TRIALS OF HYPERTENSION PREVENTION

PROTOCOL

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AIMS, BACKGROUND, AND RATIONALE

Specific Aims

The Trials of Hypertension Prevention (TOHP) is a multi-center, randomized clinical trial designed to achieve the following specific objectives:

1. To determine the feasibility of conducting a clinical trial of a program consisting of one or more nutritional and/or behavioral interventions in a population of individuals with high normal diastolic blood pressure (DBP) levels.

2. To assess the effectiveness of selected non-pharmacologic interventions in retarding or preventing an increase in DBP in this population, including a weight-loss regimen, a stress management program, reduction of dietary sodium, and nutritional supplements containing calcium, magnesium, potassium, or fish oil.

3. To assess the feasibility of proceeding with a full-scale trial of hypertension prevention through changes in lifestyle or administration of nutritional supplements, depending on the outcome of this phase of the trial.

4. To develop a non-pharmacologic intervention program to be tested in a long-term, full-scale trial if it proves feasible.

Background and Rationale

Approximately 20% of the adult population in the U.S. have elevated BP (1), an established risk factor for premature death from cardiovascular diseases (2). In addition, high BP is currently one of the major reasons for which people visit a physician and take prescription drugs (3). Substantial evidence from both population and laboratory studies suggest that lifestyle factors, and particularly diet, are associated with hypertension. While the effectiveness of antihypertensive drugs in reducing high BP and most of its complications are well established (4-10), it is becoming widely recognized that problems associated with altered quality of life, toxicity, and sometimes costs of medical care (11-12) limit the usefulness of antihypertensive drug therapy. Increasing reports of BP reductions using a variety of non-pharmacologic interventions

raise the question of whether these might be of value in preventing the progression to hypertension in individuals who may be prone to the disorder. These are reviewed briefly below.

1. Weight Reduction

In observational studies (13-16), there is a strong relationship of obesity with hypertension. Weight reduction in overweight subjects with hypertension has resulted in significant reductions in systolic and diastolic BPs (17-26). Moreover, it has been shown that achievement of ideal body weight is not necessary to obtain a meaningful reduction in BP, but that modest losses result in relatively uniform BP reductions (23). Some of these studies (17,26) showed substantial improvement of hypertension independent of salt intake. In general, there is evidence that BP after weight loss remains reduced as long as there is no marked regain of body weight (27). While efforts to treat obesity have had limited success, and the rate of recidivism is high (28), the evidence suggests the possibility for weight reduction as a means to decrease, or prevent increases in, DBP in persons susceptible to hypertension.

2. Sodium Reduction

Sodium-restricted diets have long been recommended alone or as adjuncts to the pharmacologic treatment of hypertension (29). Typical recommendations have been to reduce sodium intake to 80-100 mmols/day (30-32). It is thought that this decreases arterial BP through reduced intravascular volume, reduced vessel wall sodium content, and/or decreased vascular reactivity (33-34). Several studies have shown that extreme salt restriction (to less than 30 mmol/day) lowers BP in severely hypertensive patients (30,33-38). However, maintaining severe salt restriction is difficult in hypertensives, and may be even more difficult in normotensive individuals. Modest salt restriction has been examined in several studies reported during the 1970s, but most were poorly controlled, and some also included the use of diuretics (31-34,39). Controlled studies of small numbers of mild hypertensives have shown a modest reduction (about 4 mm Hg) in BP with sodium intake restricted to 60-100 mmol/day (40-44). Thus, while marked sodium restriction does reduce BP and there is some data to suggest a beneficial effect of moderate sodium restriction in mild hypertensives,

the long-term feasibility and effectiveness of salt restriction among normotensives for the primary prevention of hypertension remains untested.

3. Stress Reduction

An abnormality of the sympathetic nervous system has long been implicated in hypertension (45). Excess sympathetic nervous system activity can result in increased catecholamine levels, tachycardia, and increased peripheral vascular resistance (46-53). Certain behavioral factors (cumulatively termed "stress") are related to increased sympathetic nervous system activity, but their role in producing hypertension is as yet unproven (28). In laboratory settings and in a few well-controlled trials, it has been demonstrated that purposeful muscular relaxation, achieved through meditation, breathing exercises, progressive muscle relaxation, and/or biofeedback can result in substantial reduction of BP in both normotensive and hypertensive individuals. Five published trials, involving approximately 350 patients, have demonstrated consistent, but modest (average 5 mm Hg) reductions in DBP (48-52). For one of these trials (48), involving once weekly hour-long group sessions at which subjects were taught breathing exercises as well as relaxation, meditation and stress management techniques, differences in BP between the treated and control groups have been maintained after four years of follow-up (53). Another trial (51) tested a "behavioral stepped care" program that consisted of self-monitoring of BP, adding medical surveillance, biofeedback, and/or relaxation treatment for those whose BP values remained above certain previously specified limits.

4. Potassium Supplementation

More than 50 years ago, Addison reported that a high potassium diet had an antihypertensive effect in humans (54). There are several mechanisms by which potassium may lower BP: through a diuretic effect (55); by suppressing plasma renin activity (56); by acting as a vasodilator on arterial smooth muscle (57); or by altering the response of blood vessels to angiotensin II (58). Ecological studies, conducted primarily in Japan, have supported a negative correlation between BP and potassium intake in the presence of a high salt diet (59-60). However, surveys of normotensive and hypertensive individuals in the U.S. have not uniformly found an in-

verse relationship between potassium and BP (61-62). When used in conjunction with various levels of sodium restriction, potassium supplementation has been demonstrated to decrease BP in both mildly hypertensive and normotensive young men (34,63-64). At present, the independent hypotensive effect of an increased intake of potassium (through either through diet or supplementation) among normotensive individuals remains untested.

5. Calcium Supplementation

Low levels of calcium intake have been associated with increased risk of hypertension. While the mechanism for this effect is unclear, calcium is known to affect both vasoconstriction and vasodilation. It has been suggested that an elevation in BP results from a disturbance in the transport of calcium across cell membranes (65). Initial evidence of a relationship between calcium and hypertension derived from studies of preeclampsia showing that nations with higher calcium intakes had lower prevalences of gestational hypertension (66), and that dietary supplementation of calcium reduced BP in normal pregnant women and in normal young adults (67-68). Data from one case-control study showed that self-reported calcium intake was significantly lower in hypertensives than in normotensive controls (69). Results of an analysis of data from the first National Health and Nutrition Examination Survey (HANES I), found that hypertensives had a 19.6% lower estimated calcium intake than normotensives (70). In addition, this study revealed that reported calcium intake was the best predictor of BP status. Evidence from clinical investigations of the association between calcium intake and BP in patients with hypertension has been inconclusive. In a randomized, double-blind, placebo-controlled trial in which subjects received either an oral calcium supplement or placebo, overall, both systolic and diastolic BP levels were reduced in hypertensives while those of normotensives remained unchanged (71).

6. Magnesium Supplementation

Persons consuming vegetarian diets, which are usually high in magnesium, have been shown to have lower BPs than non-vegetarians (72-73), raising the possibility that dietary magnesium may be inversely related to BP. A possible mechanism for a hypotensive action of magnesium is that it suppresses parathyroid hormone levels, increases urinary excretion of calcium

and decreases serum calcium (75-77). Alternatively, magnesium may antagonize calcium-induced norepinephrine release by peripheral nerves (78).

Support for an inverse relation of magnesium and BP is derived from international studies showing an apparent protective effect of mineral-rich "hard" drinking water on hypertension (79-82). It has been proposed that subclinical magnesium deficiency has developed over the past century in industrialized countries, and that this has paralleled the increasing frequency of hypertension (74,81-83). Magnesium-rich foods have declined in the diet, and processed foods that have lost magnesium have increased. Use of water softeners to supply drinking and cooking water has further lowered magnesium intake, so that according to one estimate, average intake in the U.S. has declined from 475 mg in 1900 to about 250 mg currently (83). More specifically, lower serum magnesium is associated with the hypertension of hyperaldosteronism (84) and preecclampsia (85). Hypertension occurs when acute severe losses of magnesium from the urine or GI tract are replaced by magnesium-free solutions (78,86). Hypotension has been observed in severe hypermagnesemia (87). Mean magnesium content of red blood cells was lower in untreated essential hypertensives than in normotensives (75), and BP among hypertensives was inversely proportional to magnesium in both red blood cells (75) and serum (76). Moreover, decreases in DBP in response to parenteral magnesium for four days tended to occur in subjects with low pre-treatment serum magnesium (79). However, two recent trials of oral magnesium supplementation provided inconsistent results. In one, after six months, those given magnesium experienced significant decreases of 12 mm Hg and 4 mm Hg in systolic and diastolic BP, respectively, compared with those given placebo (88). In a smaller trial, no significant changes were reported after four weeks of supplementation (89).

