavior change is a dynamic process of moving through different motivational readiness-for-change stages. It allows for different behavioral strategies to be emphasized depending on the individual's stage of change. Congruent with these theories/models are behavioral skills training and self-regulation that are necessary to adopt and maintain a new behavior. Motivational interviewing (Miller & Rollnick, 1991) also provides a useful framework for helping participants make crucial decisions in light of these behavioral theories.

Intervention strategies that are congruent with PREMIER's theoretical foundation, and that have been used successfully in previous trials (e.g., Whelton *et al.*, 1998; TOHP1, 1992; TOHP2, 1997; Elmer *et al.*, 1991; Elmer *et al.*, 1995a, Stamler R. *et al.*, 1987; Stamler R. *et al.*, 1989; Jeffery, 1991; Grimm *et al.*, 1990; King *et al.*, 1991), are employed in this program, including frequent and extended contacts, opportunities for group interactions and social support, goal-setting and self-negotiation, problem solving, examples of new behavioral options and decision-making approaches, individual contacts which tailor the intervention to the individual's preferences and readiness to change, and other contact formats (mail, telephone, and special events) that support behavior change and provide content material, behavior cues, and reinforcement in the participant's environment.

### *Intervention Materials*

Participants in the lifestyle change programs are provided with a Personal Resource Package, with separate editions of these materials for each of the two lifestyle interventions. Both have the same physical activity, sodium, alcohol, and smoking-cessation materials but differ in the dietary sections, with the DASH dietary recommendations featured prominently in materials for the comprehensive plus DASH group.

*PREMIER Food and Fitness Guide* — a food, nutrient, and physical activity guide listing the calorie, fat, and sodium content of foods and physical activity points for physical activities. For the comprehensive plus DASH group this guide will also list calories, fat, and sodium, and highlight fruits and vegetables, low-fat dairy, and low saturated fat choices. In both arms the guide contains the treatment group specific recommendations regarding food purchasing, preparation, and key behavioral cues.

*PREMIER Participant Manual* — a manual with detail on the program content; self-assessments and goal setting procedures; approaches for self-monitoring food and activity, cooking and meal pattern guides. To help participants identify with the program and to provide ongoing visual cues for program affiliation within the individual's personal environment, we provide magnets, measuring cups, water bottles, vegetable peelers, tee shirts, tote sports bags, etc., with the trial logo.

*PREMIER Food and Fitness Diary* — a self-monitoring tool where participants record food intake and physical activity. Participants use this to self-monitor their weight and various aspects of the diet, activity and behaviors. Participants in the comprehensive arm monitor calories, sodium, and physical activity points. Those in the comprehensive plus DASH arm monitor servings of fruits and vegetables, low-fat dairy, calories, fat, sodium, and physical activity points.

### *Structure for Intervention Delivery*

Both lifestyle intervention treatment groups start with an individual counseling session conducted immediately after random assignment but before the start of group meetings. This first individual counseling session is designed to tailor the intervention to the individual's needs.

Group sessions start with three weekly meetings, then a two-week break to practice maintenance skills, then another three weekly meetings, another one-week break, and then a series of group sessions meeting every other week for the remainder of the first six months of intervention (see Table 5). Several individual counseling sessions are included between these group sessions. Individual counseling sessions focus on individual needs to further tailor intervention strategies in their personal context.

Individual sessions focus on social support, specific behavior change goals, problem solving, and maintaining motivation during challenging situations. Group sessions continue to focus on behavior change, goals, and skills; developing strategies and support for relapse prevention; and maintaining physical activity.

### *Session Content and Behavior Modification Curriculum*

Each session follows a similar structure and includes six main curriculum components: 1) main content area (e.g., meal patterns, calories and sodium, identifying alternative types of moderate physical activity, and weight loss in both interventions, and fruits and vegetables and dietary fat in the + Dash group,) 2) behavioral skills training, 3) self-monitoring activity, 4) review of progress since last session, 5) social support-group sharing, and 6) goal setting and action plans. The meetings are structured to be very interactive with participant input and smaller group activities that foster problem solving, support, and program ownership. Sessions include tasting foods, cooking, and exercise demonstrations.

### *Behavioral Self-Management*

To enhance adherence, a variety of behavior modification and social learning theory approaches are incorporated into each intervention session. The goal of this portion of the intervention is to teach the participants how to effectively manage their dietary behavior and maintain their personal exercise program when confronted with the full spectrum of daily environmental

challenges. That is, rather than have the intervention staff attempt to control the participants' behavior, the basic strategy is to train the participants to manage their own behavior to achieve and maintain diet and lifestyle change. The essential components of successful self-management include setting reasonable short-term goals, formulating specific plans of action to achieve those goals, developing reinforcement and social support for carrying out each major element of the plan, keeping a record to assess progress, and regularly evaluating and modifying plans using the self-management records (Watson & Tharp, 1989).

### *Weight Loss*

Overweight is defined as having BMI  $\geq 25$  (NHLBI, 1998). We expect a majority of the PREMIER participants to meet this definition. The goal of the weight-loss portion of the intervention programs is to help participants who are overweight lose 10 lb. (4.5 kg) or more and maintain this weight loss for the duration of the trial. The PREMIER weight-loss strategy is modeled after our previous programs that achieved successful weight loss (Elmer *et al.*, 1995a; Stevens, 1993; Whelton *et al.*, 1996; Stamler R. *et al.*, 1987). Specific strategies common to both include: 1) self-monitoring of diet and physical activity, 2) development of personalized dietary and physical activity plans, 3) moderate caloric reduction, 4) increased physical activity, 5) identifying problematic situations for undesired behavior and developing and rehearsing specific plans of action to deal with those situations, 6) graphing individual weight and behavioral progress, 7) developing core food-choice competencies, and 8) reducing portion sizes, substituting alternative foods, and modifying the original items to be lower in calories and fat. Group support and telephone follow-up are key components of this program. For those with a BMI below 25, the intervention focuses on preventing weight gain. In addition, those with a BMI between 20 and 25 are offered individual counseling to help them lose small amounts of weight if they so choose.

### *Reduced Fat Intake*

We anticipate a decrease in fat in the comprehensive group—the materials and program are geared for a diet at 30 percent kcal from total fat. In previous trials of this type of intervention reported fat intake reached 31-34 percent of total kcal. It is unlikely to decrease below these levels without special emphasis and effort. In contrast, the comprehensive plus DASH program emphasizes monitoring total fat intake to achieve fat intake of 25 percent and encourage substitution of fruits, vegetables, and low-fat dairy products (i.e., fruit as snacks/dessert). Participants have a specific goal to eat 9-12 servings of fruits and vegetables per day.

### *Sodium Reduction*

The goal of the sodium intervention is to help participants reduce sodium intake to 100 mmol per day or less. Key curriculum content and behavioral strategies include identifying the sodium content of foods using the Food and Fitness Guide and food labels, and devising sodium reduction strategies. The latter include: finding sodium-modified food products, substituting different items for very high sodium foods, learning to make more appropriate food choices in restaurants, and adapting taste preferences. Providing participants with the opportunity to taste low-sodium foods and providing product samples have been key components enhancing the success of our previous sodium-reduction programs. We employ these techniques in PREMIER and work with major food manufactures to provide product samples to the clinical centers.

During early sessions, and periodically thereafter, participants monitor their sodium intake by keeping food records.

### *Alcohol Limitation*

The alcohol component of this intervention is not designed for problem drinkers. Screening excludes those who report consuming more than 21 alcohol-containing drinks per week. For PREMIER the goal of the alcohol intervention is to limit alcohol consumption to no more than one ounce of ethanol per day (men), or no more than 0.5 ounces of ethanol per day (women). Participants monitor alcohol intake on their food records and discuss strategies for reducing alcohol if needed. Alcohol consumption is also addressed in the individual counseling sessions.

### *Physical Activity*

The goal of the physical activity component in both the Comprehensive and the Comprehensive plus DASH intervention programs is to engage in regular aerobic physical activity according to national recommendations from the Surgeon General's Report on Physical Activity and Health (USDHHS, 1996), the Centers for Disease Control and the American College of Sports Medicine (Pate *et al.*, 1995), and the National Institutes of Health (NIH Consensus Conference, 1996). The national recommendations are for 150 kcal in moderate-to-vigorous physical activity, or 30 minutes of moderate-intensity activity such as walking, on most, preferably all, days of the week.

Aerobic activity that increases heart rate to 50-69 percent of maximal heart rate or has a rating of perceived exertion (Borg, 1982) of 11-12 (i.e., fairly light to somewhat hard) meets the definition of moderate-intensity activity (USDHHS, 1996) and has been described as activity that is as intense as a brisk walk. Vigorous activity increases heart rate to 70-89 percent of maximal heart rate and is characterized by a rating of perceived exertion of 13-16 (i.e., somewhat hard to hard). Moderate-intensity activity tends to be preferred over vigorous activity by many adults (King *et al.*, 1990), is associated with lower injury rate than vigorous exercise (Pollock *et al.*, 1991), and has been tested in some efficacy studies and seen to lower BP (Braith *et al.*, 1994, Hagberg *et al.*, 1989; Roman *et al.*, 1981). Therefore, moderate-intensity activity is emphasized in the Premier interventions. However, to be consistent with the national recommendations, and to reflect the fact that most of the efficacy studies that have shown that exercise reduces BP have tested vigorous-intensity exercise (Fagard, 1995), for those participants who wish to engage in vigorous activity and have no contraindications (see the Safety section), vigorous activity is permitted.

To allow flexibility for moderate or vigorous activity, as well as to allow for patterns that include both intensities, a point system is used for instruction and self-monitoring. The participant goal is to accumulate at least 180 points per week divided into at least three different days. Each minute of moderate-intensity activity equals one point; each minute of vigorous activity equals two points. If a sedentary person who does no moderate or vigorous activity were to achieve this intervention goal by replacing sitting time with moderate or vigorous activity, the result would be an increase of 1.1 kcal/kg/day overall, or 1.7 kcal/kg/day in moderate-to-vigorous activity, measured by the 7-day Physical Activity Recall. Following are examples of activity patterns that meet this goal:

- a) Moderate-intensity activity six times per week for 30 minutes each time
- b) Moderate-intensity activity four times per week for 45 minutes each time
- c) Vigorous-intensity (very hard) activity three times per week for 30 minutes each time



d) Moderate-intensity activity two times per week for 30 minutes each time PLUS vigorous-intensity activity three times per week for 20 minutes each time.

Moderate-to-vigorous activity engaged in for 20 minutes or longer will count toward points. The 20-minute duration is selected because that is the minimum duration used in randomized trials that have shown that BP is lowered by exercise. Participants who are initially sedentary are encouraged to engage in shorter bouts of activity to work up to the 20 minutes. For those participants who wish to engage in vigorous activity, the importance of warm-up and cool-down periods and the need to work up to vigorous activity by first engaging in regular moderate-intensity activity, is emphasized in the intervention. Participants are given examples of types of activity that are moderate (e.g., brisk walking, gardening, shooting baskets) and vigorous (e.g., running/jogging, aerobic dancing, playing skilled singles tennis, walking briskly uphill), the submaximal treadmill testing provides experience estimating perceived exertion using the Borg scale (Borg, 1982), and participants are taught how to determine their target heart rate range for moderate and vigorous intensity activity and to take their pulse.

The intervention focuses on helping participants determine how best to fit physical activity into their lives and takes into account each participant's initial motivation, current activity patterns, and intensity desires. Group and individual sessions include information and behavioral skills relevant to the physical activity component of the intervention. Specific behavioral strategies for increasing physical activity include identifying pleasurable activities for participants, self-monitoring physical activity patterns, scheduling daily time to be physically active, goal-setting, identifying barriers to physical activity, and problem-solving to develop specific strategies to deal with barriers.

#### *DASH Dietary Pattern*

The DASH diet promotes low-fat dairy products, fish, poultry, and lean meats to reduce total and saturated fats and increase protein and calcium. It includes fruits and vegetables to increase potassium, magnesium, and dietary fiber. For an intake of 2000 kcal/day, this dietary pattern contains approximately four to five vegetable servings, four to five fruit servings, seven to eight servings of grains and grain products, two to three servings of low-fat dairy products, and two or fewer servings of meat, poultry, or fish. Potassium, magnesium, and calcium levels in the DASH diet correspond to approximately the 75th percentile of consumption for general Americans.

