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TRIALS OF HYPERTENSION PREVENTION

PHASE II

PROTOCOL

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AIMS

A. SPECIFIC AIMS

THE PRIMARY AIMS OF TOHP FOR PHASE II ARE TO TEST WHETHER OVER 36 MONTHS:

1. Weight loss will decrease diastolic blood pressure (DBP).
2. Sodium reduction will decrease DBP.
3. The combination of weight loss and sodium restriction will decrease DBP.

ADDITIONAL AIMS OF TOHP ARE TO TEST WHETHER:

1. Weight loss or sodium reduction or the combination of the two will reduce the incidence of combined diastolic or systolic hypertension (sustained DBP $\geq$90 mmHg or sustained SBP $\geq$140 mmHg or the initiation of treatment with antihypertensive drugs by a physician).
2. Weight loss or sodium reduction or the combination of the two will reduce the incidence of diastolic hypertension (sustained DBP $\geq$90 mmHg or the initiation of treatment with antihypertensive drugs by a physician).
3. Weight loss or sodium reduction or the combination of the two will decrease systolic blood pressure and will reduce the incidence of systolic hypertension (sustained SBP $\geq$140 mmHg or the initiation of treatment with antihypertensive drugs by a physician and, using an alternative definition, sustained SBP $\geq$160 mmHg).

BACKGROUND AND RATIONALE

Sixty million Americans, or one in 3 adults (29.8%), are hypertensive based on a single exam (1). Drug treatment trials have documented the conclusive benefits of treating hypertension (HT) to reduce mortality from vascular disease, especially stroke, congestive heart failure, HT renal disease, and, less certainly, coronary heart disease (2-9). However, concern remains regarding the risk to benefit ratio of pharmacologic treatment of patients with mild HT, especially those with a diastolic blood pressure (DBP) between

90-94 mmHg (10-15). About half the hypertensive population, or 15% of the general adult population, have mild HT, and the majority of HT related premature deaths occur in this BP range (6). A recent overview of trials of drug therapy for mild to moderate hypertension in over 37,000 patients worldwide found a highly significant 42% reduction in stroke and a 14% decrease in coronary heart disease with drug therapy (8). These studies suggest that therapy to prevent hypertension may be even more beneficial. Thus nonpharmacologic interventions, aimed at effecting a slight reduction in BP within the high normal range or to <90 mmHg in those with mild HT, may represent the most powerful public health strategy.

In observational studies, the risk of coronary heart disease (CHD), stroke, and all cause mortality rises progressively with increasing levels of BP from a level of 75 mmHg DBP upwards. While the specific causes of HT and elevated blood pressure are not yet known, several different lifestyle and nutritional variables appear to be operative, perhaps interacting with genetic factors. The most important of these are weight gain, excessive sodium intake, and high alcohol consumption. Obesity is the most consistent determinant of an increased BP. It is estimated that 60% of hypertensives are $\geq$20% overweight (16), and that obesity accounts for 1/3 of the prevalence of hypertension in men and women aged 25-64 years and 2/3 of the prevalence of HT in men aged 25-44 years. Furthermore, obesity is associated with hyperinsulinemia, hyperglycemia, and hyperlipidemia (17). The mechanisms by which weight may affect BP are not clearly understood (18), but results of observational studies have shown that BP and weight are closely related in a linear fashion (16,19,20). Even modest weight gain is associated with an increase in blood pressure, and corresponding degrees of weight loss, with lower blood pressure (21-26). A longitudinal study by Wing, Kuller et al. (27) of premenopausal

women ages 42-49 followed for about 3.5 years showed that for each pound of weight gained, the blood pressure increased by about 0.19 mmHg in premenopausal and 0.26 mmHg in postmenopausal women. Similar relationships between BP, weight gain, and the risks of HT have been noted in a five year longitudinal study of male, non-hypertensive usual care participants in the MRFIT study (28), and participants in the Framingham Study (29).

A large body of observational data supports the presence of a positive association between sodium intake and BP (30). In the Intersalt study of 10,079 men and women aged 20-59 years (drawn from defined populations in 52 centers and 32 countries), urinary sodium excretion was significantly related to BP (31). Hypertension was virtually absent in populations with a very low sodium intake. Also of note was the authors' estimate that a 100 mmol/day reduction in sodium intake between the ages 25-55 would result in a reduction in the age-related rise of BP by 9 mmHg SBP and 4.5 mmHg DBP.

Several randomized trials of nutritional intervention have been conducted in patients with hypertension and in persons with high normal blood pressure. These studies have been of two general types. Short-term experiments, of variable quality, have tested the effectiveness of substantial increases or decreases in sodium intake and weight loss (16,30). Despite many methodologic weaknesses, the results of these trials suggest that weight loss and sodium restriction are the most plausible non-pharmacologic approaches to lowering BP. Of greater relevance to the present study are the five trials in HT patients and the four trials in individuals with high normal BP that have tested the effectiveness of non-pharmacologic treatments over a longer period of time.

The trials in HT patients have demonstrated that it is possible to lower BP and minimize or eliminate the need for antihypertensive drug therapy by reducing weight and sodium intake. In the Dietary Intervention Study in Hypertension (DISH) by Langford et al., a twelve month trial of weight loss and sodium restriction in previously well-controlled HT patients, weight loss and sodium reduction in overweight participants increased the likelihood of maintaining the normotensive state by 3.43 and 2.17 respectively (32). The corresponding crude relative reductions in HT recurrence were 37% and 14% respectively. The Hypertension Control Program (HCP) by Stamler et al. demonstrated the ability of a combined weight, sodium and alcohol reduction program to maintain the normotensive state over a longer period of follow-up (33). At the end of four years, 95% of the control group as opposed to only 61% of the treatment group had recurrent HT. The Hypertension Intervention Trial (HIT) by Lasser et al. demonstrated the ability of a combined intervention of weight loss, sodium restriction and stress reduction to decrease the need for antihypertensive drug therapy by 40% in a group of previously untreated patients with mild HT (34). The ongoing Trial of Antihypertensive Interventions and Management (TAIM), being conducted by Langford et al., has reported that a combination of weight loss and anti-hypertensive drug therapy is more effective (by 2-4 mmHg DBP at one year) than drug therapy alone in reducing BP in HT patients (35). In another ongoing study, the Treatment of Mild Hypertension Study (TOMHS), 18 month follow-up results indicate that a non-pharmacologic regimen of weight loss, exercise, and decreased sodium and alcohol intake was associated with an SBP/DBP reduction of 10/8 mmHg compared to baseline (36).

Of most relevance to our study are the four trials conducted to date in individuals with high normal BP. The Primary Prevention of Hypertension by

Nutritional-Hygienic Means (PPH) study, conducted by Stamler et al., was a five-year trial involving 201 men and women, ages 30-44, with a high normal (80-89 mmHg) DBP at baseline (37). The goal of the intervention was to reduce weight, sodium intake, and alcohol consumption and to increase physical activity. After four years of follow-up, net weight loss in the intervention group averaged 5.9 lbs, sodium intake was reduced by 25%, and mean DBP was 1.9 mmHg lower than in the control group (p=0.011). Only 8.8% of the active intervention group as compared to 19.2% in the control group became HT (p=0.027), a 54% reduction. Although extremely encouraging, these results must be tempered by the knowledge that the total number of HT "events" was quite small (n=28), and significance was determined by means of a one-tailed test. Furthermore, most events (75%) were diagnosed by non-study physicians, and the number of hypertensives diagnosed in this fashion was disproportionately large in control (84%) as compared to active therapy (50%) participants, suggesting the possibility of a diagnostic bias. Since this was a multifactorial trial, it was also not possible to analyze the separate contributions of the interventions.

In the three-year randomized controlled Hypertension Prevention Trial (HPT), the value of four non-pharmacologic therapies (calorie reduction, sodium restriction, calorie reduction and sodium restriction; and sodium restriction plus potassium supplementation) was tested in 841 men and women, aged 25-49 years, with a high normal BP (DBP 78-89 mmHg) (38). After three years, follow-up rates were >90%. For high weight participants, net weight loss in the calorie reduction groups was 7.7 lbs., and net reduction in 8 hour urinary sodium excretion was 5.0 mmol. The largest net decline in BP occurred in the calorie reduction groups (1.8 mmHg DBP,and 2.4 mmHg SBP). One of the strengths of this trial was its ability to assess the effect of weight loss

and sodium restriction interventions separately and in combination. A finding of note was the greater effectiveness of weight loss alone compared to the combination of weight loss and sodium restriction; however, this seemed to stem primarily from a failure to achieve comparable weight loss in the two groups at the outset. Furthermore, although each of the four intervention groups experienced fewer HT events, the total number of events was small (as few as seven events for one treatment outcome). The reduction in HT incidence approached statistical significance for the sodium restriction group, but only when a broad definition of hypertension (SBP $\geq$140, DBP $\geq$90, or the use of antihypertensive medications) was employed. Even then, the associated significance was marginal (p=0.066). Specifically, the 3-year HT incidence rates for those in the high weight stratum were 26.9% for sodium reduction, 28.2% for weight loss, 31.2% for combined weight loss and sodium reduction, and 38.7% for controls. The relative differences thus ranged from 20-30%.

The Hypertension Is Preventable (HIP) trial was a one-year, single center randomized controlled study in 407 individuals with a high normal DBP (39). It compared the BP effects of an increase in dietary potassium intake alone or in combination with a reduction in sodium intake to the corresponding BP effects of a control health education intervention. At 12 months, the DBP reduction was significantly greater in the combined sodium reduction and potassium supplementation group (2 mmHg) than in the potassium alone (0.4 mmHg) or control (0.9 mmHg) groups. As was the case in PPH and HPT, the sodium reduction, once achieved, was well-maintained.