7. Fish Oil Supplementation

Interest in the possible beneficial effects of fish oil was first stimulated by the observation that Eskimos in Greenland, whose diet is very high in fish (90), have been reported to have very low mortality from coronary heart disease (91-92). During the past few years, considerable attention has focussed on a major component of fish, the omega-3 polyunsaturated fatty acids, the most important of which seems to be eicosapen-

taenoic acid (EPA). EPA has potent anti-aggregatory effects itself and also increases synthesis of prostaglandin I_2, which is both anti-aggregatory and vasodilatory (92-93). Prostaglandins are also essential in regulating renal handling of sodium and water (94-95). EPA may also have specific hypotensive effects due to decreasing vascular responsiveness (96) or blood viscosity (97-98). Several small studies have found that supplementing the diet with fish or fish oil preparations lowered the BP of normotensive subjects (96,99-100). However, there are a number of methodologic issues that make interpretation of their results difficult. First, the methodology for measuring BP was not objective. Moreover, only one study was conducted double blind (99), and in that study, the pronounced odor of commercial fish oil could have affected the success of blinding. Finally, the periods of treatment with fish oil were relatively brief, ranging from two to four weeks.

In summary, while a number of interventions offer the potential to reduce BP in normotensive individuals, the feasibility of these interventions for the primary prevention of hypertension remains uncertain. Clearly, the chief need, which TOHP is designed to address, is to identify the best overall approach to non-pharmacologic intervention in reducing or preventing increases in BP, whether that turns out to be a single nutritional or lifestyle intervention, or a program combining elements of all the modalities mentioned.

STUDY DESIGN

The study design of TOHP is fairly complex, owing to the large number of diverse interventions being tested. The 10 clinical centers are each testing a different combination of interventions, although they can be divided into three broad categories: clinics offering only a combination of lifestyle interventions (sodium reduction, weight loss, and stress management, plus a control group); those offering only supplements (calcium and magnesium and their placebos in Stage 1, fish oil and potassium and their placebos in Stage 2); and "hybrid" clinics offering both types of intervention. Specific clinic allocations and the approximate numbers of subjects that will be assigned to each study group if recruitment goals are met are shown in Table 1.

For the lifestyle interventions, an open design is being utilized. After the initial orientation at randomization, those individuals assigned to the control

group will be invited to the clinic for data collection visits only. Because of this design feature, particular care will be taken to maintain blindness to intervention assignments among all clinic personnel involved in collecting any study data, especially BP. To avoid differential habituation to the BP measurement environment, data collection and intervention sessions should also take place in physically separate locations if at all possible. For the supplements interventions, placebo control has been adopted so that double blindness will be maintained.

ELIGIBILITY AND EXCLUSION CRITERIA

The general aim of the eligibility and exclusion criteria in TOHP is to assemble a group of healthy, non-hypertensive individuals who can safely undertake the study interventions and who are likely to be cooperative with follow-up requirements for the duration of the trial. In order to establish an overall study cohort that is generally comparable across all clinical centers, it is necessary to have generally uniform eligibility and exclusion criteria for all participants, regardless of which interventions an individual clinic may be testing.

Specific eligibility and exclusion criteria are outlined below.

Eligibility Criteria

1. Diastolic Blood Pressure

   At each of the three screening visits, DBP will be determined as an average of all screening BPs obtained up to that time (three per visit), with the average falling within a specified range for a subject to be eligible. These ranges are:

   Screening visit #1: DBP 75-97 mm Hg (3 readings)
   Screening visit #2: DBP 77-94 mm Hg (6 readings)
   Screening visit #3: DBP 80-89 mm Hg (9 readings)

2. Age

Participants in TOHP must be between 30 and 54 years of age.

3. Body Weight

Individuals whose body mass index (BMI), defined as wgt(lbs)/hgt(in)2, is less than 0.0514 are eligible to take part in TOHP. At all those clinics testing the weight loss/exercise intervention, eligible subjects will be divided into two groups, a low-weight stratum consisting of men with BMI less than 0.0371 and women with BMI less than 0.0345, and a high-weight stratum including men with BMI from 0.0371 to 0.0514 and women from 0.0345 to 0.0514. The high-weight stratum consists of persons who are approximately 115 to 165% of ideal body weight. Those in the low-weight stratum will be eligible for randomization to all interventions except the weight loss/exercise program, while those in the high-weight stratum will be eligible for randomization to the weight loss/exercise intervention in addition to all the other study groups.

4. Gender

Both men and women are eligible to enroll in TOHP.

5. Race

Individuals of all races are eligible to participate in TOHP.

Exclusion Criteria

In general, the exclusion criteria for TOHP have been designed to eliminate individuals who are already hypertensive or who have below normal BPs, those with evidence of other existing cardiovascular disease, those for whom any of the interventions may be harmful, and those who appear 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, as defined by nine baseline DBP readings averaging 90 mm Hg or greater, or current use (within the previous two months) of antihypertensive medications.

2. Diastolic BP less than 80 mm Hg, based on the average of nine readings.

3. Gross obesity, as defined by BMI equal to or greater than 0.0514 lb/in^2.

4. History of any cardiovascular disease, including myocardial infarction, angina, intermittent claudication, congestive heart failure, and stroke.

5. History of diabetes mellitus, defined by self-report or ever use of insulin or oral hypoglycemic agents.

6. History of chronic renal failure and/or kidney stones.

7. Recent history of psychiatric disorders, defined by hospitalization within the previous five years for such a condition or current use of anti-psychotic or anti-depressant medications.

8. History of malignancy (other than non-melanoma skin cancer) in past five years.

9. Serious physical handicaps, including severe arthritis, blindness or other handicap that would contraindicate participation in any of the TOHP interventions.

10. Current alcohol intake of more than 21 drinks per week.

11. History of chronic gastrointestinal disease, such as peptic ulcer, diverticulitis, ulcerative colitis, inflammatory bowel disease or other conditions judged by a study clinician to be a contraindication to admission to TOHP.

12. Any other serious or life-threatening illness that requires regular medical treatment.

13. Current use (within the past two months) of medications that could interfere or interact with study interventions, including diuretics, beta-blockers, and anticoagulants.

14. Serum cholesterol level greater than or equal to 260 mg/dl as determined by local laboratory.

15. Serum creatinine level greater than or equal to 1.7 mg/dl for men or 1.5 mg/dl for women, as determined locally.

16. Casual serum glucose greater than or equal to 200 mg/dl as determined locally.

17. Unexplained hyperkalemia as defined by local laboratory.

18. Hypercalcemia, as determined by local laboratory.

19. Unwillingness to discontinue use of preparations of any of the micronutrient supplements being tested in TOHP.

20. Unwillingness to discontinue a dietary regimen incompatible with TOHP interventions, such as a medically supervised diet or a formal weight loss program.

21. For women, current pregnancy or intent to become pregnant during the study period.

22. Current participation in other ongoing clinical trials or prior participation in the Hypertension Prevention Trial.

23. Participation of another household member in TOHP; TOHP employees; persons living with TOHP employees.

24. Plans to move out of the study area (generally defined as more than 50 miles from the study site), such that it would be difficult to come to the study site.

25. Unwillingness to accept randomization into any study group.

26. Inability to cooperate as assessed by clinic staff.

27. Inability or unwillingness to give informed consent.

ENROLLMENT PROCEDURES

Each of the clinical centers collaborating in TOHP has an outstanding record in recruiting subjects for large-scale, long-term clinical trials. On this basis, specific recruitment procedures, including the use of prescreening, are being left to the discretion of the study personnel at each center, although all centers are sharing plans to ensure optimum procedures. If the prescreening option is selected, however, it is recommended that the clinic follow certain guidelines that will standardize procedures as much as possible and result in obtaining the maximum amount of comparable information. These include exclusion of individuals whose DBP is outside the range of 74-102 mm Hg for a single measurement in the field. In addition, the clinic may complete a TOHP prescreening log, which records information on sex, race, date of birth, and BP.

Screening of potentially eligible participants in TOHP is standard and uniform across all clinical centers, regardless of recruitment strategies, use of prescreening, or the specific interventions being tested. Screening occurs over three visits and is designed to assess, as reliably and comprehensibly as possible, each individual's true DBP, as well as his or her medical history and health status, general reliability, and specific willingness to comply with the demands of the study protocol. The screening period is also when all baseline data will be collected in order to characterize the study population according to variables of interest other than those determining eligibility.

Obtaining Informed Consent for Screening

When a potential participant arrives at the clinical center for the first screening visit, the clinic coordinator or other staff member charged with explaining the study will describe the screening process, the schedule that is followed, the various measurements that are obtained, the forms to be completed by the participant, and the laboratory specimens to be collected. The participant will then be given a copy of the Screening Informed Consent Form to review, and the study staff member will answer any questions that arise. When any questions have been answered satisfactorily, the candidate will be asked to sign the form so that the screening process can begin. Participants will be furnished a copy of the signed form if they wish, and the original will be kept on file at the clinic.

Screening Compliance Measures

A strategy that has been adopted to increase the power of the study by excluding individuals who are likely to become non-compliant involves the collection of data during the screening period that will be used as a marker of potential compliance. Completion of a food frequency questionnaire (FFQ) and collection of adequate volume for a 24-hour urine sample will be used study-wide as predictors of compliance with the study regimens. The FFQ and a 24-hour urine kit will be dispensed to all those deemed to be eligible for participation following the second screening visit (SV2) with instructions to return completed materials at the scheduled third screening visit (SV3). Only those individuals who fully complete the FFQ and whose urine volume is judged to be adequate will remain eligible to be formally randomized into the trial. This compliance data will be recorded on the SV3 form and forwarded along with other eligibility data to the CC for entry, verification, and evaluation.