The intervention strategies for translating the fruit and vegetable component into the everyday setting have been successfully developed in two previous programs for increasing fruit and vegetable intake. In these programs individuals increased fruit and vegetable consumption to an average of 11 servings per day and maintained these intakes for one year. (Elmer *et al.*, 1995b; Elmer *et al.*, 1994.)

Three specific dietary goals are emphasized during group and individual sessions in order to achieve the DASH dietary pattern: (1) eat no more than a specific number of grams of fat per day—a target based on caloric needs to achieve/maintain weight loss; reduction of saturated fat will also be emphasized by focusing on reduced consumption of red meat and regular-fat dairy products; (2) eat 9-12 servings of fruits and vegetables per day; and (3) eat two to three servings of low-fat dairy products per day. These goals are critical because each represents a key aspect of the DASH dietary pattern. In this treatment condition the first two intervention group sessions focus on the DASH dietary pattern—increasing fruits and vegetables and low-fat dairy, and

monitoring fat intake. Later sessions focus on calorie reduction and other weight control strategies, and on sodium reduction.

PREMIER uses a number of strategies to incorporate these dietary components into the daily eating pattern. For example, the fruit and vegetable pattern can include two to three servings of fruit at breakfast, typically juice and another serving of fruit, perhaps with cereal. Lunch can include three to four servings of fruit and vegetables such as soup, salads, sandwiches, juice, and fruit as dessert. Dinner can include three to four servings of fruits and vegetables. Large salads can be a part of many meals, as well as raw vegetables for pre-meal items and one to two fruits or vegetables as snacks. Typically participants increase the portion size of vegetables to increase the numbers of servings. Setting goals for meals, focusing on key fruits and vegetables for additional consumption goals, and increasing portion sizes are strategies that have been successfully used in previous fruit and vegetable intervention programs (Elmer *et al.*, 1995a; Elmer *et al.*, 1995b). In addition to emphasizing fruits and vegetables, we also emphasize low-fat dairy products, such as low-fat or skim milk, low/non-fat yogurt, and low-fat cheeses, as well as limited portions of lean cuts of beef, chicken, and fish (Elmer, 1996a; Elmer 1996b).

### *Intervention Adherence*

Intervention adherence is measured by the 24-hour diet recall; excretion of urine sodium, potassium, urea nitrogen, and phosphorus; body weight; and amount of physical activity reported on the seven-day physical activity recall. For each cohort and assessment point (six and 18 months), these variables are reported to the Steering Committee and the Intervention Committee for evaluation of intervention progress. Self-monitoring data obtained during the intervention program also are used for adherence monitoring and for individual feedback.

### *Cultural Adaptation of the Intervention*

The PREMIER investigators put a high priority on developing lifestyle interventions that are appropriate for African Americans, a group at high risk for hypertension and obesity. To this end, a Minority Implementation Committee reviews all intervention plans and materials. The PREMIER investigator group and consultants on this committee have extensive experience with clinical research in African-American populations. Previous studies have led to the identification of the following strategies that are incorporated into the design of the PREMIER lifestyle interventions. Most if not all of these strategies are effective and important for all study participants, but may require particular attention by the Minority Implementation Committee to ensure that interventions are not inadvertently biased toward the dominant culture. These strategies include: 1) adequate minority representation at all levels of implementation (i.e., interventionists, investigators, etc.); 2) social support systems for participants; 3) effective communication, including demonstrations; 4) involvement of family and community; 5) participant input into study procedures and identification with study goals (“ownership”); and 6) food guides and other intervention materials that are consonant with the various cultures represented among study participants.

Focus groups conducted in DASH and in other studies indicate that if African-American participants lack a sense of identity with intervention leaders they lose interest in the programs. Although some members may not be concerned about the race or ethnicity of group leaders, a number felt that an African-American staff would come to the program having internalized the

basic codes of conduct for the African-American culture. For this reason, centers attempt to include African-American staff as part of the intervention team.

### *Fostering Social Support and Reducing Isolation*

Although social support has been used in a variety of health interventions it is critically important for interventions that include African-American women, a group that particularly values member-to-member interactions (Kumanyika *et al.*, 1993). This axiological classification has been confirmed in our focus groups and observations in other studies. The DASH focus group participants articulated a sense of isolation they had felt as people of color participating in predominantly European-American lifestyle-change programs. They expressed a strong desire to remain in close contact with other people of color who were working to change their habits. The value placed on social interactions by African Americans has important implications for interventions involving this population. For this reason, the PREMIER intervention group sessions have an emphasis on building and maintaining social support. This includes celebrating accomplishments and hosting large group activities as well as developing a “partner” component (for those interested) during the maintenance phase.

### *Providing Information in the Form of Demonstrations*

Participants from many programs indicated a preference for a demonstration-oriented program, particularly with regard to physical activity and food preparation. One popular technique is for two to three participants to prepare a dish for tasting at a group meeting. The staff can work with the participants to modify the recipes to be consistent with their group's dietary goals. A similar approach can be used to demonstrate physical activity techniques. For example, the exercise instructor would go for walks with groups of participants and demonstrate the pace appropriate for individual participants.

### *Increasing the Sense of Ownership*

In focus groups, African Americans expressed a desire to have a sense of some ownership with the research project. Partial ownership, they feel, would improve interventions and provide vigilance about how information they provide is used. In PREMIER, group sessions are conducted in a highly interactive fashion. Participants are also included in the planning of the social events and selecting topics and recipes for group demonstrations particularly during the maintenance activities.

### *Intervention Quality Assurance*

Intervention quality assurance procedures ensure that project activities are standardized across the clinical centers and across the cohorts and that intervention process data are collected accurately. To achieve this, standardized protocols, procedures, and educational materials are prepared, and staff are systematically trained in their use. In addition, the performance of the clinical center staff is monitored routinely by the Coordinating Center, with feedback provided to the clinical centers and protocol deviations or other problems addressed and corrected in a timely manner. Further details concerning quality assurance are provided in section 14, Quality Control and Data Management.

## 10. Safety Monitoring

This chapter describes measures intended to ensure the safety of participants in the PREMIER study. In general, participants' blood pressures are closely monitored to document the safety of continued participation in the study and its interventions. Additionally, surveillance for adverse events and relevant clinical events occurs by questionnaire at regularly scheduled intervals. All abnormal lab results are reviewed by a clinical center physician. The first part of this chapter is devoted to blood pressure surveillance and escape criteria, while the remainder of the chapter describes adverse event monitoring and management. The role of screening for cardiovascular disease has been addressed in Section 5 (Eligibility) but is reviewed again in this chapter.

### *Overview*

Enrollment of individuals with above-optimal BP or stage 1 hypertension presents two challenges—namely, conduct of the trial in the setting of current guidelines (JNC VI, 1997) and the potential for initiation of antihypertensive drug therapy by personal physicians. JNC VI recommends a program of lifestyle modification as initial therapy for stage 1 hypertensives without target organ disease (TOD), clinical cardiovascular disease (CCD), or diabetes (see appendix I). If BP remains elevated after a six-month period (twelve months for risk group A) (see appendix I), JNC VI recommends initiation of drug therapy.

For the vast majority of anticipated PREMIER participants (i.e., those in risk groups A and B), all three PREMIER interventions are consistent with the JNC VI recommended standard of care. In particular, these interventions all include, at a minimum, two individual educational sessions. Also consistent with JNC VI guidelines, individuals with persistent hypertension at the six-month evaluation are referred to their provider for evaluation.

For the most part, the study's eligibility criteria are intended to exclude those in risk group C (TOD, CCD, or diabetes), for whom JNC VI recommends immediate drug therapy. However, testing for left ventricular hypertrophy and retinopathy was not deemed feasible.

The decision to initiate drug therapy is a decision of the personal physician, not a PREMIER clinician. However, formal BP escape criteria trigger referral for physician evaluation. For randomized participants, clinical center staff track the outcome of these referrals and this information is reported to the Data and Safety Monitoring Board. Randomized participants who initiate medications and/or have an elevated BP are encouraged to remain active in the trial and to attend scheduled data collection and intervention visits in order to study secondary outcomes and adherence.

### *Contact with Personal Physicians*

The PREMIER investigators recognize the appropriateness and importance of securing the cooperation of personal physicians. To this end, the personal physicians of all participants are sent a letter describing the trial. These letters explain that if a participant's blood pressure exceeds certain levels, the personal physician will be alerted. Before randomization, persons with a Rose questionnaire suggestive of angina or peripheral vascular disease require explicit approval of the personal physician and a negative ECG stress test within the past 6 months. Screenees without a personal care provider are assisted in finding one.

## ***Blood Pressure Escape Levels***

The following blood pressure escape levels and protocols have been established to ensure that participants are offered appropriate evaluation and therapy when clinically indicated. The actions taken when these escape levels are reached differ for screening and intervention periods. They are outlined below. In all cases, participants may be immediately referred for evaluation if the study clinician believes such action is appropriate based on his or her clinical judgement.

In addition to the random zero (RZ) measurements required for study data, additional non-RZ (standard mercury sphygmomanometer) measurements may be taken on a more frequent basis to ensure participant safety. All non-RZ blood pressure measurements are recorded in the participant's chart but are not used for analysis. Only RZ measurements become part of the participant's official study blood pressure record.

Blood pressure of study participants is measured at least every four months following randomization. All participants, regardless of group assignment, have the same number and schedule of blood pressure visits, and therefore the same level of surveillance. Participants reaching the escape thresholds are referred to their personal physician for evaluation and possible drug treatment. If referral is required and the participant does not have a personal physician, study personnel at the clinical site provide the participant with a list of physicians who can provide further therapy.

The clinical centers should endeavor to obtain four sets of end-of-intervention blood pressure measurements on all participants who meet one of the BP escape criteria. Care should be taken that this does not delay or otherwise interfere with appropriate clinical care. Regardless of the outcome of the referral, all participants continue in the trial and get all study measurements.

### *Prior to Randomization*

Escape Level #1: The mean blood pressure recorded at any single visit, including PSV, is  $\geq$  either a SBP of 180 mm Hg or a DBP of 110 mm Hg.

Action: Participant is excluded immediately and referred to a physician for further evaluation within one week.

Escape Level #2: The mean cumulative blood pressure recorded at SV1, SV2, or SV3 exceeds the established upper limit of eligibility (see Section 6, Table 3).

Action: Participant is referred to a physician for further evaluation within one month.

### *Intervention Period: Three-Month Visit*

Escape Level #1: The mean blood pressure recorded at the three-month visit is  $\geq$  either a SBP of 160 mm Hg or a DBP of 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two

visits is  $\geq$  SBP 180 or DBP 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is  $\geq$  SBP 160 or DBP 100, then the participant is referred to his/her personal physician for further evaluation within one month.

*Intervention Period: Six-Month and 18-Month Visit Clusters*

Escape Level #1: The mean blood pressure recorded at any single visit is  $\geq$  either a SBP of 160 mm Hg or a DBP of 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is  $\geq$  SBP 180 or DBP 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is  $\geq$  SBP 160 or DBP 100, then the participant is referred to his/her personal physician for further evaluation within one month.

Escape Level #2: The cumulative mean blood pressure recorded at the end of the six or 18 month cluster of visits  $\geq$  either a SBP of 140 mm Hg or a DBP of 90 mm Hg

Action: Participant is referred to his/her personal physician for further evaluation within two months.

*Intervention Period: 12-Month Visit*

Escape Level #1: The mean blood pressure recorded at the 12-month visit is  $\geq$  either a SBP of 160 mm Hg or DBP of 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is  $\geq$  SBP 180 or DBP 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is  $\geq$  SBP 160 or DBP 100, then the participant is referred to their personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP  $\geq$  140 or DBP  $\geq$  90, participant is referred to a physician for further evaluation within two months.

Escape Level #2: The mean blood pressure recorded at the 12-month visit is  $\geq$  either a SBP of 140 mm Hg or DBP of 90 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two

visits is  $\geq$  SBP160 or DBP 100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is  $\geq$  SBP 140 or DBP 90, participant is referred to a physician for further evaluation within two months.