The fourth and, we believe, the most important trial to date was Phase I of TOHP. Briefly, Phase I of TOHP compared the BP effects of three lifestyle change (weight loss, sodium reduction, and stress management) and four

nutritional supplement (calcium, magnesium, potassium, and fish oil) interventions to the corresponding levels of BP in no-treatment or placebo control groups. More than 2,000 individuals were recruited and randomized on schedule, and there was a high follow-up rate. Substantial intervention effects were achieved in both the weight loss and sodium restriction groups, resulting in significant reductions in BP in these groups after 6,12, and 18 months of follow-up.

In aggregate, these trials have shown that it is feasible to conduct a large-scale trial to control the rise of BP in persons with high normal BP and that at least some non-pharmacologic interventions offer a good opportunity for the primary prevention of HT. Weight loss has been the most consistent and effective means to achieve a reduction in BP. Weight loss of 10-15 pounds has been achieved in most studies. Although recidivism has been a common problem, a substantial weight difference between the intervention and control groups has been maintained because the gradual regain of weight in the intervention group has been counter-balanced by a progressive weight gain in the comparison group. In general, about two-thirds of the initial weight difference has been maintained during longer term follow-up. Most studies suggest that a 3-4 pound weight loss results in a 1 mmHg decrease in DBP. Thus, maintenance of a difference of only 6-8 pounds should result in about a 2 mmHg difference in DBP between the intervention and control groups. A BP effect of this magnitude could substantially reduce both the incidence and prevalence of HT and the associated risks of vascular disease and death. Results of a six-year follow-up among the 356,222 screenees who participated in the Multiple Risk Factor Intervention Trial (MRFIT) indicate that a 2 mmHg decrease in BP, even within the so-called normal range, would result in an annual reduction of 6% in stroke incidence, 3% in all-cause mortality, and 4% in CHD incidence (40).

Successful sodium interventions have been somewhat more difficult to achieve than weight loss. However, experience in PPH, HPT, HIP, and Phase I of TOHP suggests that reductions in sodium intake of about 40-50 mEq/day can be achieved and maintained over long periods of follow-up. A decrease of this magnitude has been associated with about a 1-2 mmHg decline in DBP.

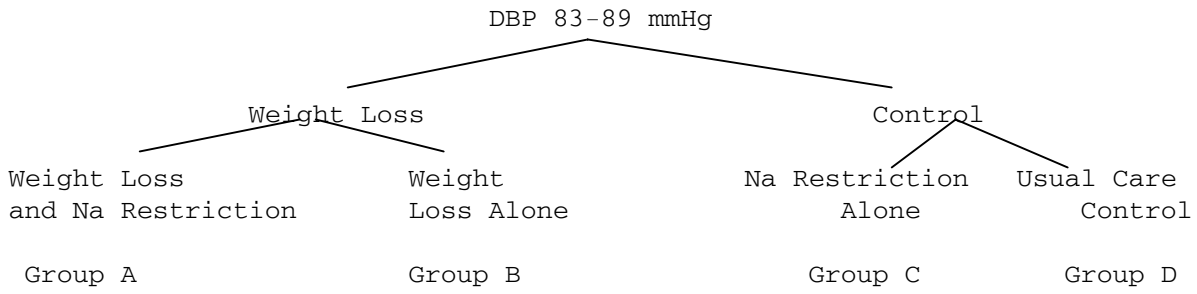
Phase II of TOHP will go beyond the aforementioned trials by providing convincing answers to the three most important clinical questions related to non-pharmacologic therapy in people with high normal BP: Can DBP and SBP be lowered and a substantial proportion of new cases of hypertension be prevented by weight loss or sodium restriction? If so, which of the interventions (combined weight loss and sodium restriction, weight loss alone, or sodium restriction alone) is effective? Whether the combination of weight loss and sodium restriction is more effective than intervention with either weight loss or sodium restriction alone is an important and unresolved question. Within the context of the available power, Phase II of TOHP will provide additional information regarding this issue. Finally, TOHP II will provide an opportunity to test whether the benefits of a non-pharmacologic intervention can be maintained over a prolonged period of follow-up. A positive result will provide valuable information on the need for a shift in public policy and clinical practice from our current virtually exclusive "high risk" hypertension detection and treatment approach to one in which primary prevention of hypertension and the high risk approach are both emphasized. The latter represents the only long-term solution to our epidemic of BP-related cardiovascular disease.

STUDY DESIGN

The study design for Phase II is based on the preliminary findings from Phase

I of TOHP and is the result of discussions among all the Principal Investigators, NHLBI representatives, and the Coordinating Center. The major concerns in the development of the design have been to meet the scientific aims of the study in the most effective and efficient manner possible.

The study design is a 2 x 2 factorial of weight loss and sodium restriction. Participants will be randomly assigned to one of four possible groups: weight loss alone (Wt), sodium restriction alone (Na), combined weight loss and sodium restriction (WtNa), or a usual care control group (usual care).



This design allows us to test the overall effect of weight loss and the overall effect of sodium restriction. The effect of the combined intervention can also be tested. In addition, we will examine the effect of the combined intervention as compared to weight loss, sodium restriction and the absence of weight loss and sodium restriction.

All nine clinics will randomize participants into all four arms and subjects will be distributed equally among the three treatment groups and the control

group (1/4 each). Randomization will be stratified by clinic to insure even distributions into the four treatment groups at each of the clinical centers.

SAMPLE SIZE AND POWER

A. The hypotheses to be tested in this factorial design are 1) the overall effect of weight loss (i.e., groups A and B vs. groups C and D); 2) the overall effect of sodium restriction (i.e., groups A and C vs. groups B and D); and 3) the effect of the combined intervention (i.e., group A vs. group D). The primary endpoint for testing these hypotheses will be change in mean diastolic blood pressure (DBP) both from baseline to termination BP and from baseline to the average of all DBP's from 6 months to 36 months. The assumptions for calculating the necessary sample size for these continuous endpoints are as follows:

1. Baseline blood pressure measurements will be taken at 3 visits with three measurements per visit. Follow-up BP measurements will be taken over 3 visits at 18 and 36 months, and 1 visit at 6, 12, 24 and 30 months, each with 3 measurements per visit. The termination BP is defined as the BP at 36 months or before starting BP medication, which will also be based on 3 visits with 3 measurements per visit. The blood pressure measure for an individual is thus an average of nine readings at baseline and at termination. The variance of the change from baseline (x_1) to termination (x_2) can be written as:

$$\sigma_1^2 = V(x_2 - x_1) = 2\sigma_p^2(1 - \rho_{0,36}) + 2(\sigma_A^2 + \sigma_e^2/k)/n$$

where σ_p^2 = between-person variance

σ_A^2 = between-visit variance

σ_e^2 = within-visit variance

n = number of visits = 3

k = number of measurements per visit = 3

$\rho_{i,j}$ = tracking correlation of the individual's true blood pressure mean from time i to time j, with 0 representing baseline

The variance of the change from baseline (x_1) to the unweighted average of the time-specific means at 6 months through 36 months (x_3) can be written as:

$$\sigma_2^2 = V(x_3 - x_1) = (\Sigma_i(\sigma_p^2 + \sigma_a^2/n_i + \sigma_e^2/k_i n_i) + 2\Sigma\Sigma_{i<j} \rho_{i,j}\sigma_p^2)/36$$

$$+ (\sigma_p^2 + \sigma_a^2/n_o + \sigma_e^2/k_o n_o) - \sigma_p^2 \Sigma_i \rho_{o,i}/3$$

where i and j represent the 6 measurement times from 6 months through 36 months

n_i = the number of visits at time i

k_i = the number of measurements per visit at time i (=3)

and all summations are over times 6 to 36 months.

The following parameter estimates are applied:

a) The variance components were based on race and gender specific estimates from a population of 991 individuals aged 30-69 years (41). These were combined by taking weighted averages using the age, sex and race distribution of the Phase I participants. This population was 30% female, 15% black, with 80% aged 30-49 and 20% aged 50-54. The average variance components are:

σ_p^2 = 100.4

σ_A^2 = 27.3

σ_e^2 = 7.6

b) Tracking correlations of 0.58 (42) for DBPs taken four years apart and 0.85 (43) for those taken one year apart have been published. For any time interval the relationship of the true correlation (ρ_t) to these observed correlations (ρ_o) is a function

of the number of visits (n) and measurements per visit (k) as follows:

$\rho_t = \rho_o \times (\sigma_p^2 + \sigma_A^2/n + \sigma_e^2/nk)/\sigma_p^2$

with the various components as defined previously. These data suggest true 4-year and 1-year correlations of 0.85 and 0.91.

Interpolating from these results, we estimate that the true tracking correlations over 6, 12, 18, 24, 30 and 36 months are 0.95, 0.91, 0.90, 0.89, 0.88, and 0.87, respectively.

Using the above parameters, the estimated variance of DBP change from baseline to termination is 6.78^2 within each treatment group. The estimated variance of DBP change from baseline to the average of all follow-up visits is 5.24^2.

2. The loss to follow-up at the termination visit is assumed to be 10%. The proportion missing at the 3-year termination visit reported in HPT is 8.6% over all treatment groups (38). In addition, subjects will be censored due to the development of hypertension. The incidence of hypertension (DBP $\geq$90 mmHg or taking antihypertensive medication) among high weight controls in HPT (38) is 30.2%. The Phase I data are consistent with this. Among high weight controls with initial DBP of 83-89 mmHg, the incidence is 12.5% after 12 months, or 33.0% extrapolating to 3 years. Using the incidence rate of 30.2% and the treatment effect estimates described below, we would expect an average incidence of hypertension of 23.4%. Combining this with the 10% loss to follow-up yields an average percent censored for blood pressure measurement at the termination visit of 31.1%. This is a conservative estimate since the incidence of hypertension reported in HPT may be

high because only one visit was used. Also, not all those with DBP readings above 90 mmHg will go on to take antihypertensive medication, and many subjects who do will have provided at least partial data, especially in the analysis using all follow-up data.

3. The power to detect a difference in mean DBP change of 1.5 mmHg between combined intervention and control groups should be 80%.