For those who fail the screening compliance tests but are still willing and eligible at SV3, each clinic will have the option of allowing the participant a second opportunity to meet the compliance criteria. Another FFQ and/or 24-hour urine kit will be dispensed to participants willing to try again and a new SV3 visit to assess compliance with that aspect of the protocol will be scheduled within 10-30 days. Only compliance data will be collected at this rescheduled visit. At that time, participants who remain non-compliant will be excluded from the trial.

RANDOMIZATION

The basic process by which TOHP participants receive their random assignment to an intervention or comparison group is standard and uniform for everyone. The preliminary steps and timing, however, vary according to what types of intervention are being offered at a given clinic. Those offering only lifestyle interventions proceed immediately to randomization, while those offering only supplements delay randomization until after the completion of a 4 to 8-week run-in period to test compliance with pill-taking and eliminate those who cannot comply adequately. Hybrid clinics utilize a preliminary allocation to one of these two tracks, after which randomization proceeds as at the single-track clinics. These procedures are detailed below.

1. Clinics Testing Lifestyle Interventions Only

Following SV3, clinic personnel will determine the provisional eligibility status of each participant and, for those judged to be eligible, provide them with a 24-hour urine kit and schedule a status review visit (SRV) between 10 and 60 days later for those judged to be eligible. All information necessary to assess eligibility will be sent to the CC for review and verification prior to formal randomization. Within five working days of receipt of SV3 data (BP measurements, compliance information, and blood work), the CC will enter, verify and validate the information, and determine continued eligibility. The CC will then provide the clinic a report of the status of each candidate seen at SV3. This status report will specify if the participant is eligible or ineligible, or whether eligibility is unclear due to incomplete, inconsistent or invalid information. Ineligible participants will be thanked for their collaboration and informed that their upcoming visit has been cancelled. For those whose status is ambivalent due to insufficient or invalid data, the clinic will take measures to clarify the problem and, if necessary, schedule a clarification visit with the participant.

Eligible participants will be contacted by phone or postcard approximately 3-5 days in advance of their scheduled status review visit as a reminder of their appointment and the need to return their 24-hour urine collection. After the participant has arrived for the status review visit, clinic personnel will call the CC to obtain a randomization assignment. Before obtaining this assignment, clinics involved in the weight loss intervention will first inform the CC of the weight stratum of the participant. In addition, in the event that several assignments are requested at the same time, the clinic should request them in the order of the participants' study ID numbers.

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 only in the event that it is not possible to make telephone contact with the CC during the visit. Each clinic will be provided with a series of sealed envelopes in numerical order, each containing an intervention assignment. In the case of clinics involved in the weight loss intervention, two sets of envelopes will be provided, one for each

weight stratum. The numbers on these envelopes correspond to those on the randomization log maintained at the CC. If more than one participant is to be randomized at the same time, the clinic will arrange a listing of these subjects, first by weight stratum, if applicable, and then by ID order. The envelopes will then be opened in this order and the assignment communicated to each subject. Otherwise, randomization assignments are given in the order of the participants' appointments. Whenever a random assignment is made, the envelope, sealed (if the clinic staff obtained the subject's assignment from the CC) or unsealed (if the CC staff was unavailable), will be returned to the CC as confirmation of the randomization process. As further confirmation, the clinic will call the CC as soon as possible (usually the next working day) to report each intervention assignment made using the back-up system.

Once the assignment has been communicated to the participant, he or she is 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 target goal is to have all lifestyle participants attend their first intervention group meeting within 30 days of randomization. Any individual who fails to appear for his or her status review visit may be rescheduled for a new status review visit at the discretion of the clinic staff, as long as the visit is within 60 days of SV3.

2. Clinics Testing Supplements Only

At the conclusion of SV3, participants who are deemed provisionally eligible to continue in the trial will be given run-in calendar packs and a 24-hour urine kit and scheduled for a status review visit in four to eight weeks (28 to 56 days). All information necessary to assess eligibility will be sent to the CC for review and verification, and the CC will determine eligibility within 5 working days of receipt of SV3 data and send an eligibility status report to the clinic. The clinic will inform participants to discontinue their pills if their status is reported as ineligibile and will take measures to clarify information if the CC reports an ambivalent status. Approximately 3-5 days in advance of their scheduled status review visit, eligible participants will be contacted to remind them of their appointment and instructed to bring their 24-hour

urine collection and all their calendar packs to the upcoming visit. At the status review visit, clinic personnel will assess pill compliance by calculating the total number of days since the last visit (SV3) and the number of pills taken (by pill count) and determine if the participant is eligible for randomization. Only participants who have taken 2/3 of their pills will be included in the trial. Compliance information will be recorded on the status review form.

Each clinic will have the option of "rerunning" participants who have failed to meet the run-in compliance test but are still willing to continue. Those whose run-in is extended will be given additional calendar packs and asked to return in about 6 weeks. At that time, compliance will be assessed again; participants demonstrating poor compliance or a desire to discontinue will be excluded from the trial.

For participants who successfully complete the run-in compliance test, randomization will proceed as described above, by phone contact between clinic and CC and envelope back-up system if contact is not possible. The sealed or unsealed envelope corresponding to the assignment will be forwarded to the CC along with the status review form. At the conclusion of the visit, randomized participants will be given their assigned intervention pills. To ensure that blindness is maintained, all supplements assignments and pill identification will be by code.

3. Clinics Offering Both Lifestyle and Supplements Interventions

Participants who are deemed provisionally eligible at the conclusion of SV3 will at that time be assigned, using a random procedure, to either the lifestyle or supplements track. This assignment is determined using a system of sealed envelopes, opened in numerical order, as described above. No direct contact with the CC is required for preliminary allocation. In this manner, participants will be told at the earliest possible moment which general type of intervention they may receive. Those assigned to the lifestyle track and willing to continue will proceed, as for other lifestyle participants, to a status review visit within 10 to 60 days later. Those assigned to the supplements track who are willing to continue will proceed, as for other supplements participants, to complete the run-in phase.

FOLLOW-UP SCHEDULE

Baseline and follow-up data, other than intervention-specific data, will be collected uniformly from all trial participants regardless of treatment assignment. Since adherence to the intervention regimens in TOHP may be problematic for participants, it is essential to collect data to assess compliance in the active intervention groups (monitoring drop-outs). On the other hand, since all of these non-pharmacologic interventions are readily available to the general public, it is equally important to assess dietary and other lifestyle changes in the comparison groups (monitoring drop-ins). For all participants, therefore, compliance means not only following any active regimen that may be assigned; it also means avoiding any alterations in dietary or exercise habits, for example, that are not part of the allocated program.

The data collection schedules for the lifestyle and the supplements interventions are outlined in Tables 2 and 3, respectively. The total duration of Phase 1B is 36 months, which includes a 12-month recruitment and enrollment period as well as a 6-month close-out period. Therefore, for the lifestyle interventions, the duration of follow-up will range from 18-27 months, with an average of 22 months. For the supplements interventions, the total study period will be divided into two sequential testing phases with a 3-month wash-out period in between. Total follow-up for each sequence will be six months.

All clinics will screen potential participants at three visits (10-30 days apart) to determine eligibility, to eliminate the obvious non-compliers, and to obtain baseline values for variables such as BP and weight. For the supplements interventions, there will be a run-in period and a visit approximately four to eight weeks after SV3 to assess compliance with the pill-taking regimen prior to randomization. In addition, those clinics testing supplements will conduct three visits to re-establish eligibility at the beginning of Stage 2.

Follow-up data will be collected for the lifestyle interventions at 3, 6, 12, and 18 months post-randomization, with a set of 9 BP readings taken over three clinic visits at both 12 and 18 months. Termination data will be collected at three visits (7-30 days apart) at the end of the study period unless this falls within three months of the 18-month visit. For the supplements interventions, follow-up data will be collected at 3 and 6 months post-randomization during each of the two testing sequences. Termination data will be collected at 3

visits (7-30 days apart) at the conclusion of each sequence, beginning approximately two weeks before the 6-month visit for that sequence. The trial-wide data to be collected are described briefly below.

1. Random Zero Blood Pressure (BP) Measurements

   Three BP measurements will be taken at each visit except SRV and FO8. Both baseline and termination BP values will be based on nine readings taken over the course of 3 visits.

2. Pulse Rate

   As part of the BP protocol, 30-second pulse rate will be recorded. This variable is also of interest as a predictor of subsequent development of hypertension.

3. Body Height and Weight Measurements

   Height and weight will be measured at the first screening visit so that body mass index can be calculated. Thereafter, weight only will be measured at SV3 and each follow-up visit <u>except</u> 1) FO8 which is the randomization visit for Stage 2 of Supplements, and 2) at F20 and F21. Baseline weight will be recorded at the third screening visit (SV3), and termination weight at the first termination visit (TV1).

4. Medical History

   Medical history data (including information on smoking, drug and alcohol use, etc.) will be used to determine eligibility during screening, and thereafter to monitor for adverse effects and to assess the possible confounding effects of changes in variables such as smoking habits and medication use.