### ***Cardiovascular Events Affecting Blood Pressure***

Participants who suffer a cardiovascular event with a lasting effect on blood pressure (e.g., myocardial infarction, stroke) may continue with the interventions and follow-up clinic visits with the approval of their primary physician and a study clinician in order to study secondary outcomes and adherence.

### ***Review of Laboratory Values***

Review of laboratory values occurs in two stages. The central laboratory notifies the clinical sites of “extreme” laboratory values as soon as results are available. Each site also has established local procedures for medical review and notification of lab values, including physician review of all abnormal lab values.

### ***Hypercholesterolemia and the Use of Lipid Lowering Medications***

Hypercholesterolemia is not an exclusionary criterion. However, participants receive copies of all clinically relevant lab results, and are encouraged to share these data with their personal physician. In addition, lipid values outside of normal ranges are flagged. Participants who are placed on lipid lowering drugs, whether before or after randomization, may continue in PREMIER.

### ***Pregnancy and Other Exclusions***

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

### ***Symptoms and Adverse Events Surveillance***

During the intervention period, participants are specifically queried about gastrointestinal, musculoskeletal, and cardiovascular symptoms at the three-, six-, 12-, and 18-month assessments. Questionnaire responses are reviewed by study clinicians and referred for additional care as needed.

Participants are also queried at these same timepoints about possible adverse events (defined below). Positive responses trigger an adverse event (AE) record, which is reviewed at the coordinating center and classified as either gastrointestinal, cardiovascular, musculoskeletal, or “other” in nature. This information is then reported to the DSMB by site and treatment arm. Similar information reported by participants at other times (e.g., during intervention classes) is duly noted and followed up with as needed to assure participant safety. To avoid possible

reporting bias, such events do not constitute AEs unless they are reported at the regularly scheduled clinic visits.

The following constitute adverse events (AEs): heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, angina pectoris, broken bone, torn ligament, and any other serious injury to the bone or muscle. Evidence of the occurrence of these events is based on participant self-report that a health care professional has diagnosed the condition, and no attempt is made to verify the diagnosis. Physician confirmed angina following a positive Rose Angina Questionnaire also constitutes an adverse event,

Though not considered AEs for this study, we also track and report the incidence of hyperlipidemia, gallbladder disease, diabetes, and cancer.

All other outcomes that may be construed as being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented, reviewed, and followed up on as needed by a study clinician.

### ***Musculoskeletal Injuries***

Subjects are screened for orthopedic or rheumatologic problems that might limit their ability to participate in the physical activity component of the intervention. Participants in the comprehensive and comprehensive plus DASH groups are taught techniques for stretching, warm-up, and cool-down as a component of the intervention to reduce risk of musculoskeletal injuries. In the case of illness or injuries during the intervention period, interventionists continue to advise the participants on adapting their physical activity program. For example, individuals who have been in automobile accidents may need to alter their physical activity patterns for a time period. This alteration in activity may require some assessment in order for the interventionist to be able to provide suggestions for adapting the participant's physical activity program. An unblinded clinician is available to advise the interventionists on the need to refer for medical care if necessary.

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

### ***Participation in Exercise Programs***

Individuals with possible angina at baseline based on the Rose questionnaire are referred to their primary physician for evaluation, and are eligible to participate in PREMIER only if they submit documentation of a negative exercise stress test within the previous six months and have been cleared by their personal physician and a PREMIER clinician. All randomized participants are eligible to participate in a *moderate* physical activity program. Women under the age of 50 and men under the age of 40 with less than two risk factors for coronary artery disease (see appendix) are eligible to participate in a *vigorous* physical activity program, if they choose to do so (ACSM, 1995). Individuals with two or more risk factors, or over the age of 40 or 50 for men and women, respectively, who are interested in initiating a vigorous physical activity program require documentation of a negative exercise stress test within the past six months and personal physician approval prior to beginning vigorous exercise. Participants who enter PREMIER



currently engaging in regular vigorous activity are allowed to continue vigorous activity, regardless of risk factor status or age.

## **11. Participant Closeout**

### ***End of Cohort***

At the conclusion of participation of each cohort, individual participants receive a summary of their blood pressure and other clinical measurements.

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

### ***End of Trial***

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

## 12. Data Analysis

Note that the data collection procedures are described in Section 8 of this protocol, including imputation methods for missing data.

### *Primary Specific Aims*

Specific aims 1-3 concern the effect of intervention on change in SBP at six months. The basic strategy is to use the conditional change model (Plewis, 1985)

$$\Delta Y = \beta_0 + \beta_1 Y_0 + \beta_C X_C + \beta_D X_D + \sum_i \alpha_i S_i + \sum_i \gamma_i C_i + e$$

The quantities in the model are defined as follows.  $\Delta Y$  is the change in SBP, computed as the average of all SBP measurements made at the six-month period, minus the average of all baseline measurements.  $Y_0$  is the initial SBP, computed as the average of all baseline measurements. It is included in the model in order (1) to account for potential regression-to-the-mean effects and (2) to legitimately reduce the residual variability in the outcome.  $X_C$  and  $X_D$  are indicators, respectively, of the comprehensive intervention condition and the comprehensive plus DASH intervention condition. The  $S_i$  terms are indicators of the performance sites, the  $C_i$  terms indicate the cohorts, and  $e$  is a random “error” term. The primary hypothesis tests are:

Specific aim 1: comprehensive + DASH vs. control,  $\beta_D = 0$

Specific aim 2: comprehensive vs. control,  $\beta_C = 0$

Specific aim 3: comprehensive + DASH vs. comprehensive,  $\beta_C = \beta_D$

The latter test is operationalized by reparameterizing the basic model as

$$\Delta Y = \beta_0 + \beta_1 Y_0 + \beta_C (X_C + X_D) + \beta'_D X_D + \sum_i \alpha_i S_i + \sum_i \gamma_i C_i + e$$

and then specific aim 3 is achieved by testing  $\beta'_D = 0$ .

The three tests of the specific aims 1-3 are carried out using two-sided procedures at the overall .05 significance level. In order to account for the multiple tests, a Holm-correction to the p-values is performed (Holm, 1979; Proschan, 1999). Specifically, the smaller of the p-values of specific aims 1 and 2 are compared to .05/2, and if it is less than .05/2 then the larger p-value is compared to .05 for statistical significance. If either of these results are significant, then the p-value for specific aim 3 is compared to .05 for significance. For other outcome variables discussed below, the same multiple testing approach is used for each set of analyses across intervention groups.

### *Specific Aims 4-6*

Specific aims 4-6 address the same hypotheses as specific aims 1-3, except that the outcome variables are change in SBP at 18 months and change in DBP at each of six and 18 months. The analysis strategy for these aims is therefore identical to that proposed for aims 1-3.

## *Other Aims*

Specific aim 7 consists of two sub-aims:

Specific aim 7a: test each of aims 1-6 within the non-hypertensive subsample

Specific aim 7b: test each of aims 1-6 within the hypertensive subsample

Since the questions are of the same form as in specific aims 1-3, the analysis strategy is the same, only now carried out separately in the two subsamples. Multiple testing adjustments are made separately for 7a and for 7b.

For aims 8 and 9, the probability distribution of hypertensive status at six months and then at 18 months is modeled in terms of previous hypertensive status, treatment group, and interactions. The model will determine the odds ratios for hypertension status for the intervention groups compared to control and compared to each other. A treatment-by-hypertension interaction term will determine whether the odds ratio for hypertension associated with treatment varies by baseline hypertension status.

Specific aim 10 is to repeat specific aims 1-6 by race, sex, obesity, and age. This is accomplished using the same conditional change model that was used for specific aims 1-6, with some additional terms as described here. The analysis starts with the saturated model, which contains (in addition to the factors cited previously) an indicator of blacks ( $X_B$ ), an indicator of males ( $X_M$ ), a measurement of obesity  $X_O$ , and age (in years). The analysis proceeds first by considering interactions between these factors and treatments, then by considering interactions among the factors themselves, and finally three-way interactions (treatment and two of the above factors). It is anticipated that such an analysis will lead to at most a few interaction terms, and potentially none at all. The final model is determined by trimming non-significant factors. If the interactions are too weak to be detected by this procedure, then they will not appear in the model. If they are substantial enough to be detected, then it will be necessary to include them in the model. Marginal models will be fitted irrespective of whether there are interactions.

Specific aim 11 is to repeat the primary analyses (1-3), replacing SBP as the outcome. The replacements are fasting lipids, fasting glucose, fasting insulin, and homocysteine. The analysis for each factor separately follows the plan for specific aims 1-3, including multiple testing adjustments separately for each endpoint analysis.

Specific aim 12 is to assess markers of adherence, including weight, urinary sodium/potassium/phosphorus/ urea nitrogen excretions, physical activity, fitness, dietary fruit and vegetable intake, low-fat dairy product intake, total energy intake, and percent of calories from total fat and from saturated fat. In each case, the model to be used for specific aims 1-3 is applied to the marker and the same analytic strategy will be pursued.

Specific aim 13 is to assess the impact of the interventions on psychosocial mediators and outcomes and by subgroups defined by psychosocial effect modifiers, and to examine relationships between the interventions, psychosocial mediators, and behavioral outcomes (diet, physical activity, BMI). The effects on mediators and outcomes, which are measured by continuous variables, will be analyzed using the same strategy as for aims 1-3. The effects in subgroups will be analyzed using the same strategy as for aim 10. Analyses will also be

conducted examining the relationships between the dose of intervention, changes in mediators, and changes in outcomes.

### ***Exploratory Analyses***

Exploratory analyses will be undertaken, to further elucidate the primary findings, and to generate hypotheses for future study. These analyses will be regression based, with either a different outcome variable than in the main study, or with the same outcome variable but including more explanatory variables. Participants in the Comprehensive and Comprehensive + DASH intervention arms may exhibit differential adherence to the elements of intervention common to both arms (i.e., weight loss, sodium reduction, increased physical activity, and alcohol moderation). To determine BP differences that can be attributable to the DASH diet, we will conduct analyses to assess differences in BP between the two arms controlling for change in weight, sodium excretion, fitness, and alcohol intake. Other exploratory analyses will focus on the impact of intervention dose (e.g., visit, attendance) on trial outcomes. Due to the exploratory nature of these analyses, customary limits on type 1 error probabilities do not apply, but in reporting the results, due care will be taken to explain the inferential strategy that produced those results.

### 13. Sample Size / Statistical Power

The determination of power to detect various effects is derived from the model described in the analysis plan. Since we do not know in advance what the effect will be of having site and cohort factors in the model, we carry out the computations for the simpler model

$$\Delta Y = \beta_0 + \beta_1 Y_0 + \beta_2 X + e$$

where  $\beta_2$  is the effect of interest. It has already been shown in the statistical literature that this is a conservative method (Aickin & Ritenbaugh, 1991). In this model, the perturbation  $e$  is assumed to satisfy  $E[e] = 0$  with  $e$  independent of  $X$  and  $Y_0$ . We make the reasonable assumption that randomization will render the correlation between  $Y_0$  and  $X$  so small that we can ignore it. It then follows that with  $n$  evaluable participants in each of two groups,

$$\text{var}(\hat{\beta}_2) = \text{var}(\Delta Y|Y_0) \frac{2}{n}$$

The variance for change in SBP on the right is estimated from preceding studies, TOHP1 and DASH2. It has been known for some time that BP measurements made on successive days are highly correlated but that there is also a long-term component of variation that makes measurements far apart more correlated than one would expect, based on the short-term correlation. The long-term effect is not seasonal, since different individuals do not show the same pattern of variation. Rather, it appears to be a within-person phenomenon. The time period of this long-term effect is poorly characterized. It can, however, have a major effect on study power and must therefore be considered in calculating power and determining study design.