4. A Bonferoni adjustment is made based on the fact that 3 comparisons will be examined.

5. The sample size is calculated from the following formula:

$$N = 2\sigma^2 (z_\alpha + z_\beta)^2 / \Delta^2 (1 - P_c)$$

where N = number in each group

Δ = difference in DBP change between the 2 groups

σ^2 = $V(x_2-x_1)$ or $V(x_3 - x_1)$ as described above

P_c = average percent censored

Z_α = 2.394

Z_β = 0.84

Using the assumptions for change from baseline to termination a sample size of 621 per group or a total of 2484 is needed to achieve 80% power for all three hypotheses. With the proposed sample size of 2250 we thus do not achieve 80% power to detect a difference of 1.5 mmHg between the combined intervention and the placebo with this endpoint. We do, however, have more than adequate power to address the main hypotheses of weight loss and sodium restriction. The power for each hypothesis for various differences in DBP change from baseline to termination is shown in Table 1. As indicated, with 80% power, we can detect an effect of 1.2 mmHg for overall weight loss or sodium restriction or a difference of 1.6 mmHg between the combined intervention and placebo groups. The last column of Table 1 reflects

Table 1 Power (%) for a primary hypothesis with a total sample size of 2250 using DBP change from baseline to termination.

Difference in DBP change	Overall effect of weight loss or sodium restriction	Combined vs. control *
1.0	69.5	36.6
1.1	78.8	44.6
1.2	86.2	52.7
1.3	91.6	60.8
1.4	95.3	68.4
1.5	97.5	75.3
1.6	98.8	81.3
1.7	99.4	86.3
1.8	99.8	90.3
1.9	99.9	93.4
2.0	100.0	95.6

* The power for the combined versus weight loss and for the combined versus Na restriction is the same as that for combined versus control.

the power to test differences between any two groups, including the combined vs. sodium restriction groups and the combined vs. weight loss groups. We thus have 80% power to detect a difference of 1.6 mmHg in the latter two comparisons, which may not be adequate.

The power using DBP change from baseline to the average of all follow-up blood pressures is given in Table 2. The power is greatly increased by using the additional data. We have over 90% power to detect an effect of 1.0 mmHg for overall weight loss or sodium restriction, and almost 80% power to detect a difference of 1.2 mmHg between the combined intervention and placebo group, or either single intervention group.

B. A secondary endpoint to be considered is the change in systolic blood pressure (SBP) over the course of the trial. Similarly to DBP, the outcomes will be defined as the change from baseline to termination SBP at 36 months or before starting BP medication, and the change from baseline to the average of all SBP's from 6 months to 36 months. The assumptions used for SBP are identical to those for DBP outlined above, with the following parameter estimates:

1. The expected variance components for SBP are:

   σ^2_p = 229.1

   σ^2_A = 43.4

   σ^2_e = 14.1

2. Observed tracking correlations for SBP of 0.67 over four years (42) and 0.81 over one year (43) have been reported. These suggest true correlations of 0.83 and 0.85 over four and one year(s), respectively. Interpolating from these results, we estimate that the true tracking correlations over 6, 12, 18, 24, 30 and 36 months are 0.92, 0.85,

Table 2 Power (%) for a total sample size of 2250 using DBP change from baseline to the average of all blood pressures from 6 to 36 months.

Difference in DBP change	Overall effect of weight loss or sodium restriction	Combined vs. control *
1.0	91.4	60.4
1.1	95.9	70.1
1.2	98.3	78.6
1.3	99.4	85.5
1.4	99.8	90.7
1.5	99.9	94.4
1.6	100.0	96.8
1.7	100.0	98.3
1.8	100.0	99.2
1.9	100.0	99.6
2.0	100.0	99.8

* The power for the combined versus weight loss and for the combined versus Na restriction is the same as that for combined versus control.

0.85, 0.84, 0.84 and 0.84, respectively.

Using the above parameters, the estimated variance of SBP change from baseline to termination is 10.27^2 within each treatment group, and the estimated variance of SBP change from baseline to the average of all follow-up visits is 7.96^2. The same assumptions about censored data are used, as is the Bonferoni adjustment.

The power using SBP change from baseline to termination is given in Table 3. As shown, with 80% power we can detect an effect of 1.7 mmHg for overall weight loss or sodium restriction, and a difference of 2.4 mmHg between any two of the intervention groups. The power is increased using the average of all follow-up blood pressures (Table 4). With 80% power, we can detect an effect almost as low as 1.3 mmHg for overall weight loss or sodium restriction and a difference of 1.9 mmHg between any two intervention groups.

C. In addition to examining the decrease in systolic blood pressure, secondary endpoints for the trial include the development of hypertension. The original intent of TOHP investigators was to use the endpoint of diastolic blood pressure $\geq$90 mmHg or taking antihypertensive medication as the primary categorical endpoint and, in addition, to consider systolic blood pressure $\geq$160 mmHg or taking antihypertensive medication as an additional categorical endpoint. However, at the March 20, 1991 Steering Committee meeting, prior to review or analyses of any prospective blood pressure data, it was decided that a combined endpoint of diastolic blood pressure $\geq$90 mmHg and/or systolic blood pressure $\geq$140 mmHg or taking antihypertensive medication would be the primary categorical endpoint. It was also decided that, as originally planned, we would look secondarily at

Table 3 Power for systolic blood pressure with a total sample size of 2250 using SBP change from baseline to termination.

Difference in SBP change	Overall effect of weight loss or sodium restriction	Combined vs. control *
1.0	31.7	15.0
1.1	38.8	18.3
1.2	46.3	22.1
1.3	53.9	26.4
1.4	61.4	31.0
1.5	68.5	35.9
1.6	75.0	41.1
1.7	80.6	46.4
1.8	85.5	51.8
1.9	89.4	57.2
2.0	92.5	62.4
2.1	94.9	67.4
2.2	96.6	72.2
2.3	97.8	76.5
2.4	98.6	80.5
2.5	99.2	84.0

* The power for the combined vs. weight loss and for the combined vs. Na restriction groups is the same as that for combined vs. control.

Table 4 Power for systolic blood pressure with a total sample size of 2250 using SBP change from baseline to the average of all blood pressure from 6 to 36 months.

Difference in SBP change	Overall effect of weight loss or sodium restriction	Combined vs. control *
1.0	53.2	25.9
1.1	62.8	31.9
1.2	71.7	38.4
1.3	79.4	45.2
1.4	85.7	52.2
1.5	90.6	59.1
1.6	94.1	65.7
1.7	96.5	71.9
1.8	98.0	77.5
1.9	98.9	82.3
2.0	99.5	86.5
2.1	99.7	89.9
2.2	99.9	92.7
2.3	100.0	94.8
2.4	100.0	96.4
2.5	100.0	97.6

* The power for the combined versus weight loss and for the combined versus Na restriction groups is the same as that for combined versus control.

the endpoint of diastolic blood pressure $\geq$90 mmHg or taking antihypertensive medication. This decision was ratified by the Data and Safety Monitoring Committee on March 28, 1991.

Furthermore, at its meeting of September 16, 1992, the Data and Safety Monitoring Committee recommended that safety monitoring be performed for systolic blood pressure of 140-159 mmHg just as for diastolic blood pressure $\geq$90 mmHg or systolic blood pressure $\geq$160 mmHg. This followed the availability of a draft of the JNCV report which labeled systolic blood pressure of 140-159 mmHg as Stage I hypertension. The recommendation was approved by the Steering Committee on September 29, 1992.

Sample size calculations for having diastolic blood pressure $\geq$90 mmHg or taking antihypertensive medication are presented first and are based on the following assumptions:

1. Power is computed using two estimates of the event rate (DBP $\geq$90 or on hypertensive medication) over an average 3.5 years of follow-up:
    a. The rate reported among the high weight controls in HPT (38) for the same endpoint is 30.2% over 3 years of follow-up. This was calculated as a proportion of all participants, and thus takes loss to follow-up into account. The data from Phase I of TOHP are consistent with this estimate. Among high weight controls with initial DBP's of 83-89 mmHg the incidence of hypertension by this definition is 12.5% in one year, or 33.0% extrapolating to 3 years. Extrapolating the HPT rate to 3.5 years yields an estimated event rate of 34.5% in the control group for this study.
    b. The HPT data are based on a single visit, and may thus

overestimate the incidence of hypertension. An event rate of 29.7% was derived from the estimates of the one year event rate in TOHP Phase I and simulations using the gamma distribution with parameters based on NHANES II data (44) and the event rates in HPT (38). This assumes blood pressure measurements over 3 visits to determine the development of hypertension, as in the current study. A 10% loss to follow-up is assumed, reducing the event rate to 26.7% in the control group.

2. The expected reductions in the event rate are 30% for weight loss, 20% for sodium restriction, and 40% for weight loss plus sodium restriction. These expected reductions were based on the results of Phase I and other trials of primary prevention (HPT, PPH, and HIP). This assumes subadditivity of effects. Under the additive model the risk reduction in the combined intervention group would be 44%.

3. The sample size is estimated to be 2250 subjects as outlined above. The number in each comparison group will be 1125 for the overall weight loss and sodium restriction hypotheses and 562 for the combined intervention versus control hypothesis.

4. A Bonferoni adjustment for three comparisons is made.

5. The power is calculated for the logrank test using the following formula (45):

$$\text{Power} = \Phi\left[\sqrt{d}\left|\frac{1-\theta}{1+\theta}\right| - z_{\alpha}\right]$$

where $d = N(2 - p_o - p_1)$

$\theta = \ln p_o / \ln p_1$

and

N = number in each group

p_o = probability of remaining normotensive in the comparison group

p_1 = probability of remaining normotensive in the active

group

$z_\alpha = 2.394$

Estimates of power are given in Table 5. The relative risks listed in the table represent the average risk reductions for the main effects of the single interventions when using all four groups. Using these assumptions the power to determine the effectiveness of weight loss alone is at least 93.6% for this endpoint while that for sodium restriction is no more than 65.4%. The power is over 97% to detect the hypothesized difference between the combined intervention and control groups in development of hypertension. This study, however, has little power to detect differences between the combined intervention and either single intervention group with these expected reductions. The power to detect a difference between the combined and sodium restriction group is at most 62%, while that for the combined vs. weight loss group is 16%.