5. Physical Activity Questionnaire

   Physical activity may also influence BP or response to intervention, and changes in this variable will also be assessed. The Physical Activity

Questionnaire contains information on both work and leisure physical activity.

6. General Well Being Scale, Lazarus' Hassles Scale, Multidimensional Health Locus of Control Scale, and Treatment Evaluation Scale

These instruments will be used to assess comparability among groups at baseline and to assess any changes in response to the interventions. The General Well Being Scale measures overall attitudes and quality of life; the Hassles Scale assesses the frequency and intensity of "hassles" or irritants ranging from minor annoyances to fairly major problems; the Multidimensional Health Locus of Control Scale assesses the extent to which participants perceive that their behavior influences their health; and the Treatment Evaluation Scale assesses treatment credibility and efficacy as well as outcome expectancy. All these forms will be administered study-wide except the Treatment Evaluation Scale, which will be administered to all subjects except those in the lifestyle interventions comparison group.

7. Demographic Information and Participant Contact Information

The demographic data will be used in the analyses for stratification purposes. The participant contact information will be used exclusively by the clinics and will be updated at mid-trial.

8. Food Frequency and 24-Hour Diet Recall Data

Dietary data will be used to characterize baseline intake and to assess dietary change over time. In addition, diet recall data may be used by the interventionists to provide feedback to participants in the dietary intervention groups. Completion of the food frequency questionnaire during screening will serve as a behavioral compliance measure at all clinics for eligibility purposes.

9. Blood and Urine Samples

Blood samples collected during screening will be split so that eligibility tests (serum creatinine, potassium, calcium, cholesterol, and glucose) can

be performed at a local laboratory and baseline measurements can be determined at a central laboratory. Blood samples collected during follow-up will be used primarily for compliance assessment and safety monitoring.

A 24-hour urine sample will be collected at each of the SV3 and the status review visits. The first of these will be used as a behavioral compliance measure. Both samples will be analyzed at a central laboratory for baseline values. At lifestyles clinics testing the sodium reduction intervention, the baseline 24-hour urine samples will collect the overnight and daytime samples separately. 24-hour urine samples collected during follow-up will be used to assess compliance with the assigned interventions and to provide descriptive indices of mean intakes of the nutrients of interest. 24-hour urine samples will be collected at 6, 12, and 18 months for the lifestyle participants (F02, F09 and F16). For supplements participants 24-hour urine samples will be obtained at the beginning of Stage 2 and at 3 and 6 months post randomization in both Stages 1 and 2 (F01, F02, F07, F12, F13).

Blood and urine tests for the lifestyles and supplements interventions are summarized in Tables 4 and 5, respectively.

10. Pill Count

As a compliance measure in the supplements interventions and their comparison groups, all participants will be asked to bring their calendar packs to all follow-up visits so that the number of pills taken since the previous data collection visit can be determined and recorded by study personnel.

Intervention-specific data to be collected at baseline and follow-up visits (e.g., skinfold/circumference measurements and physical fitness testing) are included in the following chapter on intervention methods.

INTERVENTION METHODS

From an operational viewpoint, there are four major intervention groups in TOHP: sodium reduction, weight reduction/exercise, stress management, and the

supplements. All of the intervention groups will use a case-management approach in which each participant will be assigned to a specific interventionist. The interventionist will be responsible for monitoring the participant's progress in achieving the study objectives and for initiating appropriate actions when problems arise.

The objectives and intervention strategies for each of the intervention groups are briefly described below.

Sodium Reduction

1. Objective

The objective for participants randomized into the low sodium group is to maintain an eating style that does not exceed 1400 mg (60 mEq) sodium daily over a two-year period. The goal for the group is to achieve a mean of 1800 mg (80 mEq) sodium daily based on urinary excretion data.

2. Approach

The low sodium intervention protocol designed for TOHP is unique in that its design is based on a specific behavioral analysis related to achieving a 1400 mg (60 mEq) sodium diet over an extended period of time in a non-hypertensive population. The long-term maintenance tasks are central to the overall intervention because long-term sodium restriction is difficult and lacks some of the more obvious immediate and intrinsic reinforcers that characterize other lifestyle changes, such as evidence of weight loss. The major emphasis will be on demonstration that low sodium foods can be tasty, fun (if not easy) to prepare, and part of enjoying good times with friends and family. Health consequences that are 'invisible' to the at-risk individual will be made more salient by providing urine sodium feedback and relating this to the probability that high BP can be prevented.

The purpose of each session will be to build fundamental behavioral skills and motivation to monitor and modify diet. Motivation is viewed as a function of three cognitive appraisal processes: health efficacy perceptions, self-efficacy judgement, and outcome expectancies. Health

efficacy refers to the perception that altering one's sodium intake will affect health. Participants must understand that there is a relationship between dietary sodium intake and BP, and between high BP and disease risk. Self-efficacy is the perception that one is capable of making the behavioral changes that the program requires. The initial message will be that "a few simple changes can make a big difference" and that "some change is better than no change." Thus, the program will be structured in terms of small incremental steps rather than overly ambitious ones. Outcome expectancies are the perceived benefits and costs of participating in the program. It is important that people perceive immediate as well as long-term benefits, since research has shown that emphasizing immediate benefits is likely to be more effective in controlling behavior than stressing the avoidance of long-term negative consequences. In addition to enjoying the new food and reducing one's health risk, the personal satisfaction of participating in a scientific project with the potential to benefit humanity will be emphasized. Negative consequences (costs) of the program will be acknowledged, but they will be presented as challenges to stimulate creative problem-solving.

3. The Intervention Program

The intervention program consists of three phases: intensive, transition, and maintenance. During the initial 10-week intensive intervention phase, participants will be guided through a behavioral change process using a group approach, supplemented with individual counseling and supported by self-directed and self-monitored learning activities.

The intensive intervention phase will consist of nine sessions as follows: an individual counseling session following randomization; and another scheduled approximately after group session 5 or 6; as well as eight group meetings. At the end of each session, participants will have a specific behavioral task (associated with a short-term sodium intake reduction goal) that he or she will complete prior to the next meeting. An outline of the content of the intensive intervention program sessions is shown in Table 6. Incremental dietary sodium reduction from the individual's base-line will be accomplished along a defined gradient so that participants will be below or within 10% of goal level by group session 5, assuming a

baseline sodium intake of 6000 mg per day or less. The emphasis from sessions 5 through session 7 (a four-week period) will be on the maintenance of the new dietary pattern.

The transition phase is viewed as a critical period wherein special supports will be offered to help participants maintain behaviors that are still relatively new to them. Subsequently, during the maintenance phase, participants will be seen in conjunction with the scheduled TOHP data collection visits, within the strict constraints of maintaining separation of data collection and intervention activities. They will also be invited to participate in quarterly group sessions. An individualized schedule of telephone or face-to-face contacts will be arranged according to the participant's degree of success with the low sodium lifestyle. Follow-up during the maintenance phase will be guided by a defined protocol for problem diagnosis and resolution. The schedule of individual and group contacts for the intensive, transition, and maintenance phases are outlined in Table 7.

4. Measures to Assess and Enhance Compliance

Food records will be collected to facilitate behavioral change and to promote learning about the sodium content of foods. Participants will be asked to complete a three-day record before group session 1, a seven-day record for each of the first four weeks of the intervention, and abbreviated records (food sodium scoring sheets) every other day between sessions 5 and 7.

Urine sodium values will be used to provide feedback to both participants and interventionists regarding the degree of success in achieving sodium reduction (see Table 8). Group compliance will be assessed during follow-up based on single overnight or 24-hour urine specimens. In addition, at 3 months, participants will receive data on their individual success in reducing their sodium intake to 1400 mg (60 mEq) (goal level). Participants will be classified as either full-compliers, partial-compliers, or non-compliers (with cutpoints being 13.2 and 25.9 mEq sodium) based on the average of three overnight urines collected at 8, 10 and 12 weeks. The misclassification rates associated with this classification system are shown in the table below.

		Classification		
		free	partial	full
		A	B	C
true group	A free living	0.900	0.084	0.016
	B partial	0.057	0.743	0.200
	C full	0.000	0.300	0.700

It should be noted that misclassification rates are greatest for the partial-compliers (26%) and that the direction of the misclassification is such that they will most frequently be categorized as full compliers rather than free-living individuals.

Weight Reduction

1. Objective

The objective for individuals randomized to the weight loss regimen is a 10-pound weight loss or achievement of their ideal body weight at 18 months. The goal for the group is to achieve a mean weight loss of 10 pounds at 18 months.

2. Approach

The focus of the intervention is on helping participants to develop new eating and exercise habits that they will be able to maintain comfortably for the rest of their lives. Therefore, the emphasis will be on behavioral changes in daily habits.