There do not appear to be any data on studies with the same temporal pattern of measurements as PREMIER, so it is not possible to do power calculations without some degree of uncertainty. The approach has been, instead, to estimate the variance components from studies with similar designs and then analytically reconstruct the variances in the PREMIER design. This method has been validated in the DASH2 and TOHP1 data, in the sense that the analysis predicts the observed BP variances in those studies. The TOHP1 trial, in which sets of observations were taken at baseline and at six, 12, and 18 months, closely matches the PREMIER measurement design. TOHP1 did not, however, include as high a fraction of hypertensives as PREMIER. The DASH2 study population has a more similar composition with regard to hypertensives, but the time between measurement periods was only one month. Analysis of both these datasets shows that there are four components of variance in an SBP measurement:

		<b>Components of Variance</b>		
		TOHP1	DASH2	PREDICTED PREMIER
1.	Between persons	60	80	80
2.	Long-term effect	12	23	16
3.	Short-term effect	36		36
4.	Repetitions, within days	19		19

For PREMIER we take the DASH2 between-persons component, since the PREMIER participants are more like the DASH2 participants. Because the timing of the measurements in

PREMIER is more like that in TOHP1, we use the TOHP1 long-term component, but multiplied by 1.33 (the ratio of 80 to 60) to allow for the larger fraction of hypertensives in PREMIER. This is based on the observation that the long-term effect appears to be stronger among hypertensives than among non-hypertensives. Although this is an ad hoc adjustment, it is more conservative than simply taking the TOHP1 variance component at face value. The separate day-to-day (short-term) and repetitions components are not available yet in DASH2, but their sum is 55, which is exactly the sum of the TOHP1 components, and so we assume them in PREMIER.

The effect of the long-term variance component can be reduced by spreading out the measurements taken at the six- and 18-month observation periods. In both TOHP1 and DASH2, such replicate measurements were closely spaced. It appears that SBP measurements made within one week do not show the long-term effect (suggesting that whatever produces it is relatively constant over such a short interval), but measurements as much as one month apart do show a detectable effect. This would be consistent with an intra-individual periodic fluctuation with a period of perhaps one month or more, but this extra source of variation is poorly characterized.

The *design* for collection of blood pressures in PREMIER is as follows, by study month:

Study Month Post Randomization																					
S	S	S	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
V	V	V																			
1	2	3																			
✓	✓	✓	✓			✓			✓	✓	✓				✓				✓	✓	✓

Each check mark stands for one collection day, and there are two determinations of BP on each day. Trial logistics will doubtless introduce some variability into this design. It would be optimal if the four visits prior to randomization (shown by month 0) will be far enough apart to be in four different periods with respect to the long-term effect, but this cannot be controlled, so the variance contributed to the observations may be more like that induced by four observations in two long-term periods, which would be less advantageous. Because of this possibility, power curves are displayed both for two and for four baseline long-term periods, since these should bracket the true power curve. The measurements made in months 6-8 and in months 16-18 may consist (at one extreme) of four days in four different long-term periods, or (at the other extreme) four days in two long-term periods. For example, measurements at (month,day) = (6,1), (7,1), (7,30), (8,30) would likely be in four long-term periods because of the one-month separation, but measurements at (month,day) = (6,28), (7,2), (7,30), (8,3) would probably only represent two long-term periods. Both eventualities are considered in the computations, as the potential extremes, with the truth bracketed between them.

With these assumptions, the variance of a person-mean (at baseline, 6-8 months, or 16-18 months) is

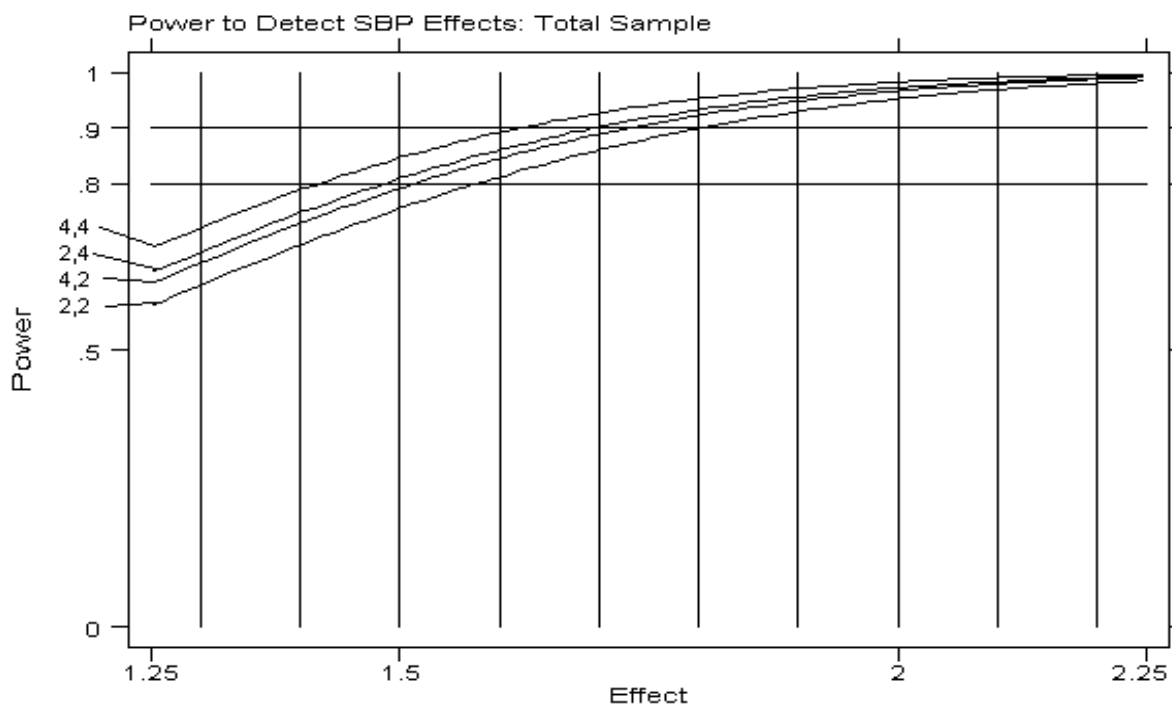
$$\text{var}(Y) = 80 + 16/4 + 36/4 + 19/8 = 95.4 \quad (\text{assuming four periods})$$

$$\text{var}(Y) = 80 + 16/2 + 36/4 + 19/8 = 99.4 \quad (\text{assuming two periods})$$

As indicated above and elsewhere in this and the preceding section, there is no good evidence from any existing studies what the exact period of the long-term effect is, and therefore the definition of the length of a period must remain vague. As indicated above, it is probably longer than one month. The above equations are computed in order to bracket the true power curve, since we do not know which assumptions will turn out to have been most accurate. The covariance between the person-means is  $cov(Y_1, Y_0) = 80$ , and so the variance of within-person change is  $var(\Delta Y) = 30.8$  or  $38.8$  (four, respectively two periods) and correlation between within-person change and initial value is  $corr(\Delta Y, Y_0) = -0.284$  (or  $-0.312$  respectively). Finally,  $var(\Delta Y|Y_0) = (1 - 0.284^2)30.8 = 28.316$  (or  $[1 - 0.312^2]38.8 = 35.023$ ), so that  $sd(\Delta Y|Y_0) = 5.32$  (or  $5.92$ , respectively).

Figure 3 shows the power to detect an effect (difference in change between two groups with  $800/3 = 267$  per group) based on the above estimates. It assumes the multiple testing adjustment for a .05 two-sided test as described in the analysis plan. Specifically, the power is computed for a test at the .025 level, which is the first step of the procedure to be used. The power for the second step is higher than that for the first step, but computing it is difficult because it depends on the outcomes at the first step. Consequently, mildly conservatively, we state the power at the first step. In this and the following figures, the upper two curves show the range of possibilities from two to four long-term periods at the endpoint assessment with four long-term baseline periods. The lower pair of curves assume two long-term baseline periods are sampled. The study is therefore projected to have 90% power to detect effect sizes on the order of 1.6 to 1.8 mmHg.

**Figure 3. Power to Detect SBP Effects: Total Sample**

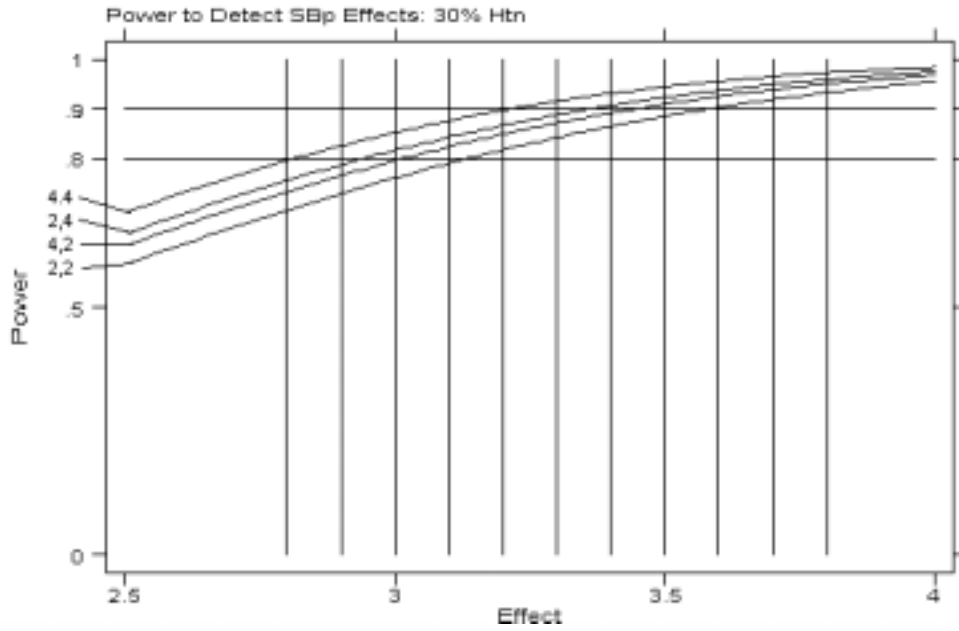


The corresponding graph for the 30% of hypertensives is shown in Figure 4. It is based on the variance components for those Portland TOHP1 control group participants whose average of all study blood pressures was > 140/90 mmHg (between person 68; long-term 20; short-term 43; repetition 21). Similar variance components were seen for hypertensive participants in DASH2. The trial should have 90% power to detect effect sizes on the order of 3.2 to 3.6 mmHg.

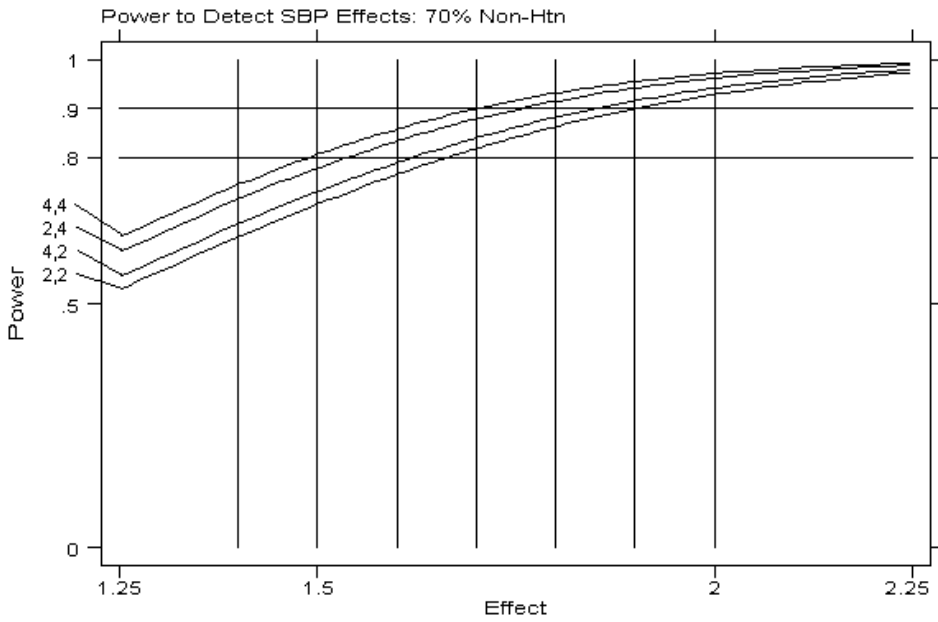
The variance components estimated for the non-hypertensives were 23, 16, 30, and 15, and the power curves within this group are shown in Figure 5. Effect sizes on the order of 1.7 to 1.9 mmHg can be detected with 90% power.