The revised primary categorical endpoint is the development of systolic or diastolic hypertension, defined as DBP $\geq$90 mmHg, or SBP $\geq$140 mmHg or taking antihypertensive medication. The HPT saw an incidence rate of 38.7% for this endpoint among high weight controls over 3 years. Extrapolating to 3.5 years leads to a rate of 43.5%. All other assumptions remain the same. The increase in monitoring for systolic blood pressure of 140-159 mmHg is likely to increase the incidence of this endpoint. Simulations were performed using a random effects model and the parameters given in sections A and B above and with the additional assumptions of population means of 128.4 mmHg for SBP and 82.0 mmHg for DBP, and a correlation of SBP and DBP of 0.80. An effect of adjustment to the study situation was also assumed (a lowering of mean BP in addition to the expected regression to the mean). These simulations suggest that the incidence of the combined endpoint may

Table 5 Power (%) for hypotheses for diastolic hypertension with a total sample size of 2250.

Comparison	Average Risk Reduction	Power (%) Event Rate from HPT	Power (%) Event Rate from Simulations
Weight Loss	28%	98.6	93.6
Na Reduction	18%	65.4	48.0
Combined vs. Placebo	40%	99.7	97.5
Combined vs. Weight Loss	14%	16.2	11.3
Combined vs. Na Reduction	25%	62.1	46.1

increase to 47.2%, given increased monitoring at the 24- and 30-month visits. The power for this endpoint using both event rates is given in Table 6. With the additional monitoring, the power for the weight loss hypothesis and the combined intervention vs. control remain high, the power for the sodium hypothesis increases to 87% and the power for the combined versus sodium restriction group increases to 84%. The power for the combined intervention versus weight loss alone, however, remains poor, increasing only to 25%.

ELIGIBILITY AND EXCLUSION CRITERIA

As in Phase I, it is planned to recruit a group of healthy, high-weight, non-hypertensive individuals who can safely undertake the proposed interventions and who are likely to be cooperative with follow-up requirements for the duration of the trial.

ELIGIBILITY:

1. Diastolic Blood Pressure

The main eligibility criterion will be a diastolic blood pressure (DBP) of 83-89 mmHg as determined by an average of nine blood pressures taken over three screening visits. The acceptable ranges for each visit are as follows:

Screening Visit #1: DBP 81-97 mmHg (mean of 3 readings)

Screening Visit #2: DBP 82-92 mmHg (6 readings)

Screening Visit #3: DBP 83-89 mmHg (9 readings)

These ranges are based on the observed screening data from Phase I. Persons falling outside the above ranges had at least an 80% chance of falling outside the 83 to 89 range based on 9 readings in the Phase I data.

Table 6 Power for primary categorical endpoint using systolic or diastolic hypertension (DBP ≥ 90 or SBP ≥ 140 or on anti-hypertensive medications) with a total sample size of 2250

		Power %	
Comparison	Average Risk Reduction	Event Rate from HPT (%)	Rate with Increased Monitoring
Wt loss	28%	99.9	100.0
Na restriction	18%	82.5	87.0
Comb. vs. Usual care	40%	100.0	100.0
Comb. vs. Wt loss	14%	22.6	24.9
Comb. vs. Na rest	25%	78.2	84.1

Procedures for prescreening in the community are left to the discretion of the clinics, as was the case in Phase I. However, it is expected that clinics will use community prescreenings since these were very effective in Phase I. It is recommended that individuals whose prescreening DBP is outside the range of 80-102 mmHg be eliminated from further screening.

The rationale for narrowing the DBP range from 80-89 mmHg to 83-89 mmHg is based on actual TOHP experience. Preliminary data from Phase I indicate that at 12 months, 1.4% of the lifestyle control subjects with baseline DBP levels from 80 to 82 had a rise in DBP to above 90 mmHg or were put on anti-hypertensive medications. For those whose baseline DBP levels were 83-89 mmHg, the corresponding event rate was 10.5%. However, that group makes up only about 55% of the Phase I population, so, although this restriction will increase the power of the study, it will also increase the recruitment challenge.

2. Systolic Blood Pressure

It is recognized that systolic blood pressure (SBP) is at least as important as a predictor of cardiovascular disease as DBP, if not more so. SBP is to be measured with the same diligence as DBP. The main eligibility criterion will be a SBP of <140 mmHg as determined by an average of nine blood pressures taken over three screening visits.

3. Age

Participants must be between 30 and 54 years of age at the time of first screen.

4. Body Weight

Men who have a body mass index (BMI) $\geq$26.1 kg/m^2 (0.037 lbs/in^2) and $\leq$37.33 kg/m^2 (0.0531 lbs/in^2) and women with a BMI $\geq$24.4 kg/m^2 (0.035 lbs/in^2) and $\leq$37.33 kg/m^2 (0.0531 lbs/in^2) are eligible. These criteria correspond

approximately to a range of 110-165% of ideal body weight, based on the 1983 Metropolitan Life tables.

5. Gender

Both men and women will be eligible to enroll in TOHP.

6. Race

As in Phase I, recruitment of minorities will be a high priority.

EXCLUSION:

In general, the exclusion criteria for TOHP have been designed to eliminate individuals who are already hypertensive or who have low normal BPs, those who have evidence of other existing cardiovascular disease, those for whom any of the interventions may be harmful, and those who may be unable to comply with the treatment and follow-up requirements of the trial. The specific exclusion criteria are listed below.

1. Evidence of current hypertension, defined as 9 baseline DBP readings averaging 90 mmHg or greater, 9 baseline SBP readings averaging 140 mmHg or greater, or current use (within the past two months) of antihypertensive medication.
2. History of any cardiovascular disease, including myocardial infarction, angina, intermittent claudication, congestive heart failure, and stroke.
3. History of diabetes mellitus, as defined by self-report or use at any time of insulin or oral hypoglycemic agents.
4. History of malignancy (other than non-melanoma skin cancer) during the past five years.
5. Any other serious life-threatening illness that requires regular medical treatment.
6. Current use (within the past two months) of medications that affect blood pressure, including diuretics and beta-blockers.

7. Serum creatinine level $\geq$1.7 mg/dl for men or 1.5 mg/dl for women, as determined locally.
8. Casual serum glucose $\geq$200 mg/dl as determined locally.
9. Current alcohol intake of more than 21 drinks per week.
10. Unwillingness to discontinue a dietary regimen incompatible with TOHP interventions, such as a medically supervised diet or a formal weight loss program.
11. For women, current pregnancy or intent to become pregnant during the study period. Participants are requested to inform the study immediately if they become pregnant during the course of the trial.
12. Current participation in any other ongoing research project.
13. Participation of another household member in TOHP; TOHP employees; persons living with TOHP employees.
14. Residence or planned residence distant from the clinical center (generally defined as more than 50 miles from the clinic), such that it would be difficult to come to the study site.
15. Unwillingness to accept randomization into any study group.
16. Inability to cooperate, as assessed by clinic staff.
17. Inability or unwillingness to give informed consent.
18. Individuals who participated in the weight loss or sodium reduction arms of Phase I of TOHP. (All other Phase I participants are eligible.)

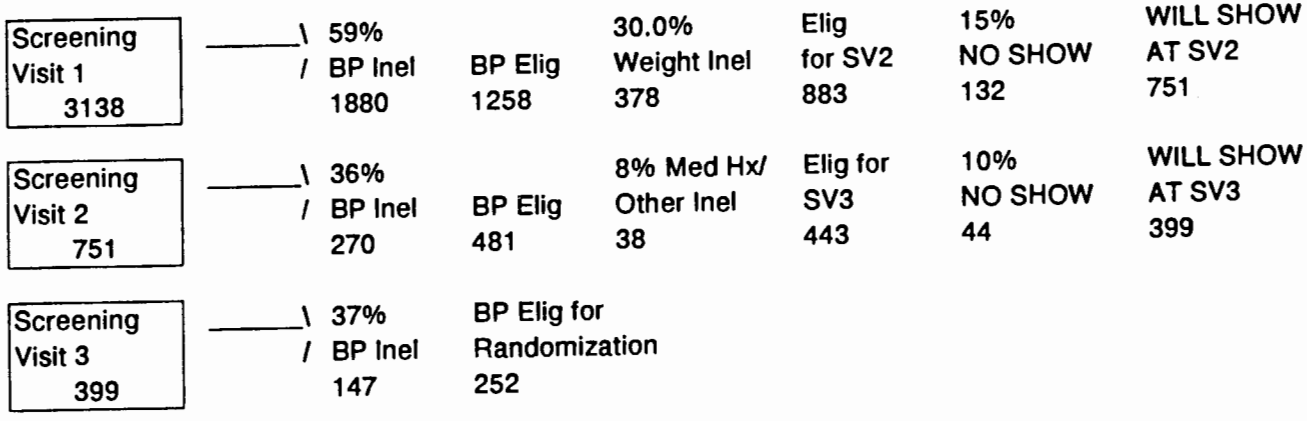
Projected screening yields for Phase II based on Phase I data are shown in Table 7. This table suggests that 3138 individuals will have to be screened at each clinic to yield about 252 persons eligible for randomization (8.0%).

SCREENING AND ENROLLMENT

Specific recruitment procedures will be left to the discretion of study

Table 7

Projected Screening Yields for Phase II
Based on Phase I Data



personnel at each clinic, although all centers will share plans to ensure optimum efficiency and NHLBI will use its channels to disseminate information on the trial nationally. Each clinic will be expected to recruit an equal number of the trial participants. Recruitment will begin on November 1, 1990 and randomization ends on March 31, 1992 (Table 8). It is assumed that 60% of subjects will be randomized during the first year and 40% during the second. TOHP investigators have committed themselves to achieve the overall objective of a total of 2250 randomized participants. Administratively, procedures have been put in place to review continuously the recruitment achieved at each center. The TOHP investigators have authorized the study leadership to recommend to the NHLBI reallocation of available funds to compensate for extra expenditure by those centers which recruit more than their required quota (i.e., 250) and vice-versa.