The nutrition component of the intervention will focus on a steady progression toward a reduced calorie eating style. Overall calories will be reduced to a level low enough to maintain the target weight of the individual (defined in terms of body mass index). Subjects will use a calorie-counting technique. In the eighth week, a food exchange system, will be introduced. Those subjects who have been successful using calorie counting will be urged to continue and those who have had difficulty with

this approach will be encouraged to adopt the alternate food exchange approach. The exercise component of the intervention will consist of sustained, moderate exercise. This is the most appropriate level of exercise for participants in a weight loss program based on the relationship of exercise to weight loss, long-term subject adherence, and safety. Participants will be encouraged to gradually increase the number of days and duration of exercise until they reach the long-term goal of exercising 4 to 5 times per week for 30 to 45 minutes per exercise session at an intensity of 40-55 percent of heart rate reserve.

3. The Intervention Program

The weight loss/exercise program will have a 3-month intensive intervention phase followed by a maintenance phase and will be primarily group-based. During group meetings, the nutritionist will present information on basic nutrition and focus on ways of reducing total calories. Reduction in fat, sugar, and alcohol will be emphasized as they are the primary sources of extra calories for most Americans. It will be recommended that participants make a series of small progressive changes toward the goal. Weight reduction efforts will be supported by a moderate exercise program.

During the intensive intervention phase, subjects will attend weekly group meetings for 3 months (14 sessions). These 90-minute meetings will be led by two staff members. The groups will consist of about 10 subjects plus support people invited by the subjects. Each session will consist of at least four components including nutrition, exercise, behavioral self-management, and social support. At the midpoint of each intervention session, the group will be divided into two small groups for intensive review of each person's progress and plans for the next week. Subjects will display their weight change/exercise graph and discuss their self-management efforts for the past week. Leaders will guide the discussion toward individual problem-solving and developing specific and detailed action plans, and the small group meetings will end with each subject describing their behavioral goals and action plans for the next week. Initially, participants will be asked to begin exercising moderately 2-3 times per week, and supervised exercise sessions will begin at the third group meeting. An outline of the intensive intervention sessions is shown in Table 9.

After completing the intensive phase, subjects will be asked to attend monthly meetings for the remainder of the intervention period. During this maintenance phase, several initial intervention groups will be combined into two follow-up groups, each of which will meet monthly. Subjects will be given the option of attending one or both of the monthly follow-up meetings. The format of the maintenance meetings will be similar to the initial intervention meetings. These meetings will feature formal presentations and group discussions on selected nutritional and behavioral change topics as well as small group meetings at every session. Attendance will be encouraged by the addition of special events such as cooking demonstrations and special dinners.

Relapse prevention will be particularly important during the maintenance phase. Subjects will prepare for potential relapse situations by:

a. Identifying difficult situations in which relapse is likely to occur;

b. Developing a reasonable coping strategy and alternative behavior; and

c. Practicing the alternative behavior in response to a simulation of the trigger situation.

4. Measures to Assess and Enhance Compliance

Subjects will keep food diaries as an essential component of the weight loss/exercise regimen. The food diary assignment in the first week will be two days of diaries increasing to five or more days per week by the fourth week of intervention. To increase adherence to the food diary protocol, subjects' food diaries will be reviewed by group leaders and returned with comments at the next meeting.

Each subject will be weighed privately before each session by a staff member. Records of weight change and exercise will be kept in the form of a graph with weight plotted in terms of change from baseline and exercise plotted as a bar graph in terms of minutes of exercise per day. Subjects will also be given feedback on their level of fitness based on a sub-maximal exercise test which will be administered at baseline, at the

end of the active intervention phase (when the amount of weight loss is anticipated to be maximal), and at termination of the study.

Stress Management

1. Objectives

The overall objective of the TOHP stress management program is to reduce the stress level in its participants. Individual goals include achieving formal relaxation (7 minutes or more) at least four times per week, as well as attendance at a minimum of 8 out of 10 of the initial weekly sessions and a minimum of 15 out of 20 of the first year's sessions. It is also expected that individuals will be rated at 2 or lower on the 10-point Behavioral Relaxation Rating Scale (one is completely relaxed) by interventionists. Group objectives will be a minimum of 70% of the individuals formally relaxing at the level described above, 70% of the individuals attending 8 of 10 of the initial weekly sessions, a minimum of 65% attending 15 of 20 of the first year's sessions, and a minimum of 70% of the individuals rated by interventionists at 2 or lower on the 10-point Behavioral Relaxation Scale.

2. Approach

Both cultural and individual factors are involved in the development and maintenance of excessive stress levels. Generally, current cultural values define stress as a loss of emotional control through the experience of very intense anger, anxiety, frustration, or grief. By defining only excessive intensity levels as "stress" (rather than "challenge", etc.), individuals are discouraged from intervening on less intense, more frequently occurring stress signs that might be used as a signal to initiate preventive strategies. In addition, excessive stress levels are generally interpreted as either good and necessary for achievement, or not good but unavoidable, so that the only available coping strategy is endurance. These culturally influenced definitions and interpretations tend to desensitize people to the significance of changes in their stress signs and undermine belief in the possibility and benefit of change. In addition to the cultural factors described above, a number of individual variables can come into play as well, including excessive autonomic

arousal and the possibly related dimension of excessive autonomic reactivity, stressful situations, and the individual's way of thinking about the events in his or her life. The TOHP stress management intervention assumes that all of the cultural and individual factors described above may contribute to excessive stress levels and all of them need to be addressed in a comprehensive and effective program.

3. The Intervention Program

Achieving adherence with any behavioral intervention to lower BP in a normotensive population is likely to be a challenge. A variety of strategies to enhance adherence have therefore been built into the protocol. The program has been designed with a variety of topics to maintain interest. For example, a number of stress management strategies will be presented, and personalization of the methods will be encouraged. Furthermore, the group experience produces accelerated learning and engenders enthusiasm through exposure to fellow members' discoveries and achievements. To encourage attendance, periodic "symbolic" awards and incentives will be provided. Finally, in stress management, the lifestyle change process is intrinsically rewarding; participants learn to be more relaxed, comfortable, and have more influence over their reactions and events in their own lives.

The intervention is primarily group-oriented and consists of 23 sessions. The initial eight sessions are weekly, followed by four biweekly, eight monthly, and three bimonthly sessions. There are two components to this program: (a) interventions to increase awareness of stress level indicators (physical sensations, thoughts, feelings, images, activities), and (b) interventions to lower stress level. An outline of the intervention sessions is shown in Table 10.

The first task of intervention is to build awareness in individuals of event-to-event changes in their stress indicators. This will be accomplished by presentation of case examples, group discussion of participants' experiences, and daily self-monitoring. Following the development of this increased awareness of changes in stress indicators, participants will be encouraged to discover the connections between

changes in their stress signs and related patterns of events and cognitions using the same techniques.

As individuals become aware of how stressful events and stress responses are linked, intervention will focus on training in various components of stress level reduction. A key component will involve training in a variety of relaxation methods, which will increase the likelihood that all participants will find a method they can employ successfully and enjoy. While the variety helps maintain participant interest, all of the methods are variations on the same theme of staying more relaxed and comfortable throughout the day. Relaxation training can influence a number of the contributors to excessive stress levels by reducing excessive autonomic arousal and reactivity, as well as increasing sensitivity to changes in stress indicators. A second component will involve training in methods of managing reactions to stressful situations. This component is similar to anger and anxiety management training and focuses on rehearsing staying calm and relaxed in stressful situations. A third component will involve training in methods of altering cognitive contributions to stress. Finally, the fourth component will involve training in methods of managing stressful situations, focusing on methods of communication, assertiveness, and time management.

4. Measures to Assess Compliance

The TOHP stress management program will have two types of process measures to assess compliance with the intervention program: measures of dose-related activities and measures of intermediate response. The primary measure of dose (i.e., exposure to the intervention) will be increases in the Stress Management Activities Scale. An example of an item from this instrument is: "In the last seven days, I relaxed formally for 7 minutes or more on (0 1 2 3 4 5 6 7) days." Other measures of dose will include measures of intervention attendance and interventionist ratings of participation. The primary measure of intermediate response will be reductions in scores on Lazarus' Hassles Scale. Other measures will include ratings of depth of relaxation and, possibly, changes in cardiovascular reactivity and/or urinary free cortisol and catecholamines.

Lifestyle Control Group

Participants in the lifestyle control group are unblinded - that is, they know that others are receiving various active interventions and that they are not. Two serious problems may result from this situation. The first is that participants may adopt the lifestyle changes assigned to individuals in one or more of the active intervention groups (drop-ins to the intervention). On the other hand, they may lose interest in the trial because they believe that there is no benefit to be gained from their involvement, and they may not wish to return to the clinical center for the follow-up data collection visits (drop-outs). The "intervention" protocol for the lifestyle control group has been designed to deal with these problems.

1. Objective

The objective for those randomized into the lifestyle control group is maintenance, with no modification, of the lifestyle led before enrollment in the trial.

2. Approach

The approach to the lifestyle control participants is to be straightforward and honest at all times. Individuals randomized to the comparison group will be told that we are asking them to maintain the eating habits and other activities to which they are accustomed. They should also be informed that only by comparing changes in BP between those in the active weight loss, sodium restriction, and stress management programs and those in the comparison group can we learn whether the interventions are effective.

As health questions arise, particularly those pertaining to the benefits of any of the active interventions, a TOHP staff member assigned to be the case manager for the control subjects should answer the questions. In giving such explanations, it should be pointed out that the lifestyle changes in question have not been proven to be effective for people in the upper-normal range of BPs, and that it is the objective of TOHP to determine whether this is, in fact, the case.