**Figure 4. Power to Detect SBP Effects: 30% Htn**



**Figure 5. Power to Detect SBP Effects: 70% Non-Htn**



The last curve (Figure 6) gives power for the same test, applied only within the African-American subsample. It assumes the same variability as was used for the total sample, because there is no appreciable difference in the variance component estimates. Effect sizes on the order of 2.6 to 2.85 mmHg can be detected with 90% power.

**Figure 6. Power to Detect SBP Effects: 40% African American**

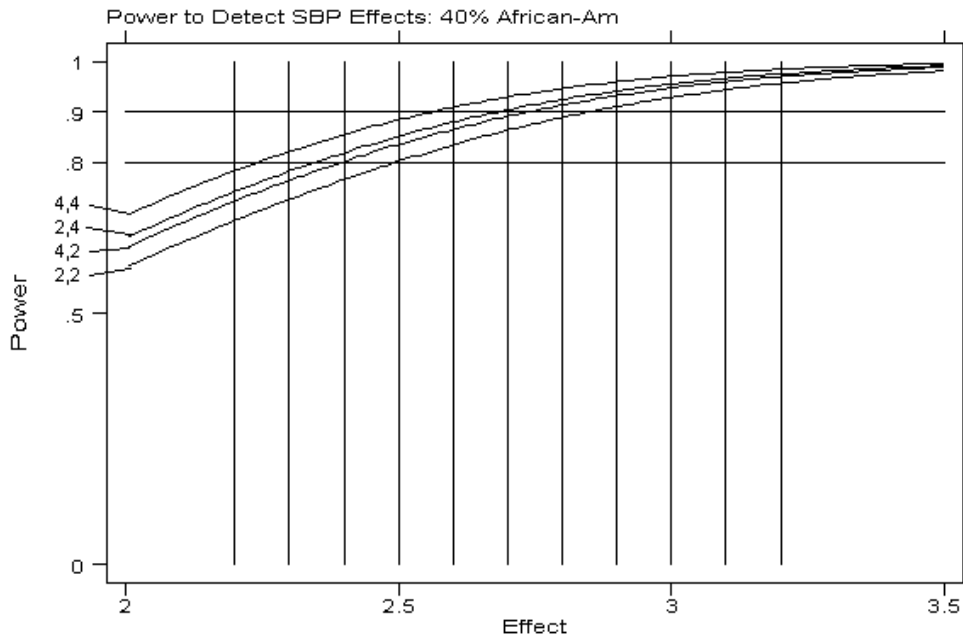


Table 7 summarizes selected information from these curves.

**Table 7. Detectable Effect Sizes for SBP (in mmHg) Corresponding to Power of 80% and 90% for Various Subgroups and Design Options**

Subgroup	Design option <sup>1</sup>	80% Power	90% Power
Total			
	4,4	1.4	1.6
	2,4	1.5	1.7
	4,2	1.5	1.7
	2,2	1.6	1.8
Hypertensives <sup>2</sup>			
	4,4	2.8	3.2
	2,4	2.9	3.4
	4,2	3.0	3.4
	2,2	3.1	3.6
Non-hypertensives <sup>2</sup>			
	4,4	1.5	1.7
	2,4	1.5	1.7
	4,2	1.6	1.8
	2,2	1.7	1.9
African Americans <sup>3</sup>			
	4,4	2.2	2.6
	2,4	2.3	2.7
	4,2	2.4	2.7
	2,2	2.5	2.8

<sup>1</sup> number of long-term periods at: endpoint, baseline

<sup>2</sup> assumes 30% of sample are hypertensive at baseline

<sup>3</sup> assumes 40% of sample are African Americans

### ***Interim Stopping Guidelines***

Participants in the PREMIER Trial are not thought to be subject to significant adverse risks as a part of their participation; they are healthy and the study treatments are not expected to cause clinically important side effects. Also, PREMIER is not testing a new drug or medical therapy which, if shown to be beneficial in interim analyses, might ethically compel the Data and Safety Monitoring Board (DSMB) to recommend early termination of the trial so that the results could be disseminated.

On the contrary, all three treatment arms being evaluated in PREMIER are consistent with national recommendations for the nonpharmacologic prevention and control of high blood pressure (JNC VI, 1997). They differ only in the intensity with which participants are encouraged and/or assisted in their efforts to adopt these recommendations. Finally, participant blood pressure is monitored regularly throughout the trial, and blood pressure escape limits have been set to assure that participants with untreated hypertension are referred for evaluation after six months in accordance with JNC-VI recommendations (JNC VI, 1997).

In addition, because participants are recruited into one of four cohorts over roughly a two-year period, the maximum number of formal interim analyses that are possible is three (i.e., after each of the first three cohorts). Given that the most popular interim monitoring strategies (e.g., O'Brien-Fleming, Lan-DeMets) (O'Brien & Fleming 1979) (Lan & DeMets, 1983) are designed to control the type I error rate and are very conservative during the initial looks at the data, it would be extremely difficult to reject the null hypothesis until after the third cohort. At that point, most of the participants for the fourth and final cohort will have already been recruited and randomized.

For all of these reasons, the PREMIER Steering Committee chose not to adopt formal stopping rules for efficacy as part of the PREMIER protocol. Rather, the Steering Committee feels strongly that the study should be continued until its scheduled conclusion unless evidence arises that participation in PREMIER is placing participants at undue risk for adverse clinical outcomes. Early termination of PREMIER for positive outcomes will only limit the precision with which the primary study outcomes can be estimated and may limit our ability to address key secondary aims of the trial. These aims include the following questions.

1. Estimate the effects of the PREMIER interventions in subgroups defined by race, sex, age, obesity status, and hypertension status.
2. Estimate the effects of the PREMIER interventions on hypertension status at six and 18 months post-randomization overall and in subgroups defined by baseline hypertension status.
3. Estimate the effects of the PREMIER interventions on fasting lipids, glucose, insulin, and homocysteine.
4. Estimate adherence to, and impact of, the PREMIER interventions as indicated by changes in: a) body weight, b) 24-hour urinary excretion of sodium, potassium, phosphorus and urea nitrogen, c) estimated energy expenditure, d) cardiorespiratory fitness, e) number of daily servings of fruits, vegetables, and dairy products, f) intake of total energy and percent of energy from total fat and saturated fat, and g) intake of alcohol, and h) serum carotenoids, folate, and vitamin B-12.

Furthermore, it is unlikely that early termination of the trial due to a positive outcome could significantly advantage study participants. In fact, the opposite may be true. Two-thirds of the PREMIER participants will be randomized to receive one of the two intensive interventions, each consisting of a series of individual and group intervention sessions. Historically such interventions are more effective than usual care or “advice only” interventions in helping participants achieved the targeted behavior changes of this trial, all of which are known to lower blood pressure (JNC VI, 1997). Even the one low intensity intervention includes three individual counseling sessions over the course of the 18-month follow-up period, which is more than these participants will typically receive in the absence of their participation in PREMIER.

A monitoring tool that the DSMB may wish to employ is the use of conditional power analyses (Lan, *et al.* 1982) (Lan & Wittes 1988). The conditional power at information time  $\tau$  is the probability of obtaining a statistically significant result at the end of the trial given the observed results up to time  $\tau$  and the hypothesized treatment effects. Unlike the O'Brien-Fleming or Lan-DeMets boundaries, conditional power is used to justify terminating a trial which has no realistic chance of producing a statistically significant result. The trial may be stopped if the conditional

power is very low even assuming a large treatment benefit for the remainder of the trial. The formula for computing conditional power is given in the Appendix. The Steering Committee recommends that if conditional power is greater than 15% for detecting a reasonably large effect for the primary outcome, this should be considered evidence that continuation of the trial is warranted. Even in the case of less power, the DSMB may still propose to continue the trial so that study outcomes may be estimated as precisely as possible.

### *Summary*

A decision to stop the trial early should be based on many factors. It is the PREMIER Steering Committee's belief that the PREMIER trial should be continued until its scheduled conclusion unless evidence arises that participation in PREMIER is placing participants at undue risk for adverse clinical outcomes. Alternatively, the DSMB may choose to recommend that the trial be discontinued if it becomes apparent that continuation of the trial is not likely to produce a statistically significant result. The DSMB would review the conditional power results for the primary outcomes and for various subgroup hypotheses to determine whether the cost of continuing the study outweighs the potential benefits.

### *Conditional Power Formula*

Let  $\delta$  be the hypothesized difference in means for the remainder of the trial,  $\sigma$  be the standard deviation of the change in blood pressure from baseline to end of study, and  $n$  be the number of subjects planned for each diet arm ( $n=200$  in our case). Let  $b$  denote the current B-value, which is the current z-score multiplied by the square root of the information time  $t$ . Then conditional power at information time  $t$ ,  $CP(t)$ , is given by

$$CP(t) = 1 - \Phi \left[ \frac{Z_{\alpha/2} - b - \lambda(1-t)}{\sqrt{(1-t)}} \right],$$

where  $\lambda = \delta(2\sigma^2 / n)^{1/2}$ .

## **14. Quality Control and Data Management**

### ***Principles and Philosophy***

Quality control efforts ensure that project data and activities are standardized, accurate, and timely, thus minimizing variation not associated with treatment effects. To this end, staff are trained and certified rigorously and all trial activities are monitored routinely.

### ***Staff Training and Certification***

PREMIER staff are trained and certified in three main areas: clinical evaluations, data collection and management, and intervention. In addition, detailed procedures cover the collection and handling of blood and urine specimens.

#### ***Clinical Evaluations***

Clinic staff from each site are trained to administer and record the following clinical measurements: RZ blood pressure, height, weight, fitness, waist circumference, and physical activity. Staff are also trained in procedures for drawing and processing blood specimens and for processing 24-hour and spot urine specimens. In addition, staff receive training in the proper administration and review of study questionnaires.

PREMIER uses the same RZ blood pressure training materials as the TOHP, DASH, and DASH2 studies. This includes centralized training of trainers, who must have at least six months experience taking blood pressures and who are certified to conduct local training of other technicians with similar qualifications. Recertification of trainers is done semi-annually through a central, trial-wide process. Recertification for all technicians also occurs semi-annually and is done locally. Each PREMIER site must maintain on staff at least two certified, practicing blood pressure technicians. The Coordinating Center monitors certification training, recertification, and quality control.

PREMIER uses the same fasting blood and 24-hour urine collection procedures as DASH2. Staff are trained in procedures for instructing participants on collection, processing specimens, and shipping samples to the central lab. Appropriate staff from each site are centrally trained as trainers in all other relevant procedures. Following their certification as trainers, these individuals are responsible for training and certification of local clinic staff at their sites. Trainers and local staff are recertified semiannually.

#### ***Data Collection and Management***

PREMIER employs a system of distributed data entry. The majority of data, including all clinical measurements and eligibility information, are entered into a PC-based application at the clinical centers. The 24-hour recall data are collected, coded, and entered at Pennsylvania State University prior to transfer to the Coordinating Center. Similarly, fasting blood and 24-hour urine samples are analyzed by a centralized contract lab, which then sends results to the Coordinating Center.

All staff involved in data collection are trained on the instructions for administering each of the questionnaires. At each site, one key person is trained and certified in data entry procedures. Sites may also train one to two backup data entry people. Sites need one unblinded data entry person who can enter intervention forms.

The clinic coordinators and some of the assistant clinic coordinators are trained and certified in data management procedures. These include reviewing forms, entering forms that require overrides, and editing data that have been entered. A centralized training session for data entry and data management personnel is held at the beginning of the study, and recertification sessions are held annually. The Coordinating Center monitors data quality regularly and conducts additional training as needed.

### *Intervention Training and Certification*

Intervention protocols, participant materials, and detailed procedures are developed by the Intervention Committee. To ensure uniform delivery of the interventions, staff are trained in three main areas: content and delivery of the PREMIER interventions; facilitation of the group process and behavior change; and trial-specific procedures for data collection and reporting. Intervention staff participate in a central group training program prior to initiating the PREMIER intervention program. In addition, the chair of the Intervention Committee reviews the progress of intervention activities and resolves problems during its monthly conference calls.