Data for the three screening visits will be collected uniformly across all clinics. In an attempt to increase the efficiency of data collection, the majority of data collection will take place at the third screening visit. The prescreen procedures for BP measurement have been described previously under eligibility criteria. Details of participation will be thoroughly explained to each participant as part of the informed consent process. At the first screening visit, height and weight will also be measured and BMI will be determined for eligibility assessment. At the second screening visit, all participants will be given a written document (informational page) describing what is known about weight loss and sodium restriction in the treatment and prevention of hypertension and explaining the various groups to which they may be randomized. Laboratory blood samples will be obtained and a medical history taken. As an adjunct to the medical history, each candidate will be asked to complete a Rose Questionnaire as a screen for angina pectoris. A

Table 8

TIMETABLE
FOLLOW-UP

		*** Screen Rand	6-mo.	12-mo.	*** 18-mo.	24-mo.	30-mo.	*** 36-mo.	42-mo.	48-mo.
1990	N	1								
	D	2								
1991	J	3								
	F	4								
	M	5								
	A	6								
	M	7	1							
	J	8	2							
	J	9	3							
	A	10	4							
	S	11	5							
	O	12	6							
	N	13	7	1						
	D	14	8	2						
1992	J	15	9	3						
	F	16	10	4						
	M	17	11	5						
	A		12	6						
	M		13	7	1					
	J		14	8	2					
	J		15	9	3					
	A		16	10	4					
	S		17	11	5					
	O			12	6					
	N			13	7	1				
	D			14	8	2				
1993	J			15	9	3				
	F			16	10	4				
	M			17	11	5				
	A				12	6				
	M				13	7	1			
	J				14	8	2			
	J				15	9	3			
	A				16	10	4			
	S				17	11	5			
	O				///	12	6			
	N					13	7	1		
	D					14	8	2		
1994	J					15	9	3		
	F					16	10	4		
	M					17	11	5		
	A						12	6		
	M						13	7	1	
	J						14	8	2	
	J						15	9	3	
	A						16	10	4	
	S						17	11	5	
	O							12	6	
	N							13	7	1
	D							14	8	2
1995	J							15	9	3
	F							16	10	4
	M							17	11	5
	A							///	12	6
	M									
	J									
		Screen & Rand	6 mo.	12 mo.	18 mo. ***	24 mo.	30 mo.	36 mo. ***	42 mo. (70%)	48 mo. (33%)

KEY

*** = 3 Visits

/// = Last groups return for 2nd/3rd Visit

candidate with a positive Questionnaire may be excluded or referred to a clinic physician for further review. If the determination is that the symptoms are not cardiac related, the candidate may continue with screening. However, if the physician concludes that the chest pain is possibly or equivocally cardiac related, the candidate will not be allowed to continue in the study unless clearance is provided by his/her physician or a stress test is conducted at the clinic to provide clearance. A 24-hour urine sample will be requested for the final screening visit to be used as a baseline measurement. The ability of a participant to provide an adequate sample will be used as a compliance measure. However, because of the difficulty of characterizing urinary sodium excretion in an individual, baseline urinary sodium excretion will not be used as an exclusion criterion. In addition, participants will be asked to complete a 3-day food record as a compliance measure. At the third screening visit, eligibility will be determined after obtaining a final set of blood pressure readings. Eligible participants will be randomized into the trial and will then be asked to complete forms to provide baseline measures on body circumference, physical activity, and nutrient intake. The information to be collected is discussed in detail in the Follow-Up section.

RANDOMIZATION

After eligibility has been ascertained, clinic personnel will telephone the Coordinating Center (CC) to obtain a randomization assignment. To give the clinics the greatest degree of flexibility in scheduling appointments, each will be equipped with a back-up randomization system to be used if it is not possible to make telephone contact with the CC during the visit. This will consist of a series of sealed envelopes in numerical order, each containing an intervention assignment.

Once the assignment has been made, the participant will be considered to be officially randomized, and every effort will be made to obtain complete follow-up information for the duration of the trial. Active intervention will begin at the discretion of the clinic; however, the minimal goal is to have all active treatment participants attend their first intervention group meeting within 60 days of randomization.

FOLLOW-UP

Data collection and safety monitoring visits will be held every 6 months throughout the trial. A major data collection visit (9 BP measurements over 3 visits) is scheduled to take place 18 months following randomization. This interim data collection is designed to increase sensitivity of detection of events and to protect against the effects of excessive censoring on the evaluation of the continuous endpoints. Final data collection for the continuous endpoint will be collected from all participants after 36 months of follow-up (9 BP measurements over 3 visits). Trial-wide data to be collected are described below, and the data collection schedule is presented in Table 9.

1. Random Zero Blood Pressure Measurements: Three blood pressure measurements will be taken at each visit. Baseline, 18-month, and 36-month blood pressure values will be based on nine readings taken over the course of three visits, held at weekly intervals.
2. Height and Weight Measurements: Height and weight will be measured at the first screening visit for eligibility determination. Thereafter, weight only will be measured at each visit. Waist to hip ratio will be assessed at baseline, 18 months, and 36-months.
3. Medical History and Medication Use: Medical history data (including information on smoking, drug and alcohol use, etc.) will be used to

TABLE 9

TOHP PHASE II DATA COLLECTION SCHEDULE

Data	Screening & Randomization			Months of Follow-Up																							
				6			12			18			24			30			36			42			48		
	SV1	SV2	SV3	F11	F12	F13	F21	F22	F23	F31	F32	F33	F41	F42	F43	F51	F52	F53	F61	F62	F63	F71	F72	F73	F81	F82	F83
BPA + Weight	A	A	A	A	S	S	A	S	S	A	A	A	A	S	S	A	S	S	A	A	A	B	S	S	C	S	S
Elig + Rand Form			A																								
Med Hx & Demo		A																									
Medical Hx				A	S	S	A	S	S	A	A	A	A	S	S	A	S	S	A	A	A	B	S	S	C	S	S
Medication Use		A		A	S	S	A	S	S	A	A	A	A	S	S	A	S	S	A	A	A	B	S	S	C	S	S
Physical Act.			A								A									A						
Lab.		A1	A2	A3							A2									A2							
24-Hour Recall/3 Day			sam	sam+							sam									sam							
Waist-hip			A							A									A							
Intervention Attendance*																											
Follow-Up Status Updates**																											
																			100% of study population			70% of study population			30% of study population		

A = All cases
S = Safety monitoring only
B = All except those terminating study at 36 mos.
C = All except those terminated at 36 or 42 mos.

A1 = All cases – serum/local lab: glucose, creatinine, cholesterol
A2 = All cases – 24 hour urine/central lab: sodium, potassium, creatinine
A3 = Sample of 25% to collect 24-hour urine/central lab: sodium, potassium, creatinine

sam = sample of 900 to complete 24 Hour Recall and sample of 160 to complete 3 Day Food Records
sam+ = sample of 160 to complete 3 Day Food Records only
* = Form submitted every 2 months after randomization whether or not sessions attended
** = prn, to document participant needing special attention or follow-up for data collection

determine eligibility during screening and, thereafter, to assess the possible confounding effects of changes in medication use. All changes in medication status of participants will be recorded as they occur throughout the trial.

4. Physical Activity Questionnaire: Physical activity may also influence BP or response to intervention, and this variable will also be assessed. The Physical Activity Questionnaire contains information on both work and leisure physical activity. These data will be collected at baseline, 18-months, and 36-months.

5. Demographic Information and Participant Contact Information: The demographic data will be used in the analyses to assess comparability of the randomized groups and for various subgroup analyses. The participant contact information will be used exclusively by the clinics and will be updated at mid-trial. The Coordinating Center will receive only coded data which will not allow individual identification.

6. Dietary Data: Dietary assessment will: 1) provide information on how any observed changes were made by analyzing caloric and sodium intake by food groups, 2) quantify the caloric and sodium intake in the control and intervention groups, 3) provide data to test and correct for dietary confounders and 4) provide data to compare nutritional changes in active treatment and control groups and to adjust BP changes for dietary confounders; such as, magnesium, calcium and alcohol, if necessary. A random sample of 900 participants (equally distributed across the four treatment groups) will complete a 24-hour diet recall at baseline, 18 months, and 36-months. The 24-hour dietary recall technique was chosen as the most appropriate general assessment instrument to obtain unbiased, actual intake in order to

determine group data on the various nutrients of interest. This sample will provide 80% power to detect a 20 mmol (approximately 15%) difference at termination in the group mean of dietary sodium intake between the control and intervention groups. A smaller random sample of 160 subjects (equally distributed across the four groups) will complete three-day food records (3DFR) at baseline, 6 and 18 months, and 36-months. The 3DFR will provide data on intra-individual variation of the nutrients of interest and a measurement of individual intake. Using the 3DFR we can determine the variance ratio for caloric intake and sodium intake that can be used to correct for misclassification by the recall. This sample will provide a standard deviation of the correlation coefficient of the food record and 24 hour recall at a value less than or equal to 0.1.

7. Blood and Urine Samples: Blood samples collected during screening will be tested at a local laboratory for serum creatinine, glucose, and cholesterol content. The serum creatinine and glucose levels will be used for eligibility determination. The cholesterol analysis will be used to enhance recruitment. When subjects are informed of their cholesterol levels, they will be provided with recommendations for follow-up based on current National Cholesterol Education Program guidelines. There will be no systematic exclusion on the basis of cholesterol level.

A single 24-hour urine sample will be collected at the final screening visit for baseline characteristics. 24-hour urine samples collected at 18 and 36 months will be used to assess compliance with the assigned interventions and to provide descriptive indices of mean intakes of sodium. Completeness of the 24-hour urine collections will

be evaluated by 24-hour creatinine output, volume, and collection times.