If at any time a participant should express a desire to attempt a lifestyle change, such as losing weight, the TOHP staff involved should reiterate that the purpose of the comparison group is to permit observation of BP levels in individuals not undergoing any lifestyle changes, and that TOHP would not be able to support them in such an effort. They should be requested to forego such lifestyle changes temporarily, if possible, for the duration of the study.

Although the approach recomended here will not guarantee that lifestyle control subjects will refrain from attempting lifestyle changes, it should be effective in keeping the conscientious participant from actively pursuing such changes. Even if a lifestyle change is initiated, the probability is that such an attempt will be only transient and that the old eating habits or other behaviours will return over time.

3. The Intervention

The intervention for the lifestyle control group is, ideally, to maintain the status quo. TOHP is organized so that all participants in this group will serve as controls for all lifestyle interventions at a particular clinical center. For example, if a center is offering stress management and sodium restriction, then the lifestyle control group at that center would provide comparisons for both interventions and undergo all intervention-specific protocols pertinent to those interventions. The one exception is that for comparisons involving the weight loss intervention, the controls will be drawn from individuals at the clinical center who, like those randomized to that intervention, are in the high weight stratum.

4. Measures to Enhance Compliance

Achieving and maintaining high compliance with the follow-up visit schedule among individuals in the lifestyle control group poses a challenge because those participants are receiving no active intervention. Three strategies will be used in an attempt to maximize participation. The first is making participants aware of the benefits that they are receiving from their involvement in TOHP, including regular monitoring of their BP, which will provide early identification of the approach or onset

of hypertension. If they should develop high BP, this monitoring will permit them to receive immediate treatment, if necessary. In addition, the study data may be made available as a health information profile to the participant and his/her physician at the end of the trial. This profile could include measures of sodium intake, BPs over the two years of the study and, depending on the active interventions for which they were controls, data on cardiovascular fitness and reactivity. Participants should be told that this information may be helpful to their personal physicians in assessing whether they might benefit from continued BP monitoring or other preventive medicine procedures.

The second strategy to enhance compliance in the lifestyle control group is to emphasize the fact that all TOHP participants are making an important contribution to the public health by helping find ways to prevent and control high BP. This cannot be overemphasized, as it may be the major factor in the continued participation of many individuals in this group. Such individuals should be reminded that with their help, this trial is attempting to identify ways to prevent the onset of the major risk factor for heart disease and stroke, two conditions which together account for almost half of all deaths in the United States each year.

The final approach to maintaining high attendance and compliance among the lifestyle control group involves making clinic visits as convenient, brief, and comfortable as possible. The responsibility for accomplishing this objective rests on the data collectors and the case managers at the clinic. In addition to administering the required protocols, data collection personnel must work efficiently and maintain friendly interactions with the participants. They must also make every effort to remain blinded to the intervention in which a participant is involved so that possible biases can be minimized. It is essential that the data collectors should not answer health questions that arise during the course of the study. Instead, a nurse or other health professional who is not involved in data collection should be made available to answer any such questions as they arise.

The case manager will function as a link between the study staff and each TOHP participant. The establishment of rapport between the case manager and the lifestyle controls is particularly crucial because such

participants will not have frequent contact with an interventionist or intervention group members. The case manager will make all appointments, check the participant in and out of the clinic, and answer questions about the study that arise. Ideally, this position should be held by a nurse or other health professional. The case manager may wish to keep an updated index card on each lifestyle control, including any problems a participant may be having with the study, the most convenient times for clinic visits, as well as some personal facts and a photograph of that individual to permit personalized interactions. This information should facilitate the development of a positive relationship between each individual in the lifestyle control group and his or her case manager. For example, the personal information on the index card, which should include notes about that individual's hobbies, recent vacations, family members, etc., may be used as a source for informal conversations during the check-in or check-out process. The individual attention that such interactions provide will serve to convey to the participants in the lifestyle control groups that someone on the study staff cares and appreciates his or her participation. Other trials have found that such an approach was extremely effective in maintaining high compliance with scheduled visits. This method, coupled with the benefits of regular BP monitoring, the availability of detailed health information, and the contribution of participants to the public health, should maximize motivation and compliance in the lifestyle comparison group.

Supplements

The supplements to be tested in TOHP include calcium, magnesium, potassium, and fish oil (the only agent for which an Investigational New Drug approval is necessary). For subjects in the supplements arm of the trial, the total study period will be divided into two sequential phases of six months duration interrupted by a three-month wash-out period during which subjects will be maintained on placebos of their assigned Stage 1 agent. A set of entry and termination BP measurements will be obtained for each of the active intervention phases. Calcium and magnesium will be tested during Stage 1. Participants will be randomized to one of four regimens: calcium, magnesium or their respective placebos. Since the placebo controls are shared (i.e., the same group of controls serves as the comparison series for both the active calcium and the active magnesium groups), approximately half of those randomized to the control

group will receive placebo calcium and the other half will receive placebo magnesium. For Stage 2, participants who are still willing and eligible to continue will be randomly assigned to either fish oil, potassium, or their respective placebos. As with Stage 1, the placebo controls will be shared.

1. Dosages

The dosages selected for calcium, magnesium and potassium represent an approximate doubling of usual dietary intake in Western countries. The dose of fish oil is equivalent to that which would be obtained by ingesting approximately a half pound of salmon per day and is consistent with a level of supplementation that could be achieved by diet. The specific dosages and number of daily pills required for each of the supplements are as presented in Table 11.

All supplements will be administered in two doses per day, taken in the morning and evening, as this schedule is more convenient for participants than more frequent administration and thus more likely to enhance compliance. For calcium, magnesium, and fish oil, the pills will be divided into two equal doses. For potassium, participants will be instructed to take two pills in the morning and one in the evening to minimize the likelihood of esophageal irritation. A missed morning dose can be made up in the evening, and a missed evening dose can be made up the following morning; however, participants should never take more than a full daily dose at one time.

2. Run-In

In addition to the behavioral compliance measures that have been described previously, there will be a pre-randomization run-in period for the supplements arm of the trial. The purpose of the run-in is to allow individuals likely to become non-compliant to the study regimens to be eliminated prior to randomization. During the run-in, potential participants will have an opportunity to try a pill-taking regimen similar to that which will be required during the active intervention phases. This strategy has particular applicability to the supplements arm of TOHP, since the use of placebo control and the lack of major side-effects associated with any of the supplements make it possible to test the exact intervention regimen

(i.e., pill taking) prior to randomization without contaminating the study groups.

Magnesium placebo capsules (six per day) will be used for the run-in. Magnesium placebos were chosen because they are relatively large and six is the maximum number of pills per day which a participant will be required to take in either the first or second testing periods. Thus, it is anticipated that participants able to comply with this pill-taking regimen will also be able to comply with any of the other supplement regimens involving fewer numbers and smaller capsules or tablets.

3. Clinic Procedures

All participants randomized to the supplements arm of the trial will be assigned to a specific health counselor who will see them individually at each intervention visit and who will be responsible for tracking their progress in achieving the study objectives. The nature of the counseling sessions will be tailored to the individual and could include specific instruction regarding the administration of the supplements, positive reinforcement, motivational talks, videotapes and discussion of suspected side-effects.

Termination data for Stage 1 will be collected at three visits (7-30 days apart) scheduled at the conclusion of Stage 1 and beginning with the 6-month follow-up visit. In addition to study-wide termination measurements, participants will be asked whether they thought they were taking active or placebo pills. At the final termination visit, calendar packs will be collected and new cards will be dispensed to each subject for pill-taking during the wash-out period. These cards will contain placebo components of the participant's Stage 1 assignment. A follow-up appointment will be scheduled in approximately three months for the collection of eligibility information for Stage 2.

Eligibility on BP for Stage 2 will be re-evaluated at three eligibility visits scheduled 7-30 days apart at the conclusion of the wash-out period. At each of the visits, DBP will be determined as an average of all BPs obtained up to that time at the eligibility visits (three per visit) with the average falling within specified ranges. New baseline data will also

be collected at these visits. There will be some participants who no longer satisfy the original BP eligibility criteria for entry into the trial, or who might have other reasons for disqualifaction, such as non-compliance or use of BP-lowering medications. However, participation in Stage 2 will be available to all Stage 1 participants, as part of the original understanding at the time of signing the informed consent. Randomization at entry into the Stage 2 will be stratified as follows: a stratum for those meeting the qualifications as described in the protocol, a stratum for those whose BPs are now too low to meet the original criteria, and a stratum for those with any other reason for disqualification. The analyses will exclude the latter two groups, except for descriptive purposes. Participants who are willing will be randomized to either fish oil, potassium or their respective placebos at a randomization visit scheduled within 10 days of the final eligibility visit. Randomization will proceed as for other treatment arms of the trial.

Termination data for Stage 2 will be collected at 3 visits (10 days apart) scheduled at the conclusion of Stage 2 and beginning with the 6-month follow-up visit.

The schedule of follow-up visits and data collection for the supplements interventions is shown in Table 3.