### *Quality Control of Dietary Assessment*

The NDS database contains many internal data entry and edit checks designed to minimize errors on food records. The CC also has created data check routines that will be used to conduct QC checks on the dietary data. Additional quality control checks will be instituted to improve the quality of dietary data. These include: training and routine certification of interviewers, review of recalls collected by the interviewers, observing interviewers (listening in on interviewer call) and of recalls by other interviewers.

All dietary assessment interviewers are required to complete a comprehensive training program. Each interviewer is required to spend a minimum 30-40 hours of training prior to conducting telephone recalls in actual participants of on-going studies. Components of training are as follows:

- **Training:** Pennsylvania State University (PSU) conducts extensive training for new interviewers. The topics covered in the curriculum are outlined below.
  1. Description of Interviewers Responsibilities and Current Projects
  2. Overview of the Software (Nutrition Data System for Research – NDS-R)
  3. NDS-R Software Tutorial
  4. Practice Data Entry Exercises/Use of 2-D Food Portion Poster:
  5. Listening to Interviews/Training on Interview Technique
  6. Practice Interviewing Other Interviewers or Co-workers Practice Interviewing Others (adults and children)
  7. Practice with Data Manager
  8. Conducting Interviews with Other Trained Interviewers Present

- **Certification:** Tests to determine the reliability of the data entry personnel are conducted upon completion the training. These tests consist of conducting 3 diet recalls from a scripted prepared recall and are administered by the data manager. The interclass correlations of the interviewers are calculated. Previous reliability checks of interviewers or dietary data entry personnel have shown correlation's to be 0.95 or greater for all nutrients examined (Smiciklas-Wright, *et al*, 1991) indicating a high degree of internal reliability for calculating nutrient intakes using NDS-R
- **Review of recalls:** each nutrition interviewer will be asked to review and edit 100% of the recalls that she or he collects. Editing includes review and clarification of substitutions for missing foods, clarifying notes regarding the recall, and when necessary, entering missing foods into the nutrient database. Interviewers other than those collecting data for Premier will also review a proportion of the Premier records for clarity, verification of missing foods and overall quality of the information collected.
- **Observing interviewers:** Each interviewer will be observed at least once every 3 months. The observer will evaluate the interviewer's skill using the special skills checklist (see manual of operations) designed for this purpose. The observer will then check the recall record, and provide immediate feed back to the interviewer. Every 6 months re-certification or reliability tests are conducted similar to those conducted following training.

## ***Data Management and Reporting***

### *Data Management System*

Each site keeps the official copy of its data on its workstation. These data are backed up daily to a second hard drive. A summary study database is maintained at the Coordinating Center and is updated regularly via modem access to the workstations. These data are merged at the Coordinating Center with the 24-hour diet recall data and the results of central laboratory analyses. The database is monitored regularly for completeness.

Randomization assignments are generated locally using the workstation. Prior to randomization, the computer checks the master database to make sure that all screening activities have occurred, that the participant meets all eligibility criteria, and that all required baseline data have been collected. Participants are assigned to one of the three intervention arms from a predetermined allocation table stored on each site's workstation. Intervention assignments are stratified by site and baseline hypertensive status, and varying block sizes are used to ensure a balance of randomization assignments over time.

### *Quality Control*

The data management system performs range, logic, and missing data checks on all data at the time of data entry. Cross-form edit checks are also performed locally and for the integrated data maintained at the Coordinating Center. Forms that do not pass these checks are rejected. At this point, the clinic coordinator reviews the form and decides how to resolve the problem. Either the form is corrected, or the clinic coordinator enters the form and overrides the relevant edit check. These overrides are tracked and reviewed regularly. Standardized override reports that summarize problems in the database provide an additional method of assuring data quality.



If problems or changes are discovered after a form has been entered, the data entry person or clinic coordinator can use the data entry system to apply edits to the data. These edits are tracked and reviewed regularly. Standardized edit reports that summarize problems in the database provide an additional method of assuring data quality.

### *Reporting*

The Coordinating Center prepares regular reports summarizing the performance characteristics of the study as a whole and of individual clinical centers. These reports are distributed to the members of the Steering Committee, to appropriate subcommittees, and selected reports to the Data and Safety Monitoring Board. Selected reports are also available on a daily basis on the site workstations and on the PREMIER Web site.

### *Site Visits*

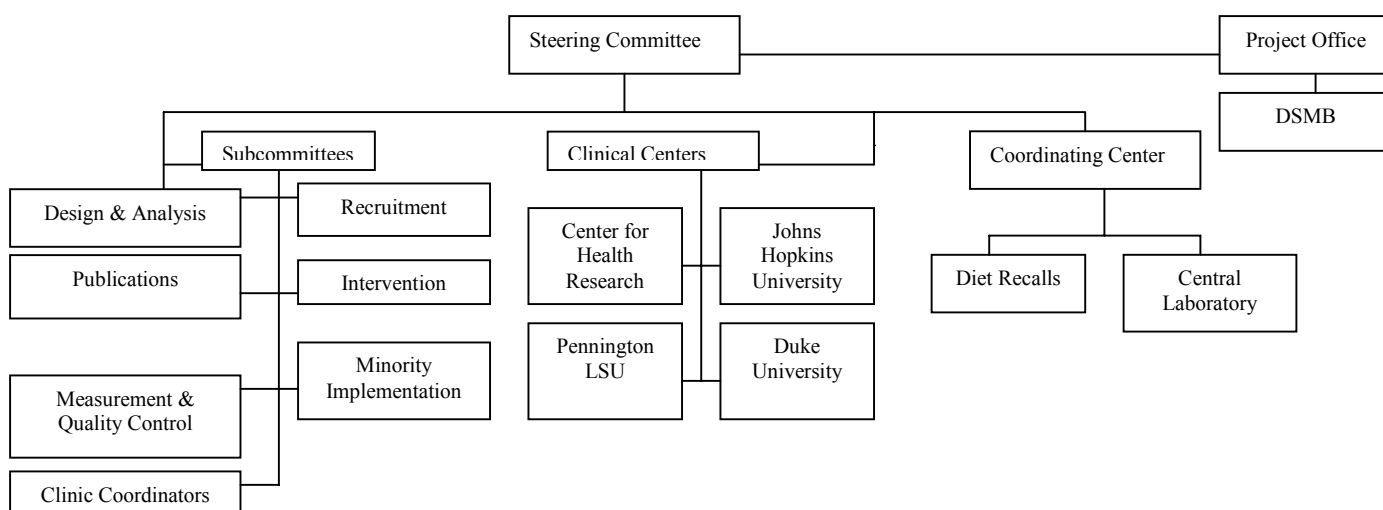
The Coordinating Center annually conducts routine site visits to the four clinical centers and distributes reports of these visits to the site PI, the study chair, and the Project Officer. Additional, non-routine site visits may also be needed to deal with events, such as computer hardware maintenance or local QC problems, that may occur but are not predictable in advance. Cross-site visits by clinical and intervention staff are also encouraged. Site visits of the coordinating center are also anticipated.

## 15. Trial Administration

### *Trial Governance*

PREMIER is a multicenter, randomized trial with four participating clinical centers, the Coordinating Center, and the NHLBI Project Office acting together to implement a common protocol and to administer the trial. The study is structured similarly to DASH, TOHP, and other successful collaborative trials (see Figure 7).

**Figure 7. PREMIER Organizational Chart**



### *Participating Sites*

Participating institutions include the NHLBI Project Office, the Coordinating Center (Kaiser Permanente Center for Health Research in Portland, Oregon), and four clinical centers: Johns Hopkins University in Baltimore, MD, Pennington Biomedical Research Center in Baton Rouge, LA, Duke University Medical Center in Durham, NC, and a clinical center also located at the Kaiser Permanente Center for Health Research in Portland, OR. The Diet Assessment Center of the Pennsylvania State University performs diet recalls, and a central laboratory (the Core Laboratory for Clinical Studies) performs analysis of blood and urine specimens. These are contracted through the Coordinating Center.

### *Trial Committees*

The Steering Committee is the primary decision-making body for the trial. Standing subcommittees include: Design and Analysis, Recruitment, Measurement and Quality Control, Minority Implementation, Intervention, Clinic Coordinators, and Publications. An independent Protocol Review Committee (PRC) and subsequently a Data and Safety Monitoring Board (DSMB) also serve the study. The functions of these committees and the PRC/DSMB are summarized below.

### *Steering Committee*

**Membership:** Principal investigators (PIs) from each of the four clinical centers and from the Coordinating Center each have one vote, as does the NHLBI project officer. Committee chairs (if other than PIs) attend and participate in discussions but do not have voting privileges.

**Functions and Responsibilities:** Ensure clear delineation of roles and responsibilities among participating institutions; review and approve all policies, protocols, and trial-wide procedures; monitor performance of PREMIER overall and of each clinical center, including recruitment, adherence, data collection, quality control, and data analysis; consider and approve any ancillary studies and access to study data. The Steering Committee meets face-to-face three times during year 01 and approximately twice a year thereafter, with conference calls or additional meetings as needed and with regular sharing of information. Meetings are open to all study personnel.

### *Clinic Coordinators*

**Membership:** Clinic coordinators from each clinical site and the data manager from the Coordinating Center.

**Functions and Responsibilities:** Serve as primary liaison when communicating with the Coordinating Center on issues of data management and quality assurance and implementation of training and certification procedures; also serve as forum for sharing experience and problem solving among clinic coordinators. In order to maximize communications, one member of this committee serves on each other committee.

### *Design and Analysis Committee*

**Membership:** Key trial personnel appointed by Steering Committee with each center and the Project Office having a representative; includes mix of disciplines and skills needed to conduct trial.

**Functions and Responsibilities:** Recommend to the Steering Committee the basic design components of the trial and recommend changes in and additions to the protocol. This committee also recommends policies for the conduct of ancillary studies, reviews all ancillary study proposals, and makes recommendations to the Steering Committee regarding ancillary study proposals.

### *Measurement and Quality Control Committee*

**Membership:** Key trial personnel including representatives from each clinical center, the Coordinating Center, and the Project Office.

**Functions and Responsibilities:** Recommend to the Steering Committee measures, processes, and procedures for assuring quality control of the trial, including training, certification, quality control measures and procedures, and other activities directed at ensuring that data are valid and reliable.

### *Intervention Committee*

**Membership:** Key trial personnel from each clinical site, the Coordinating Center, and Project Office with expertise in lifestyle interventions, including behavior change, counseling, nutrition, and physical activity.

**Functions and Responsibilities:** Recommend to the Steering Committee policies, practices, and procedures relating to development, implementation, and quality control for conducting the interventions.

### *Recruitment Committee*

**Membership:** Recruitment coordinators from each clinical site, selected PIs appointed by the Steering Committee, and a Coordinating Center representative.

**Functions and Responsibilities:** Facilitate the successful recruitment of study participants, monitor and report on progress to the Steering Committee, and recommend actions to be taken to improve recruitment.

### *Publications Committee*

**Membership:** Representatives from each clinical site, the Coordinating Center, and the Project Office appointed by the Steering Committee.

**Functions and Responsibilities:** Develop and recommend to the Steering Committee policies on publications and presentations and oversee the implementation of these policies.

### *Minority Implementation Committee*

**Membership:** This committee includes a PI, clinic coordinator, recruitment coordinator, and other investigators and staff members with a special interest or experience in minority health research. The concerns of this working group cut across all aspects of the trial with a focus on adapting the recruitment and intervention materials to be culturally appropriate for African Americans.

**Functions and Responsibilities:** Review materials, protocols, and procedures for cultural appropriateness to African Americans and make recommendations to the Intervention, Recruitment, and Steering Committees for maximizing full participation of African Americans in the trial.

### *Protocol Review Committee (PRC) and Data and Safety Monitoring Board (DSMB)*

**Membership:** Research scientists not otherwise connected with the study are appointed by NHLBI. Their expertise includes the disciplines and skills needed to initially review the protocol (PRC) and then to monitor trial progress, quality of data, and safety of the participants (DSMB).