INTERVENTION METHODS

Overview: Participants are assigned randomly to one of four conditions: weight loss (Wt), sodium reduction (Na), combined weight loss-sodium reduction intervention (WtNa), or a usual care control. Table 10 summarizes the major features of the three intervention programs. The Phase II interventions are based on the successful weight loss and sodium interventions developed during the first phase of TOHP, and further refined as a result of the Phase II Pilot of the WtNa intervention program. To permit the most powerful comparison between the three interventions, the combined WtNa intervention will share the objectives and, as much as possible, the structure of the Wt and the Na interventions.

The three lifestyle intervention groups will have similar intervention schedules: all will start with an individual visit. The Wt and WtNa will have 14 weekly sessions followed by 6 biweekly sessions and the Na group will have 10 weekly followed by 4 monthly sessions with a telephone contact between. After this phase, participants in Wt and WtNa will have biweekly contacts until the end of the trial, with the Na having at least monthly contacts. Until the first cohort has completed initial intervention, the Wt and WtNa contacts will involve at least monthly face-to-face meetings, with other contacts taking place by participant initiated mail or telephone contacts. After this, there will be seasonal mini-modules offered 6 times a year, consisting of a minimum of four sessions for Wt and WtNa and three sessions for Na. Participants are expected to attend at least three of these modules annually. Maintained contact and participation will be facilitated

TABLE 10

SUMMARY: INTERVENTION PROGRAM FEATURES FOR TOHP PHASE II

	WEIGHT (Wt) (a)	SODIUM (Na) (b)	WtNa (c)
GROUP GOAL	≥ 10 lb weight loss 6 months post randomization and maintained throughout	24 hour urinary Na+ excretion ≤ 80 mEq (1800 mg) by 6 months post-randomization and maintained throughout	(a) + (b)
PARTICIPANT OBJECTIVE	Weight loss ≥ 10 lb or achievement of ideal weight; evidence of caloric restriction and increased physical activity in self-reports	Decrease in dietary Na+ intake to 1600 mg by six month estimated from dietary self-reports and urinary excretion data	(a) + (b)
CONTENT	-Information about weight control -Directed group process -Behavioral counseling -Food experience -Social support for adherence -Experiences in moderate physical activity	-Information about Na+ -and all other items on (a)	(a) + (b)
CONTACT SCHEDULE	Intensive: 1 individual, 14 weekly sessions, 6 biweekly sessions Extended: biweekly contacts with monthly face-to-face meetings until the intensive intervention is completed for the first cohort then mini-modules to be offered with continued bi-weekly contact Specially tailored follow-up where indicated	Intensive: 1 individual, 10 weekly sessions, 4 monthly sessions *Extended: monthly contacts with bi-monthly meetings until intensive intervention completed for the first cohort then mini-modules offered with a min. of quarterly overnight urine collections with a face-to-face contact. Specially tailored follow-up where indicated.	Same as (a)
CONTACT MODE	Primarily group; individual contacts at post-randomization, and as needed thereafter	Same	Same
ADHERENCE FEEDBACK	-Attendance records -Weigh-ins -Food records -Physical activity records	-Attendance records -Food records -Overnight urine Na+ or other urine monitoring methods	(a) + (b)
SAFETY ISSUES	-Diet quality -Physical activity-related injuries -Weight cycling	excessive sodium restriction	(a) + (b)

throughout the extended intervention through a return mailer and tracking system. If participants fail to report or report a problem such as weight gain or cessation of exercise, that participant will be reviewed in case conference with individual strategies to enhance intervention results developed. The mini modules will offer a variety of topics to keep participants interested and will also focus on problem solving with regard to adherence. Progress will be monitored throughout. Delivery of interventions will be facilitated by the Intervention Planning Committee under the direction of the Chairperson of the Intervention Committee in consultation with the intervention consultant.

Protocol Development: A detailed intervention manual was developed for use during the TOHP Phase II pilot study. Based on the experience gained from conducting the pilot, complete manuals and protocols have been developed and distributed for use by the local clinical centers to guide the conduct of the specific intervention programs.

Intervention Goals and Objectives: The weight reduction and sodium reduction goals will be the same as in Phase I: i.e., a group mean weight loss of 10 pounds for Wt and WtNa; and, for Na and WtNa, urinary sodium excretion of 80 mEq ($\pm$15%) per 24 hours. Staff will attempt to achieve these goals with each participant by the end of 6 months of intervention and will continue to work towards achieving or maintaining these goals with all participants throughout follow-up. In working with individual participants, staff assist participants in setting long-term behavioral goals based on a 10 pound weight loss or the participants' personal goal, whichever is greater, and sodium intake not to exceed 1600 mg daily as indicated by self report and urinary sodium excretion data.

Contact Pattern: As in Phase I, intervention contacts will be separate from follow-up data collection visits. Phase I results suggest that the intensive and transitional intervention counseling will enable the majority of participants to make acceptable progress by 6 months. To maintain progress in these participants, and to enhance performance of those whose motivation is lagging or whose behavior change falls short of study goals, mini modules will be used in conjunction with individual counseling, as determined by case conference decision. The longer period of initial intervention and the formal transition phase will also enable participants to accept the necessary behavior changes to maintain the study intervention goals. The contact frequency thereafter is designed to maintain changes.

Counseling Approach: TOHP Phase I weight and sodium interventions were based on a synthesis of the most current dietary behavior change strategies that have been used effectively in other nutrition intervention trials. Briefly, behavior change is approached from the perspective of (a) targeting specific behaviors to be changed to achieve a new overall pattern, (b) analyzing problems posed by attempts to change these behaviors, (c) building the individual's self-confidence in his or her ability to change long-time habits and meet situational challenges, (d) developing an incremental sequence of behavior changes to gradually shape a new behavior pattern, and (e) teaching skills and strategies to equip the individual to maintain newly established behaviors (46).

Group meetings are the primary mode of contact because groups are efficient from a staffing point of view and also provide social support and facilitate certain aspects of behavioral counseling. Involving spouses and significant

others in intervention meetings while providing samples of low calorie or low sodium food items also facilitates social support.

For the combined intervention, the approach to introducing and integrating sodium topics is based on a review of protocols from other studies in which weight and sodium interventions have been combined successfully (e.g., HIT and TOMHS), as well as the experience of the TOHP Phase II Pilot. Both sodium and calorie content of foods will be addressed simultaneously. Counseling related to food content will be approached from an eating-occasion orientation (i.e., food choices at breakfast, lunch, dinner, social occasions, etc.). Adoption of a regular moderate physical activity program will be emphasized as critical to both weight loss and long term weight maintenance, with exercise opportunities provided in the group meeting.

The purpose of the bi-weekly transition phase of intervention will be to provide a bridge between intensive intervention and the extended intervention phases and to reduce recidivism over the 3 to 4 year follow-up period. The curriculum of these meetings will focus on building relapse prevention skills using the general approach of Marlatt and Gordon (47). Basically, this approach to relapse prevention training includes the following components: identifying high risk situations in which relapse is likely to occur for each participant, teaching participants strategies for minimizing the occurrence of high risk situations, developing alternative active coping strategies for situations which cannot be avoided, and then practicing the selected coping strategies to build confidence and skill. Transition intervention meetings will focus on the full spectrum of intervention goals including adherence to dietary changes, physical activity, and behavioral self-management efforts.

At the end of the bi-weekly transition phase of intervention, all participants will begin the extended period of intervention. For the weight and weight/sodium intervention groups, biweekly contacts or attendance at mini-modules are encouraged for the duration of the trial. For the sodium alone intervention, less frequent monthly contacts and bimonthly meetings are recommended. For efficiency, randomization cohorts will be combined for mini-module group meetings during the extended intervention period, but only within the same intervention (i.e., either Wt, Na or WtNa).

Adherence Enhancement: Several types of strategies will be used to enhance adherence. Items that will help with sodium reduction or weight change will be used as incentives (e.g., coupons for modified foods or samples of these modified foods). Participants will keep daily, then less frequent food records throughout the study. These food records will not be used for data collection. Self-monitoring of food intake provides a framework for planning nutritionally-adequate food substitutions in consultation with the nutrition counselor. In addition, calculating caloric and sodium intake from food records, although subjective and imprecise, helps participants to develop a working knowledge of food content and to keep themselves in the right range for caloric or sodium intake. Participants in weight management intervention are expected to continue self-monitoring their regular physical activity throughout the program.

Weigh-ins at intervention meetings or visits provide objective evidence of weight loss or maintenance. Overnight urine collections will be used to provide objective evidence of adherence to dietary sodium goals. An average from two overnight urine collections will be obtained midway through and at the end of the intensive intervention and periodically during the remainder of

follow-up. This is similar to the successful urine sodium monitoring approach used in Phase I.

Intervention Support and Quality Control: An Intervention Quality Control Subcommittee has been formed to ensure that the interventions delivered at each clinical center site will be standardized and of high quality. Guidelines were developed to ensure the training and certification of intervention personnel, the monitoring of the delivery of the protocol in all sites, and periodic training for interventionists, and other strategies for enhancing the quality and consistency of the intervention over time. This group will also monitor and respond to the performance of individual sites using regular data reports on attendance at group meetings, weight loss, and overnight urinary sodium excretion.

ENDPOINTS

Both primary and secondary outcomes for TOHP are determined from measurements and laboratory tests taken at follow-up visits. Outcome measurements will be made by data collectors blinded to the treatment assignment of participants and not involved in delivering any intervention. Due to the subjective nature of BP measurement, it is particularly important that the BP observers are not involved in any way with the delivery of any intervention and have no access to intervention-specific data. Insofar as possible, data collection visits should take place on different days and at different locations from intervention visits so that those in the active intervention groups do not become more habituated to the data collection environment than those in the comparison group.

Ascertainment of Blood Pressure: The outcome of primary interest is change in

DBP from baseline to termination, with the mean at each of these two points being determined from nine BP readings (taken over three visits). There will also be the opportunity to examine BP measurements at 6 month intervals (3 BP readings at one visit) and at the 18 month follow-up (nine BP readings over three visits). Therefore, it will be crucial to establish methodology to ensure obtaining accurate and complete BP measurements on every subject for the duration of the trial.