4. Measures to Enhance Compliance

The following measures will be taken to enhance pill compliance:

a. Pills will be packaged in convenient calendar packs.

b. Individual instruction regarding administration of the supplements, positive reinforcement, and/or discussion of suspected side effects and what to do about them will be provided by the participant's health counselor, preferably a nurse with experience in reinforcing medication compliance among patients.

c. Calendar packs will be dispensed in such a manner that the participant will have a sufficient supply of pills to last from one follow-up

visit to the next. An additional card will be dispensed at the beginning of each phase to serve as a reserve pack in case a visit is missed or a card lost.

d. At the beginning of the trial each participant will be provided with a set of study guidelines as an aid to compliance. The guidelines will cover such topics as what to do if calendar cards are lost, how and when to take the supplements, what multivitamins and supplements to avoid, and what to do if suspicious of side-effects.

5. Side Effects

Because of the benign nature of the supplement interventions, we expect a low incidence of side effects attributable to the study pills, although they will be monitored at the follow-up visits. The major potential concern in this regard is the possibility of bleeding problems among individuals assigned to fish oil. Specific procedures pertaining to safety monitoring of the fish oil component are described below.

At each follow-up session a health counselor will discuss with the participant any reported side-effects attributed to the pills. When necessary, the participant will be referred to a licensed physician on the clinic staff who will respond to each individual case using his or her best clinical judgment. In general, participants will be advised to seek medical attention from their own physician as needed and may alter their participation in the light of such counsel. Every effort will be made to maximize compliance consistent with the health and welfare of the participant.

The following procedures have been adopted to monitor the safety of those taking fish oil supplements.

a. Prior to Stage 2, individuals with a bleeding history will be identified based upon responses to the Supplements Form administered at SV3, SRV, 6 weeks, 13 weeks, and 26 weeks and reviewed by a clinic physician. Those individuals identified by the clinic physician as having a potential bleeding disorder based upon responses to the follow-up forms, will be asked to undergo evaluatory tests for

bleeding time, platelet count and VWF level for possible exclusion from Stage 2 based upon a history of recurrent abnormal bleeding.

b. Individuals identified by the clinic physician as having a potential bleeding disorder, who do not wish to submit themselves to testing, will be excluded from Stage 2.

c. During Stage 2, individuals assigned to the fish oil component who develop a bleeding history based upon responses to the Supplements form administered at 6 weeks and 13 weeks of Stage 2 or other self-reports will have their case reviewed by a clinic physician. If in the judgement of the physician it is clinically warranted, the individual will be asked to undergo tests immediately to evaluate the bleeding problem. Participants will be asked to discontinue their pills for the duration of the trial if, in the opinion of the clinic physician, the tests reveal an abnormal bleeding problem or if the participant refuses to undergo the recommended evaluation procedures.

ASCERTAINMENT OF ENDPOINTS

Both primary and secondary outcomes for TOHP are determined from measurements and laboratory tests taken at follow-up visits; therefore, ascertainment of endpoints is relatively simple and straightforward. Outcome measurements will be made by data collectors blinded to the treatment assignment of participants and not involved in delivering any lifestyle 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, for which the sample size and power calculations were performed, is diastolic BP; a major secondary endpoint is

systolic BP. The main endpoint of interest is change in BP 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 taken throughout the follow-up period. 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. Procedures for obtaining final BP measurements for participants who terminate early from the trial are discussed later in this chapter.

The chief concern in studies having BP as an endpoint is the amount of variability inherent in obtaining BP levels, partly due to actual variation in an individual's BP, and partly due to errors and biases in its measurement. With respect to the former, BP varies constantly due to factors such as position, emotional state, recent physical activity, room temperature, and recent consumption of certain drugs. Sources of measurement error include observer bias due to knowledge of a subject's treatment status, incorrect cuff size, non-standardized measurement practices, and digit preference.

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. These procedures are discussed in detail in Chapters 8, 18 and 19 of the TOHP Manual of Operations. Training of observers will include a review of written and audiovisual materials on BP measurement and Korotkoff sounds, as well as practice sessions with double stethoscopes. After completion of training, which will also include becoming familiar with the TOHP protocol, each observer will be certified, and this certification will be renewed at six-month intervals to ensure that appropriate procedures are being followed.

1. Diastolic Blood Pressure

   DBP is defined as the disappearance or first absence of the fifth Korotkoff sound, <u>not</u> as the last sound heard.

2. Systolic Blood Pressure

SBP is defined as the appearance of the first Korotkoff sound.

3. Ascertainment of Final BP Measurements for Participants Who Terminate Early From the Trial

It will be crucial to obtain final BP measurements from those participants who terminate early from the trial. Of particular relevance in this regard will be subjects who become frankly hypertensive during the course of the trial and for whom antihypertensive medications may be recommended. Other subjects may move away from the study area and a few may simply refuse to continue their participation in the trial.

a. Development of Hypertension or Other Conditions for which Hypotensive Drugs May Be Prescribed

Some subjects may be told by a non-study physician that their BP is high and pharmacologic therapy may be recommended or, alternatively, BP readings by study staff may on occasion be in the hypertensive range. In order to obtain termination BPs on all participants prior to the initiation of BP medications or medications for other conditions which may lower BP, the following procedures have been developed.

In an attempt to prevent study participants from being put on antihypertensive medications by non-study physicians before a set of termination BPs are obtained, both participants and their identified personal physicians will be informed of the desirability of having a set of termination BP readings prior to initiating antihypertensive medications. Upon notification of the study staff of an elevated BP reading either by the participant or the treating physician, three very brief visits will be scheduled, at 10-day intervals if possible, to determine the true mean or "underlying" BP which will be promptly reported to the subject and the treating doctor. If the physician decides to treat with antihypertensive medications after knowing the underlying BP, the participant will be terminated from the study, and this set of readings will constitute the terminating BP. If the

physician decides that treatment is not needed, the participant will be continued in the study and this procedure can be repeated if the question of a need for drug treatment arises again.

Initiation of medications for reasons other than elevated BP may also result in BP lowering which may confound the effects of the study intervention. For this reason, participants and their private physicians will also be asked to inform study staff and consider agreeing to a set of termination BPs prior to starting a drug with hypotensive effects, if such a delay is consistent with good medical practice. Examples of such medications might be diuretics, beta-adrenergic blockers, calcium channel blockers, and other drugs with hypotensive effects which may be prescribed for a wide variety of medical conditions other than hypertension.

b. Participants Who Move Out of the Study Area

If a participant moves out of the study area beyond a distance that allows continued participation to be practical, every attempt should be made to obtain a set of termination BPs prior to the move. Those who know that they plan to move during the course of the study will be excluded from participation. However, participants should also be reminded during the course of the study to inform the study staff of an upcoming move as soon as possible so that the nine termination BPs can be obtained prior to the move. After obtaining these nine readings, if a participant in one of the supplements groups expresses a desire to continue on the supplements for the duration of the trial and agrees to travel back to the study center for the nine termination readings at the end of the study, continued participation can be tried. This seems less realistic for the lifestyle groups where ongoing contact with the study staff may be more important.

If a participant is moving to a location convenient to another TOHP clinical center, the option of transferring should be considered. Any such transfer should be coordinated by the CC with the full cooperation of both the old and new clinical centers. If the participant is willing and the new clinic offers the same intervention as the original center, it may be possible for that individual to

continue full participation in the trial. If not, the participant should be encouraged to attend the new clinic for scheduled data collection visits. Transfers who are in the supplements arm of the trial should be maintained on study pills without interruption, with a sufficient number of pill packs dispensed by the original center. Data from transfers will be stored and analyzed under the participant's original study ID number with the other data from the original clinical center.

Temporary absence from the study area for more than 3 months should be preceded, if possible, by obtaining the nine termination BPs. For example, a participant who plans to go to Florida for 3 months in the winter should have a set of termination BPs obtained prior to leaving. If the participant agrees to continue following his or her study program (both intervention and comparison groups) faithfully during this absence and plans to be back in the study area at least two months prior to scheduled termination, continued participation can be attempted. However, if the participant fails to return for subsequent BP measurements, then the set of measurements obtained prior to his/her departure will constitute the terminating BP.

Ascertainment of Secondary Endpoints Specific to Interventions

In addition to BP endpoints collected on all participants in the trial, there are also secondary endpoints specific to the interventions being tested. These endpoints will be assessed in participants enrolled in the active intervention group and their corresponding controls. The secondary endpoints to be used in each of the intervention groups are described briefly:

1. Sodium restriction

Secondary endpoints for the sodium-restricted group include urinary sodium excretion and measures of sodium intake as determined from food/nutrient data including food frequency questionnaires and 24-hour diet recalls. Of these measurements, urinary sodium excretion provides the most convincing data because it is not as subject to bias as is self-reported nutrient data. The schedule for collection of 24-hour and overnight urines for measurement of sodium excretion is as described in the sodium intervention

protocol and listed in Table 8 and that for food/nutrient data as described in the chapter on Follow-Up Schedule.

2. Weight reduction

The secondary endpoints for the weight reduction group include weight, fitness (based on predicted heart rate response during submaximal exercise testing), total and HDL-cholesterol, and skinfold and girth measurements. Weight is an important secondary endpoint as it is well established that weight reduction in overweight subjects with hypertension results in significant reductions in BP. Standardized procedures for weighing participants are detailed in Chapter 9 of the TOHP Manual of Operations and the schedule of measurements are as described in the protocol chapter on follow-up measurements.