**Functions and Responsibilities:** The PRC reviews the protocol prior to implementation and makes recommendations to improve it, and considers whether or not the risks associated with implementation of the protocol are reasonable and are minimized appropriately. Subsequent to

the adoption of the protocol, the DSMB serves in an advisory capacity to the NHLBI in order to monitor, review, and assess study progress. The DSMB has access to unblinded outcome data during the trial, and, in order that participants are not exposed to unreasonable or unnecessary research risks, recommends early termination of one or more arms of the trial if the data suggest significant adverse risk to participants, if the questions posed by the trial appear to have been answered and there are no ethical or other reasons to continue the trial, or if continuation of the trial is futile. The DSMB also reviews the timeliness of recruitment and the timeliness and quality of the data, based on data monitoring reports and other materials submitted by the Coordinating Center.

The DSMB meets at least annually throughout the trial. Meetings are attended by representatives from the Coordinating Center, the Steering Committee (including the chair, vice-chair, and chair of the intervention committee), and the NHLBI, in addition to DSMB members. Only the DSMB members may vote. None of the clinical center investigators are exposed to blinded study data until the end of the trial and/or until the DSMB recommends that unblinding should occur.

The "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Sponsored Multi-Center Clinical Trials", published in the NIH Guide for Grants and Contracts on June 11, 1999, requires all multi-site clinical trials with a DSMB to forward summary reports of Adverse Events to each IRB associated with the trial. Each summary report includes:

- a statement that a DSMB review of data and outcomes across all centers took place, and the date of the review
- a summary of the DSMB review of the cumulative adverse events reports from all participating sites without specific disclosure by treatment arm, unless safety considerations require such disclosure, or a statement indicating that no adverse events were reported from the participating sites
- the DSMB's conclusion with respect to progress or need for modification of the protocol.

These summary reports are in addition to all other adverse event reporting procedures required by the NHLBI, the trial protocol, each organization, and each local IRB, and are distributed to each Principal Investigator by the Coordinating Center within 30 days after each DSMB meeting. Principal Investigators are required to forward Summary Reports of Adverse Events to their local IRBs. Adverse events are defined in section 10 of this protocol, Safety Monitoring.

#### *Dissemination of Project Documents*

PREMIER uses a version of Web technology to provide access to all project documents. The MOP, data collection forms, minutes from committee meetings, queries and answers, and other key documents are posted on the Coordinating Center computer server and are accessible to all authorized Coordinating Center and clinical center staff via the PREMIER computer network. Access is controlled by password checks. Although this system uses Web technology, it is not accessible without an individual specific password. Using this system, any authorized PREMIER staff member can have instant access to the current version of the MOP and other key aspects of the protocol. They also have access to all trial minutes and other communications. All documents on the PREMIER Web site are stored in a read-only format; that is, they can be read or printed at the local site, but not edited.

**Staff Training and Certification.** Clinical center staff are trained and certified in all key elements of the protocol, including blood pressure certification; height, weight, and waist circumference measurements; adherence monitoring; lifestyle intervention; and use of the data management system. In each case, master trainers at each site receive central training by Coordinating Center staff or trainers designated by the Steering Committee. These master trainers in turn conduct local training and certification twice yearly. Master trainers are re-certified at each annual training meeting. The Coordinating Center schedules all training sessions and keeps a log of all certified staff. In addition, the Coordinating Center develops and conducts the training and certification modules for: the data management system; trial communications; the protocol, MOP, forms manual, and analysis guide; and all intervention activities.

**Trial Communications.** The Coordinating Center is responsible for coordinating all trial-wide communications, including distributing and archiving all physical mail, electronic mail, and facsimiles; scheduling and documenting conference calls; maintaining incident logs for individual phone calls; and scheduling and arranging national meetings. The Coordinating Center is represented in all committee meetings and conference calls and promptly produces and distributes their minutes.

A Microsoft Windows NT Web server is located at the Coordinating Center for data collection and information dissemination. In addition, a Windows NT workstation is located at each clinical site. Microsoft Remote Access Services over standard telephone connections are used for secure, confidential communication between these systems. A second, redundant telephone connection is established at each clinical site, to facilitate access to site servers by Coordinating Center system support staff without interference with normal clinic operations.

Workgroup collaboration and information dissemination is accomplished using Microsoft's Exchange Server and Internet Information Server. Web-based technology provides the mechanism for developing applications to collect study data; to disseminate information, including manual of operations and documentation; and to facilitate investigator and study staff collaboration (electronic mail and newsgroup capability). Microsoft Back Office products such as Exchange and System Management Server (SMS) are used to develop a command console interface to automate study site server administration, data management, backup, and archival.

## 16. Human Subjects

### *Informed Consent*

All PREMIER participants provide written informed consent using procedures reviewed and approved by each clinical center's local Institutional Review Board (IRB). The process and timing of consent may vary by clinic, but at minimum included separate consents for the screening and intervention phases of the trial. Descriptions of each clinical center's consent procedures are included as part of the manual of procedures. The consent forms cover all procedures done as part of screening, randomization, and intervention.

### *Confidentiality*

All participant information, and even the fact that an individual is participating in the study, is considered confidential. This confidentiality is assured in PREMIER through several mechanisms. First, each participant is assigned an anonymous study ID, which is then used on all study forms.

Second, all study forms, biological specimens, and paper records that contain participant information (e.g., address lists, phone lists) are kept in secured, locked areas when not in use. In addition, such materials, when in use, are kept away from public scrutiny. Materials and specimens that need to be discarded are destroyed.

Third, access to all participant data and information, including laboratory specimens, is restricted to authorized personnel. In the case of computerized data, this restricted access is assured in several ways. At the clinical centers, the data are maintained on stand-alone personal computers (PCs) that are not networked to any other PC. Further, access to the study data on these machines is password-protected. Staff members receive individualized account numbers and passwords that allow them access only to those elements of the data management system to which they are authorized. At the Coordinating Center, access to computerized data is restricted in two ways. First, only authorized personnel are granted access to the data, and, second, this access is further restricted by password protection. In addition, Coordinating Center personnel are annually required to sign a confidentiality statement affirming that they agree to abide by the Center for Health Research's policies on research confidentiality and ethics.

When the study database is made available to clinical centers and to the Project Office, it does not include actual identities and contact information of participants. Such information is retained at the individual clinical centers for use in the event that future follow-up of the study participants is necessary.

Finally, participants are not identified by name in any reports or publications, nor are data presented in such a way that the identity of individual participants can be inferred.

Although this study should not pose any major health risk to participants, the protocol includes many features to minimize any potential risks. Participants in this study are selected for their elevated blood pressure. Prospective participants go through several screening visits and are excluded if they have or have had atherosclerotic disease or target organ damage from elevated blood pressure. We minimize the risk of untreated hypertension during the trial by excluding

subjects who, at baseline, exhibit blood pressure elevations greater than stage I hypertension or who are currently taking antihypertensive medication.

Blood pressure is measured at least every four months during the intervention, which exceeds clinical recommendations for follow-up of blood pressure at our eligibility levels (JNC VI, 1997). If at any time during intervention or screening blood pressure exceeds pre-determined escape thresholds, the participant is referred to a clinician for further evaluation. Participants who reach an escape threshold before randomization are excluded from the study. Participants who reach an escape threshold after randomization are referred to their personal physician. All participants whose mean blood pressure at six months exceeds SBP of 140 mmHg or DBP of 90 mmHg will be referred back to their personal physician for possible initiation of medication.

Following enrollment, the principal investigators continuously monitor safety issues and report any problems to the Coordinating Center, which summarizes this information in regular trial monitoring reports to the Steering Committee and to the external Data and Safety Monitoring Board. All PREMIER centers have one or more study clinicians to ensure the satisfactory disposition of medical issues (referral to physician or decision to exclude from the study for medical reasons) and any adverse events.

Gastrointestinal upset (e.g., bloating) or increased frequency and bulk of stools may accompany increased fruit and vegetable intake. These effects are either transitory or readily reversible by moderation of fruit and vegetable intake. Our experience suggests that GI discomfort is generally minor and subsides quickly. Participants are instructed to increase fruit and vegetable intake gradually in order to minimize potential GI discomfort. Participants are monitored for reactions to the diets, and if necessary, the diet can be modified or terminated (although this has not been necessary during the DASH and DASH2 studies). Gastrointestinal upset from increased consumption of dairy products is also possible in lactose intolerant individuals. Such individuals will be advised to select dairy products that are reduced in lactose and to use lactase products, such as Lactaid, as needed.

Participants in the two active intervention arms are also exposed to a slightly increased risk of musculoskeletal injuries associated with moderate-intensity physical activity. Risk of injury is minimized by instruction on proper exercise technique, the importance of warm-up and cool-down exercises, and proper stretching techniques. The risk of cardiovascular complication associated with physical activity is low—less than 1 per 187,500 person hours of exercise (American College of Sports Medicine, 1995). These same low-level risks are associated with the proposed fitness testing protocol.

Finally, blood drawing may cause some discomfort and/or bruising at the site of the puncture or, less commonly, the formation of a small blood clot, swelling of the vein and surrounding tissue, and/or bleeding from the puncture site. Occasionally, blood drawing can cause someone to become dizzy, lightheaded, or nauseated. In such a case, appropriate medical attention is available at the clinical center.

### ***“Right-to-Know”***

Information obtained during screening is shared with the participant. Abnormal values found at screening are reported to the participant and also, upon request, to his or her personal physician. Abnormal laboratory results from samples collected during the trial are likewise reported. A



report containing information on laboratory results is mailed to participants following the completion of the study. Participants are also told their BP measurements during screening and after the six- and 18-month assessments.

### ***Benefits***

Potential benefits for study participants include participation in long-term lifestyle modifications that may result in improved diet, nutrition, and physical activity patterns, which in turn should decrease blood pressure and lead to an overall reduction in cardiovascular and cancer morbidity. Laboratory tests are performed at no cost, and individuals are informed of clinically significant abnormalities. An additional benefit for some participants may be the personal satisfaction of being part of a national study with major public health implications.

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## Appendix 1

The following tables are excerpted from JNC VI (1997) and are referred to throughout the text of the PREMIER Protocol.

<b>CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGE 18 AND OLDER *</b>			
Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal <sup>†</sup>	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension <sup>‡</sup>			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	≥180	or	≥110
<p>* Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mm Hg should be classified as stage 2 hypertension, and 174/120 mm Hg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as SBP of 140 mm Hg or greater and DBP below 90 mm Hg and staged appropriately (e.g., 170/82 mm Hg is defined as stage 2 isolated systolic hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment (see table 5).</p> <p>† Optimal blood pressure with respect to cardiovascular risk is below 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.</p> <p>‡ Based on the average of two or more readings taken at each of two or more visits after an initial screening.</p>			

## RECOMMENDATIONS FOR FOLLOWUP BASED ON INITIAL BLOOD PRESSURE MEASUREMENTS FOR ADULTS

Initial Blood Pressure (mm Hg)*		Followup Recommended†
Systolic	Diastolic	
<130	<85	Recheck in 2 years
130-139	85-89	Recheck in 1 year‡
140-159	90-99	Confirm within 2 months‡
160-179	100-109	Evaluate or refer to source of care within 1 month
≥180	≥110	Evaluate or refer to source of care immediately or within 1 week depending on clinical situation

\* If systolic and diastolic categories are different, follow recommendations for shorter time followup (e.g., 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

† Modify the scheduling of followup according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

‡ Provide advice about lifestyle modifications (see chapter 3).

## COMPONENTS OF CARDIOVASCULAR RISK STRATIFICATION IN PATIENTS WITH HYPERTENSION \*

### Major Risk Factors

Smoking

Dyslipidemia

Diabetes mellitus

Age older than 60 years

Sex (men and postmenopausal women)

Family history of cardiovascular disease:  
women under age 65 or men under age 55

### Target Organ Damage/Clinical Cardiovascular Disease

Heart diseases

- Left ventricular hypertrophy
- Angina/prior myocardial infarction
- Prior coronary revascularization
- Heart failure

Stroke or transient ischemic attack

Nephropathy

Peripheral arterial disease

Retinopathy

\* See table 5.