To enhance the overall reproducibility of BP measurements in TOHP, standardized procedures for both training observers and taking measurements will be employed. Standardization of procedures for BP measurement include a uniform protocol for preparing the subjects, positioning of the participant, selection of an appropriate cuff, and imposing restrictions on smoking for a specified time period prior to BP measurement; use of a random-zero sphygmomanometer to minimize observer biases; maintaining observer blindness concerning the subject's treatment allocation; and careful maintenance of all equipment.

An Endpoints Committee appointed by members of the Design and Analysis Subcommittee, including representatives from the Project Office at NHLBI and the Coordinating Center, will conduct a blind (without knowledge of treatment assignment) review of the study forms and, as necessary, the medical records of participants who are considered to have had hypertensive endpoints. By simple majority vote, the Endpoints Committee will confirm or disconfirm each potential hypertensive endpoint.

Any of the hypertensive endpoints occurs if, at any time during the course of the trial, the Endpoints Committee determines that a participant has been

treated for hypertension with medication.

The combined endpoint of diastolic hypertension or systolic hypertension is defined as sustained DBP ≥90 mmHg or sustained SBP ≥140 mmHg . The criteria for this combined endpoint are met if diastolic hypertension (DBP ≥90 mmHg) or systolic hypertension (SBP ≥160 mmHg) occurs at any follow-up interval as described below. In addition, this combined endpoint occurs if the mean of nine SBP is ≥140 mmHg at the 18- and 36-month follow-up points.

The endpoint of diastolic hypertension (sustained DBP ≥90 mmHg) occurs if DBP is ≥90 mmHg based on nine readings over three visits at any follow-up point. At the 18- and 36-month follow-up points, all participants come for three visits. At the 6-, 12-, 24-, 30-, 42-, and 48-month follow-up points, all participants come for at least one visit consisting of three BP measurements. If the mean of three DBP is ≥90 mmHg at this visit, then the participant returns for a second visit seven to ten days later. If the mean of six DBP is ≥90 mmHg, then the participant returns for a third visit seven to ten days later. If the mean of nine DBP is ≥90 mmHg after the third visit, then the participant is considered to have diastolic hypertension and is asked to notify his/her physician.

The endpoint of systolic hypertension,* **(see 12/03/92 modification below)** defined as sustained SBP ≥160 mmHg, occurs if SBP is ≥160 mmHg based on nine readings over three visits at any follow-up point. At the 18- and 36-month follow-up points, all participants come for three visits. At the 6-, 12-, 24-, 30-, 42- and 48-month follow-up points, all participants come for at least one visit consisting of three BP measurements. If the mean of three SBP is ≥160 mmHg, then the participant returns for a second visit seven to ten days

later. If the mean of six SBP is ≥160 mmHg, then the participant returns for a third visit seven to ten days later. If the mean of nine SBP is ≥ 160 mmHg after the third visit, then the participant is considered to have systolic hypertension and is asked to notify his/her physician. The endpoint of systolic hypertension, alternatively defined as sustained SBP ≥ 140 mmHg, occurs if the mean of nine SBP is ≥ 140 mmHg at the 18- and 36-month follow-up points, since at these follow-up visits participants come for all three visits without regard to cutpoints based on SBP ≥ 160 mmHg as the endpoint. The endpoint of SBP ≥140 mmHg also occurs if the criteria for SBP ≥160 mmHg are met.

12/03/92 Modification:

* **The definition of SBP endpoint was modified on December 3, 1992. At that time, to achieve alignment with the JNC V classification of elevated blood pressure, the endpoint of systolic hypertension previously defined at 160 mmHg was shifted down to 140 mmHg. Therefore, after December 3, 1992, for any sequence of nine BPs, if mean DBP was ≥90 and/or mean SBP was ≥140 mmHg, the participant was considered to have had an endpoint.**

Urinary sodium excretion and weight change will be collected as secondary endpoints on all participants.

SAFETY MONITORING

The chief safety concern is for individuals who may become hypertensive during the trial. Individuals found to have elevated BP (DBP ≥90 or SBP ≥140) during the screening process will be referred to their physicians. The interim follow-up visits provide procedures for monitoring and referring for treatment any individuals who may become hypertensive during the follow-up period. These opportunities are more frequent than that which is usually provided for

such individuals. A participant with mean DBP $\geq$90 or SBP $\geq$160* **(see 12/03/92 modification below)** based on nine readings at any follow-up visit will be referred to his/her physician for possible treatment. If possible, the principal investigator should negotiate an agreement with the participant's physician to have the participant stay in the trial and to have the BP readings for each subsequent visit reported to the personal physician. Should these participants go on antihypertensive medication, they and their physicians are strongly encouraged to inform trial personnel before treatment is initiated so that termination blood pressures can be obtained for the dichotomous endpoint.

The need for a safety monitoring visit or possible termination BP visit arises if a participant reports that he/she has been informed (by non-study personnel) that he/she has elevated BP, if a participant reports that he/she is starting antihypertensive medication or medication that affects blood pressure, or if a participant indicates that he/she will not be returning for subsequent visits (i.e., dropping out or moving). Procedures, such as monitoring of physician appointments, study identification cards, and contacts with participants' physicians, will be utilized to anticipate the initiation of medication for hypertension, or of other medications that affect blood pressure, so that termination blood pressures may be obtained. If the participant is starting antihypertensive medication or medication that affects blood pressure or if the participant will not be returning for subsequent visits, clinic personnel are asked to conduct three safety monitoring visits, if at all possible, so that a termination BP assessment based on nine readings can be made. If the participant reports an elevated BP reading by non-study personnel and if it seems clear that the participant is not starting treatment and will return for subsequent visits, clinic personnel are asked to conduct

at least one safety monitoring visit. If the mean of three DBP ≥90 mmHg or if the mean of three SBP is ≥160 mmHg at this visit, then the participant returns for a second visit seven to ten days later. If the mean of six DBP ≥90 mmHg or if the mean of six SBP ≥160 mmHg,* **(see 12/03/92 modification below)** the participant returns for a third visit seven to ten days later. If the mean of nine DBP ≥90 mmHg or if the mean of nine SBP ≥160 mmHg after the third visit, then the participant is considered to have diastolic or systolic hypertension and is asked to notify his/her physician.

There is also some concern about participants who may develop SBPs within the range of 140-159 mmHg, considered borderline systolic hypertension in the 1988 Joint National Committee report (14), with DBPs <90 mmHg. As stated above, the endpoint of systolic hypertension, defined as SBP ≥140 mmHg based on nine readings, is determined at the 18- and 36-month follow-up points. In the semi-annual reports to the Data and Safety Monitoring Committee, the Coordinating Center will include a report of the number of participants who have mean SBP ≥140-159 mmHg based on three readings at any follow-up visit. If the national guidelines for the definition of systolic hypertension or the recommendation regarding treatment of systolic hypertension change, then the monitoring procedures for participants with SBP ≥140-159 mmHg may have to be modified.

12/03/92 Modification:

The preceding safety monitoring procedures were modified on December 3, 1992. At that time, in alignment with the JNC V recommendations, all participants with a mean SBP ≥140 mmHg over nine readings were considered to have systolic hypertension and were asked to notify their physicians for follow-up and possible treatment. For SBP, the safety monitoring rule

remained as previously described for SBP ≥160 mmHg, using 140 mmHg as the new level.

The nutrient data collected on a sample of the participants will be reviewed to monitor for potential nutritional deficits. In addition, the interventionists will educate participants on how to prevent nutritional deficiencies and will informally monitor nutrient intake. For safety purposes, all participants assigned to the Wt or combined Wt/Na intervention will monitor their heart rate before and after undertaking their program of continuous physical activity. The goal of this assessment will be to achieve a heart rate based on 40-55% of heart rate reserve. Additionally, participants will also be instructed that any physical activity which makes them feel out of breath may be at a higher level of exertion than recommended. This modest level of physical activity should not place most participants at risk. However, participants assigned to the weight reduction arms and also identified as at higher risk for developing cardiac disease as defined by greater than age 50 and the presence of two or more cardiovascular risk factors (male gender, total serum cholesterol ≥240 mg/dl, history of cigarette smoking, history of diabetes mellitus, or family history of coronary or other atherosclerotic disease prior to age 55) will be further monitored. This information will be recorded prior to the start-up of intervention on the data form for the assessment of risk level in the TOHP physical activity program. It will be the responsibility of interventionists to note in their files for people in the weight/physical activity intervention arms only whether a participant is at higher risk with regard to the possibility of having cardiac disease. Interventionists will also ask these individuals if they are participating in regular physical activity with heart rate in the range of 40-55% of heart rate reserve. If above 55%, that is above program guidelines,

they will be referred to their personal physician for evaluation. Alternatively, instead of referring a participant to their personal physician, the clinical center could elect to do its own ECG stress test to determine clearance prior to allowing the participant to resume the physical activity component of the intervention.

QUALITY CONTROL

At the clinical centers, quality control will encompass the following areas:

- training and certification of personnel responsible for measuring blood pressure, height and weight;
- training and certification of staff responsible for conducting each of the intervention protocols;
- training and certification of diet interviewers;
- calibration and maintenance of BP devices, including random zero and standard mercury devices;
- calibration and maintenance of other equipment, including scales, height boards;
- inspection and certification of the physical environment of the clinic, with particular attention to the separation of all data collection activities from those related to the delivery of the interventions;
- validation of data collection and coding procedures including monitoring adequacy of the 24-hour urine specimens; and
- review of laboratory specimen handling, shipping, and storing.

The Coordinating Center will be responsible for the verification and validation of all data entry, the computer editing of forms, and the generation of reports monitoring the quality of the data being collected. These monitoring reports will include reports on the screening and

randomization process, on the performance of the central laboratory and nutrition center, on the accuracy of form completion and of BP readings, and on the completeness of the data base.

To implement quality control monitoring, the clinic coordinator will be responsible for certification and recertification procedures, and local data collection, including the "blindness" of data collectors to group assignments. She or he will report problems to the local clinical center Principal Investigator and the Coordinating Center on a regular basis. A Quality Assurance Subcommittee, including representatives from the clinical centers, the NHLBI Program Office, the Coordinating Center, the central laboratory and the nutrition center will periodically review reports, provided by the Coordinating Center, tabulating errors and citing deviations from protocol and will help clinical centers which have been recognized as having a problem or who have requested help in any of these areas.

DATA ANALYSES

To assess the effects of weight loss, sodium restriction, and their combination, the mean changes in DBP at 36 months in the various groups will be compared. Additionally, the average of all BPs obtained during the trial in the various groups will be compared. The analysis of variance for a two-by-two factorial design will be used to test the main effects of weight loss and of sodium restriction. Multiple regression analyses will be performed to adjust for other covariates, such as age, sex, and initial weight and urinary sodium. To reduce the impact of regression to the mean and to improve the error variance, as well as to adjust for any imbalance, mean initial DBP will also be included in the model. To compare DBP changes in two of the four groups, such as the combined intervention versus placebo, comparisons of means

with a t-test and multiple regression analyses will similarly be used. These methods can also be used to explore the effect of the combined intervention compared to a single intervention such as weight loss alone. More sophisticated methods of longitudinal data analysis such as computing slopes over time or the use of autoregressive models will be used to explore more complex changes in DBP over time in the various treatment groups (48-50).

Because the effect of treatment may not be uniform across all members of a group, we will also examine the distribution of blood pressure changes. Should these appear not to be normally distributed, we will perform nonparametric tests of significance. To examine the effect of actual compliance to the treatment regimen, we will consider change in DBP as a function of actual change in weight and urinary sodium. This is of particular importance because some members of the control group may seek to implement the intervention strategies on their own.

Censoring of this continuous variable due to incidence of hypertension is a potential problem in this analysis. Once antihypertensive medications are prescribed, blood pressure readings become biased in those subjects who should have the highest levels. For this reason we will attempt to acquire and use termination blood pressures obtained prior to initiation of antihypertensive therapy. Furthermore, individuals who are told they are hypertensive may begin some nonmedical intervention; such as weight loss, on their own, perhaps under the advise of their physicians, even if they do not take medications.

Several strategies may be used to deal with the effects of such biases. The primary analysis will use the termination blood pressure as defined in Phase I of TOHP. This is the last recorded blood pressure prior to the initiation of

drug therapy. This includes blood pressures measured after becoming an endpoint according to the definition of SBP $\geq$140 mmHg or DBP $\geq$90 mmHg, but prior to starting medication. Because it is recognized that these latter measurements may be biased, secondary analyses will be performed to confirm the results of the primary analysis. These include an analysis of blood pressures taken at the time of diagnosis for those who become hypertensive, imputing minimum values of 90 mmHg for DBP and 140 mmHg for SBP for those who go on BP medications, and also a multivariate repeated measures analysis. The latter approach would use all measured blood pressures on an individual either including or excluding those following diagnosis. In this way, both the within-person variation as well as an effect of "self-intervention" could be taken into account.

Secondary endpoints in the trial, including changes in SBP and the development of diastolic and systolic hypertension, will also be examined. The former will be evaluated in the same manner as changes in DBP described above. For the hypertension endpoints, crude relative risks and a chi-square test will be calculated for each hypothesis to compare cumulative incidence rates over the duration of the study. We will compute Kaplan-Meier incidence-free survival curves and the logrank test statistic. A Cox proportional hazards regression analysis will be performed to adjust for potential confounders such as baseline BP, age, sex, and race.

Intermediate variables such as urinary sodium and body weight will be monitored on a regular basis and compared across intervention groups.

This trial will also provide the opportunity to explore any differential response to intervention by race, and gender, as well as body mass index,

waist to hip ratio, cigarette smoking habits, pulse rate, family history of hypertension, and baseline electrolyte excretion. Currently we expect to recruit a sample with approximately 21% blacks and 33% women. While power will not be adequate to test the effect of the interventions within these subgroups, we will explore any differences among them.

STUDY ADMINISTRATION

The administrative structure of TOHP consists of committees and subcommittees with representatives from the participating units.

1. Steering Committee

The Steering Committee will be the central governing body of TOHP. It will be made up of the principal investigators from each of the clinical centers as well as one representative each from the Coordinating Center and the NHLBI. Each participating unit will have one vote, normally cast by the Principal Investigator. In addition, officers of the study (Chairman and Vice Chairman) will each have one vote regardless of whether or not they are attached to a clinical center. During Phase II, the Steering Committee will meet face-to-face at least semi-annually to review the progress of the trial. Each center will be required to be represented at each meeting by at least the Principal Investigator (or designated co-investigator) and one other representative from that clinic. The Study Chairman will serve as chairman of the Steering Committee.

The six subcommittees of the Steering Committee that were active in the first phase of TOHP will continue. Their activities are summarized below:

The Design and Analysis Subcommittee will be responsible for reviewing overall design features, e.g., sample sizes, blinding, and stratification;

for proposing specific data analyses; for reviewing requests from investigators for data analyses and recommending priorities for analysis.

The Eligibility and Recruitment Subcommittee will recommend the inclusion and exclusion criteria for participant eligibility and is responsible for development of strategies and resources to aid the clinical centers in effective and efficient recruitment. It will also be responsible for reviewing recruitment reports from the Coordinating Center in order to identify problems and propose solutions on a clinic-by-clinic basis.

The Interventions Subcommittee will develop intervention methods and materials, monitor compliance outcomes, and, if necessary, propose modifications to the intervention protocols for review and approval by the Steering Committee.

The Data Collection and Quality Assurance Subcommittee will recommend to the Steering Committee the data set to be collected from TOHP participants, review data forms, and be responsible for collaborating with the CC in the development and implementation of quality assurance programs.

The Clinic Coordinators Subcommittee will be composed of one representative from each clinical center, who will be responsible for assisting the Principal Investigator in organizing the center staff, facilities, and tasks, and representatives from the Coordinating Center.

The Publications and Presentations Subcommittee will be responsible for establishing and implementing procedures for review of publications and presentations of TOHP materials.

In Phase 2, an Endpoints Subcommittee will conduct a blind review of the study forms and, as necessary, the medical records of participants who are considered to have had hypertensive endpoints. By simple majority vote, the subcommittee will confirm or disconfirm each potential hypertensive endpoint.

2. Executive Committee

The TOHP Executive Committee will be composed of the study chairman and study vice-chairman, selected by the Steering Committee, the NHLBI Project Officer, and the Director of the CC. This group will discuss and help formulate and implement all Steering Committee decisions related to the maintenance and conduct of TOHP within the guidelines established by the protocol.

3. Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) will be responsible for reviewing the initial study protocol, for assessing accumulating study data for adverse and/or beneficial intervention effects, and ensuring that risks to subjects are minimized. DSMC members will be appointed by the NHLBI Project Office based on consultation with the Executive Committee.

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Table 5 Power (%) for hypotheses for diastolic hypertension with a total sample size of 2250.

		Power (%)	
Comparison	Average Risk Reduction	Event Rate from HPT	Event Rate from Simulations
Weight Loss	28%	98.6	93.6
Na Reduction	18%	65.4	48.0
Combined vs. Placebo	40%	99.7	97.5
Combined vs. Weight Loss	14%	16.2	11.3
Combined vs. Na Reduction	25%	62.1	46.1

Table 6 Power for primary categorical endpoint using systolic or diastolic hypertension (DBP $\geq$ 90 or SBP $\geq$ 140 or on anti-hypertensive medications) with a total sample size of 2250

		Power %	
Comparison	Average Risk Reduction	Event Rate from HPT (%)	Rate with Increased Monitoring
Wt loss	28%	99.9	100.0
Na restriction	18%	82.5	87.0
Comb. vs. Usual care	40%	100.0	100.0
Comb. vs. Wt loss	14%	22.6	24.9
Comb. vs. Na rest	25%	78.2	84.1

TABLE 10

SUMMARY: INTERVENTION PROGRAM FEATURES FOR TOHP PHASE II

	WEIGHT (Wt) (a)	SODIUM (Na) (b)	WtNa (c)
GROUP GOAL	≥ 10 lb weight loss 6 months post randomization and maintained throughout	24 hour urinary Na+ excretion ≤ 80 mEq (1800 mg) by 6 months post-randomization and maintained throughout	(a) + (b)
PARTICIPANT OBJECTIVE	Weight loss ≥ 10 lb or achievement of ideal weight; evidence of caloric restriction and increased physical activity in self-reports	Decrease in dietary Na+ intake to 1600 mg by six month estimated from dietary self-reports and urinary excretion data	(a) + (b)
CONTENT	-Information about weight control -Directed group process -Behavioral counseling -Food experience -Social support for adherence -Experiences in moderate physical activity	-Information about Na+ -and all other items on (a)	(a) + (b)
CONTACT SCHEDULE	Intensive: 1 individual, 14 weekly sessions, 6 biweekly sessions Extended: biweekly contacts with monthly face-to-face meetings until the intensive intervention is completed for the first cohort then mini-modules to be offered with continued bi-weekly contact Specially tailored follow-up where indicated	Intensive: 1 individual, 10 weekly sessions, 4 monthly sessions *Extended: monthly contacts with bi-monthly meetings until intensive intervention completed for the first cohort then mini-modules offered with a min. of quarterly overnight urine collections with a face-to-face contact. Specially tailored follow-up where indicated.	Same as (a)
CONTACT MODE	Primarily group; individual contacts at post-randomization, and as needed thereafter	Same	Same
ADHERENCE FEEDBACK	-Attendance records -Weigh-ins -Food records -Physical activity records	-Attendance records -Food records -Overnight urine Na+ or other urine monitoring methods	(a) + (b)
SAFETY ISSUES	-Diet quality -Physical activity-related injuries -Weight cycling	excessive sodium restriction	(a) + (b)