## RISK STRATIFICATION AND TREATMENT \*

Blood Pressure Stages (mm Hg)	Risk Group A (No Risk Factors No TOD/CCD) <sup>†</sup>	Risk Group B (At Least 1 Risk Factor, Not Including Diabetes; No TOD/CCD)	Risk Group C (TOD/CCD and/or Diabetes, With or Without Other Risk Factors)
High-normal (130-139/85-89)	Lifestyle modification	Lifestyle modification	Drug therapy <sup>§</sup>
Stage 1 (140-159/90-99)	Lifestyle modification (up to 12 months)	Lifestyle modification <sup>‡</sup> (up to 6 months)	Drug therapy
Stages 2 and 3 (≥160/≥100)	Drug therapy	Drug therapy	Drug therapy

For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as **Stage 1, Risk Group C**, and recommended for immediate initiation of pharmacologic treatment.

\* Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.

<sup>†</sup> TOD/CCD indicates target organ disease/clinical cardiovascular disease (see table 4).

<sup>‡</sup> For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.

<sup>§</sup> For those with heart failure, renal insufficiency, or diabetes.

## **Appendix 2**

### **Local Blood Pressure Referral Procedures**

#### **A. Baltimore**

##### **Blood Pressure Safety Procedures**

Blood pressure is monitored regularly throughout the Premier study, and “escape levels” are established to identify and ensure proper follow-up of individual with potentially dangerous blood pressure elevations. Participants may also be referred to a physician if deemed appropriate based on symptoms and clinical judgments, by Dr. Appel or Dr. Erlinger even though the BP is below the escape thresholds.

In addition to the random zero RZ measurements required for Premier data, additional non- RZ measurements may be taken on a more frequent basis to ensure participant safety.

Dr. Appel should be notified if a participant and or staff is concerned about a participant bp.

If escape levels are reached, a BP Escape Tracking Record (form # 32, 83, 84, or 52) is filled out. The original is placed in the participant’s chart and a copy is sent to the CC. Letitia/Jeanne should be notified of any BP Escapes. If the participant requires a physician’s evaluation and does not have personal physician, Jeanne/Letitia should be notified to give them a list of area physicians.

##### **Premier Blood Pressure Escape Criteria**

The following blood pressure escape levels and protocols have been established to ensure that participants are offered appropriate evaluation and therapy when clinically indicated. The actions taken when these escape levels are reached vary somewhat for screening and intervention. Participants may be referred for evaluation at any time if Dr. Appel or Dr. Erlinger feels it is necessary.

All escape blood pressures should be documented by completing the appropriate BP Escape form and documented in progress notes.

In the event that a randomized participant is referred to a clinician for evaluation, we will try to obtain four sets of end-of-intervention blood pressure measurements prior to treatment.

##### **Screening (Prior to randomization)**

###### Escape Level #1

- The mean blood pressure recorded at any single visit, including
- PSV, SV1, SV2, SV3 or the 4<sup>th</sup> Baseline Blood Pressure, is
- SBP> 180 or DBP> 110 mm Hg.

###### Action:

- Notify Jeanne or Letitia
- Participant is excluded immediately and referred to a physician for further

- evaluation within one week.
- Contact participant in 2 weeks and document outcome.

### Escape Level #2

The mean blood pressure recoded at SV1, SV2, SV3 exceed the established upper limit of eligibility (see Protocol, section 6, Table 3).

#### Action:

- Notify Jeanne or Letitia
- Participant is excluded and referred to a physician for futher evaluation with one month.
- Contact participant 1½ month and document.

### **Intervention Period: 3-Month Visit**

#### Escape Level #1:

The mean blood pressure recorded at the three-month visit is SBP>160 or DBP> 100 mm Hg.

#### Action:

- One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP>180 or DBP> 110, participant is referred to his her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP>160 or DBP> 100, then the participant is referred to his/her personal physician for further evaluation within one month.

### **Intervention Period 6-Month and 18-Month Visit Clusters**

#### *Escape Level #1*

The mean blood pressure recorded at any single visit is SBP>160 or DBP> 100mm Hg.

#### Action:

One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP $\geq$ 180 or DBP  $\geq$  110, participant is referred to his/her personal physician for further evaluation within on week. If the cumulative mean from the two visits is SBP $\geq$ 160 or DBP  $\geq$  100, then the participant is referred to his/her personal physician for futher evaluation within one month.

- Notify Jeanne or Letitia
- Document in participant chart.

- Record on BP escape log.
- Do appropriate follow up calls (3 times if necessary).

### Escape Level #2

The cumulative mean blood pressure recorded at the end of the six or 18 month cluster of visits is SBP $\geq$ 140 or DBP $\geq$  90mm Hg.

#### Action:

- Notify Jeanne or Letitia
- Document in participant chart
- Record on BP escape Log
- Do appropriate follow up calls (3 times if necessary)

### ***Intervention Period: 12-Month Visit***

### Escape Level #1

The mean blood pressure recorded at the 12-month visit is SBP $\geq$  160 or DBP $\geq$  100 mm Hg.

#### Action:

- Notify Jeanne or Letitia
- Document in participant chart
- Record on BP escapes Log
- Do appropriate follow up calls (3 times if necessary).

### Escape Level #2

The mean blood pressure recorded at the 12 month visit is SBP  $\geq$  140 mm Hg or DBP  $\geq$  90 mm Hg.

#### Action:

One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP  $\geq$  160 or DBP  $\geq$  100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP  $\geq$  140 or DBP  $\geq$  90, participant is referred to a physician for further evaluation within two months.

- Document in participant chart
- Record on BP escapes Log
- Do appropriate follow up calls (3 times if necessary).



## **B. Baton Rouge**

### **BP Escape Procedures**

1. When a person hits a BP Escape the severity of their blood pressure is determined based on the guidelines of Premier.
2. Based on that determination the subject is scheduled for a follow-up visit to reassess blood pressure.
3. Upon reassessment of blood pressure a bp escape form is filled out and faxed to the coordinating center. The shipping log is filed in a binder in the coordinators office with the ID of the participant on it as well.
4. If they are not scheduled for a follow-up visit to the clinic then they are referred to their primary care physician.
5. All subjects who are referred, blood pressure sheets are placed in a bin on the coordinators desk to be followed up on at a later time. Depending on the timeline of the referral. Therefore, giving the subject a chance to see his/her primary care physician.
6. A follow-up call is done to the subject to find out if they have followed up with their primary care physician in regards to their blood pressure reading.
7. A statement is written based on the conversation with the participant onto the bp escape sheet. Once this is done the sheets are filed into the participants chart.
8. If the subject can not be reached by three calls it is noted on the bp escape sheet that the subject could not be reached and it is then filed.

## **C. Durham**

### **BP escape at 3m**

- Schedule participant for follow-up visit with-in 1 week
- Complete form #51
- Choose first applicable box on form #51 and refer as needed
- Call referred participant to confirm appointment with physician

### **BP escape at 6m and 18m**

1. Cluster 1 escape level 1
  - Schedule participant for follow-up visit with-in 1 week
  - Complete BP escape form #52
  - Choose first applicable box on form #52 and refer as needed
  - Call referred participant to confirm appointment with physician
2. Cluster 2 escape level 1
  - Schedule participant for follow-up visit within 1 week
  - Complete BP escape form #52
  - Choose first applicable box on form #52 and refer as needed
  - Call referred participant to confirm appointment with physician
3. Cluster 3 escape level 1
  - Schedule participant for follow-up visit within 1 week
  - Complete BP escape form #52
  - Choose first applicable box on form #52 and refer as needed
  - If no referral is needed, check the sum to see if escape level 2 is indicated; if so, refer participant within 2 months.
  - Call referred participant to confirm appointment with physician
4. Cluster 3 escape level 2
  - No follow-up BP needed. Refer to physician within 2 months
  - Call referred participant to confirm appointment with physician

### **BP escape at 12m**

1. Escape level 1
  - Schedule participant for follow-up within 1 week.
  - Complete BP escape form #84
  - Choose first applicable box on form #84 and refer as needed
  - Call referred participant to confirm appointment with physician
2. Escape level 2
  - Schedule participant for follow-up within 1 month.
  - Choose first applicable box on form #84 and refer as needed
  - Call referred participant to confirm appointment with physician

Summary of procedures for contacting ppts who reach escape BP:

<i>Escape level 1</i>	<i>Required timing of referral</i>		<i>Documentation</i>
	1 week	1 month	
Call to confirm appointment scheduled	Within 1 week of follow up BP	Within 2 weeks of follow up BP	<b>BP escape form</b>
If no answer	Call or e-mail in 1 week (repeat 1 more week)	Call or e-mail in 1 week (repeat 1 more week)	BP escape form
If unable to reach	Document on BP escape form	Document on BP escape form	BP escape form
Letter to participant	At the end of cluster visit 3 for that participant	At the end of cluster visit 3 for that participant	Copy of letter in participant clinic folder

<i>Escape level 2</i>	<i>Required timing of referral</i>		<i>Documentation</i>
	1 month	2 month	
Call to confirm appointment scheduled	Within 2 weeks of follow up BP	Within 4 weeks of follow up BP	BP escape form
If no answer	Call or e-mail in 1 week (repeat 1 more week)	Call or e-mail in 1 week (repeat 1 more week)	BP escape form
If unable to reach	Document on BP escape form	Document on BP escape form	BP escape form
Letter to participant	At the end of cluster visit 3 for that participant	At the end of cluster visit 3 for that participant	Copy of letter in participants clinic folder

All BP escape cluster visit and escape forms and follow-up generic BP form are faxed to CC. A copy is filed in the BP escape folder and in the individual participant's folder.

Letters are sent to all participants with their average blood pressure readings after 3 cluster visits are completed. In general, this letter goes out at the end of the window for the entire cohort.

However, for participants who have reached an escape level, this letter will go out as soon as the individual has completed all 3 measurements, and the letter will re-state the recommendation to see a physician within the study referral time frame.

All escapes will be tracked using the tracking form below, with an example of a ppt who hit escape at 3 months (referral confirmed) and 18 months (referral not confirmed) at 6m was escape level 1 with no referral needed but became level 2(referral confirmed):

*Escape BP tracking form*

<i>Participant ID #</i>	<i>3month Level 1</i>	<i>6 month Level 1 / 2</i>	<i>12 months Level 1 / 2</i>	<i>18 month Level 1 / 2</i>
<i>Outcome</i>	<i>X O Z L</i>	<i>X O Z L</i>	<i>X O Z L</i>	<i>X O Z L</i>
Svetla403	X O L	X K / X O L		X Z L

X hit escape  
 O reported appointment or other medical f/u  
 Z couldn't reach  
 L letter sent  
 K no referral needed

**D. Portland**

**POST RANDOMATION ESCAPE  
 BLOOD PRESSURE REFERRAL**

**PURPOSE:**

Appropriate blood pressure escape levels have been established to ensure that participants are offered evaluation and therapy when clinically indicated. Participants may be immediately referred for evaluation if indicated.

**POLICIES:**

1. All clinic staff will be trained to evaluate Random Zero blood pressure measurements, which includes referral of participant to medical care clinician.

**PROCEDURE:**

**RESPONSIBILITY:**

**ACTION:**

- Staff
1. Outcome the result of the blood pressure reading at each visit advice the participant of their need to return to the clinic for a blood pressure measurement.
  2. Escape levels for each visit are incorporated into the visit blood pressure form.
    - 2a. Participants completing 3-, 6-, 12-, and 18- month visits with blood pressure at escape level one are required to return to the clinic within one week to have a blood pressure measurement completed.
    - 2b. Participants completing a 12- month visit with blood pressure at escape level two are required to

return to the clinic with one month for a repeat blood pressure measurement.

- 2c. Participants completing 6- and 18-month visits with blood pressure at escape level two are required to follow-up with their primary care provider (PCP).

3. Refer the participant to their PCP. Inform them how soon they should see their provider. Refer to form # 51 or form #52 for follow-up time frames.

*Data Coordinator*

4. Monitor KARE the week following the referral to verify when the participant makes an appointment with their PCP. When appointment is made record date on BP escape form in the date referral confirmed field.
5. Return participant chart to clinic coordinator for follow-up if no appointment found by one week following the referral.

*Clinic Coordinator*

6. For participants with escape level 2 at their 6-month visit send the participant their BP report (manage26) the next working day after there are referred. On the request of the participant, a letter with recent BP results will be sent to their PCP.
7. If the participant fails to schedule an appointment in the week following their referral call participant to encourage follow-up on BP escape and send letter from the study clinician.
8. Complete the blood pressure escape form recording the date the letter was sent as the "Date referral confirmed."

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