A submaximal bicycle ergometer test will be used to determine predicted heart rate response, thus providing an objective measure of adherence to the exercise component of the weight loss/exercise regimen. This will be administered to all participants in the active intervention group, to a 80 to 90% sample of high weight controls and to a 20% sample of high weight individuals in all other active intervention groups at each clinic at baseline, at 3 months of follow-up, and at termination of the study. Standardized procedures for administration of this test are described in Chapter 11 of the TOHP Manual of Operations.

Skinfold thicknesses and body circumference measurements will also be used as secondary endpoints and obtained from the same groups as for the bicycle ergometer test. From these measurements, estimates of body fat content and ratios describing the distribution of body fat can be derived. The mid-biceps, mid-triceps, subscapular, and suprailiac skinfolds and the biceps, waist and hip circumferences will be measured. Assessments will be made initially at baseline, and changes will be assessed at the end of the active intervention phase (6 months) and at termination of the trial. Procedures for anthropometric measurements are described in Chapter 13 of the TOHP Manual of Operations.

3. Stress Management

Measures of secondary endpoints relevant to the stress management intervention include both study-wide and intervention-specific instruments. Among the former are the Lazarus' Hassles Scale, a Treatment Evaluation scale (not given to Lifesytle controls), the Multidimensional Health Locus of Control, and Ware's Psychological General Well Being Scale. The intervention- specific forms include a Stress Management Activities Scale, Siegel's Multidimensional Anger Inventory, the Framingham Anger Subscale, and Lazarus' Uplifts Scale. Cardiovascular reactivity testing will also be done. These intervention-specific measures will be obtained from all members of the active stress intervention group, about 80% of the life-style controls, and 20% of those in the other active intervention at each center offering stress management.

4. Supplements

Secondary endpoints used for the supplements arm of the trial will provide an indication of changes in the levels of intake of the supplements over the course of the trial. For magnesium, both urine (based on 24-hour specimens) and serum levels will be assessed, while for potassium, urine levels only will be a secondary endpoint. Similarly, urine calcium will serve as a secondary endpoint for the calcium supplemented group and plasma fatty acid phospholipids for the fish oil supplemented group. Total and HDL cholesterol may serve as secondary endpoints, pending allocation of funds. Because of the expense of analyzing the fatty acid phospholipids, they will be collected on all participants and controls at baseline, 3 months and 6 months, but analyzed only on a 50% sample of these groups at 3 months and 6 months (termination). The analyzed data collection schedules for the laboratory tests for all the supplements groups are summarized in Table 5.

SAFETY MONITORING

The non-pharmacologic interventions being tested in TOHP are all moderate and of a level that is encountered frequently among free-living populations. Moreover, the eligibility and exclusion criteria for the trial have been designed

to exclude any individuals who are at particular risk, such as those with pre-existing conditions that might make participation difficult or contraindicated. Specifically, those with a history of heart disease, cancer, renal disease, diabetes, chronic gastrointestinal problems, physical handicaps that would affect participation in an exercise program, high cholesterol, and elevated serum potassium or calcium will not be permitted to enroll in TOHP. Nonetheless, there are certain parameters that will be monitored throughout the study period.

The chief safety consideration relates to individuals who may become hypertensive during the follow-up period of the trial. Clinic personnel will be instructed to implement the following procedures whenever a set of BP readings falls in the hypertensive range. A BP level that would raise the possibility of termination is a true DBP of 95 mm Hg or greater as determined by the mean of nine separate readings. Thus, if a subject's mean DBP at any single monitoring visit is greater than or equal to 93.5 (the sum of three readings greater than or equal to 281 mm Hg), that individual will be asked to return for a second visit at least one week later, at which time three additional readings will be taken. If the mean of these six readings over two visits is less than 93.5 mm Hg, the participant will be continued in the study. If, on the other hand, the mean of the six readings is 93.5 mm Hg or greater (the sum of six readings greater than or equal to 561), then the subject will be asked to return in a minimum of one week for a third set of BP measurements. At that time, if the mean DBP over nine readings is greater than or equal to 95 mm Hg (the sum of nine readings greater than or equal to 855 mm Hg), then that participant will be terminated from the study. Note that if the second or third set of three readings comprising this set of nine safety monitor readings averages 93.5 or greater, the cycle is <u>not</u> started again. In other words, one set of three readings triggers the collection of the set of nine safety monitoring readings, and it is the result (sum or average) of that set of <u>nine</u> BPs that is the basis for any future action.

If the sum of these nine readings is less than 810, the subject will continue in the study as usual. If the sum is less than 855 but greater than 810 mm Hg (90-94 mm Hg), <u>and</u> the sum of at least two of the three sets of three readings is less than 285 but greater than 270 mm Hg (90-94 mm Hg), then specific procedures need to be followed to inform the subject and, with permission, his/her personal physician, of the participant's actual BP readings. The principal investigator or other study physician should call or write to the

participant's physician and explain that this notification does not constitute a referral for treatment, since the literature suggests that treatment in this range is optional, but that we are notifying him/her out of an obligation to keep the physician informed about his/her patient. If possible, the principal investigator should negotiate an agreement with the participant's physician to have the participant stay in the trial on his/her assigned intervention and to have the BP readings for each subsequent visit reported to the personal physician. The participant should be contacted prior to each follow-up visit to determine if s/he has been placed on antihypertensive medication. If so, a missed visit form should be completed. If, at a subsequent visit, the subject has been off medication for at least two months, then full involvement in the study should be encouraged.

For those individuals who go on and off antihypertensive medication during the study, the final decision as to which data to use in analyses will be made at the termination of the trial. Unless contraindicated, participants should be encouraged to remain on their assigned intervention. Specific contraindications would include potassium supplementation for individuals placed on potassium-sparing diuretics, and calcium supplementation for patients placed on thiazide diuretics.

Although the level of exercise being prescribed as part of the weight loss intervention program is very moderate, as an added safety precaution, all individuals assigned to that group will undergo submaximal bicycle ergometer testing to identify participants who may need to obtain permission from their physicians before beginning the exercise component. In addition, the bicycle ergometer test will be used among both weight loss program participants and high-weight lifestyle controls as a measure of compliance with the exercise regimen. Precautions taken at the clinic to ensure the safety of these individuals include identifying those who are at increased risk of a cardiovascular event, performing a resting ECG on such persons for review by a physician, and monitoring them more closely during the test. Each clinic will have staff members certified in cardiopulmonary resuscitation available at the test site as well as ready access to an ambulance and trained emergency teams.

Other variables to be monitored periodically as a safety precaution include serum creatinine, serum potassium, and serum magnesium. All follow-up forms will also collect information on possible side effects of the interventions, such as fatigue, faintness, skin rash, or diarrhea. In addition, at each

follow-up visit, participants will be asked about their current status with respect to all of the medical conditions that constituted exclusions from the trial, including pregnancy, and a positive response may raise the possibility of early termination from intervention.

QUALITY CONTROL

Quality control of all training, intervention, data collection, and data processing procedures for TOHP is essential to the ultimate success of the trial. There are several basic principles underlying the approach to quality control that has been adopted.

1. Standardization of measurements and interventions through certification and recertification of study personnel.

2. Use of clear and specific protocols for all study activities, including training for all aspects of the trial, data collection, interventions, equipment maintenance, and data processing.

3. Validation and verification of all data collection and data management procedures through double entry and checking, followed by random checking of a sample by a third person or computer program.

4. Periodic meetings and progress reports to provide specific, well-documented feedback to the centers experiencing difficulties as well as sufficient follow-up to ensure that problems are resolved in a timely fashion.

To carry out quality control monitoring, a quality control officer will be appointed at each clinical center to oversee the designated certification and recertification procedures, equipment maintenance, monitoring of data collection, and ensuring that data collectors remain blinded as to the intervention status of the participant. These representatives will report problems to the CC on a regular basis. The CC will then generate reports tabulating errors in data forms, deviations from protocol, etc. An ongoing Quality Assurance Committee, which will include representatives from the clinical centers, the NHLBI Program Office, the CC, and the central

laboratories, will meet periodically to review the reports provided by the CC. In this way, problems will be identified as they develop and can thus be dealt with efficiently and effectively.

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

- certification of personnel responsible for measuring BP, height/weight, anthropometric measures, and reactivity testing

- certification of staff responsible for conducting each of the intervention protocols at that center, including exercise testing, if applicable

- certification of diet interviewers

- calibration and maintenance of BP devices, including random zero, standard mercury, and ambulatory devices

- calibration and maintenance of other equipment, including scales, height boards, skinfold calipers, exercise bicycles

- 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 any intervention

- validation of data collection and coding procedures

- review of laboratory specimen handling, shipping, and storing

At the CC, quality control will focus on verification of all data entry, computer editing of forms, and the generation of reports on departures from protocol, deviations from the prescribed visit windows, error rates in form completion, delays in form transmittal, errors in the randomization process, and monitoring of the performance of the central laboratory.

POWER CALCULATIONS: DBP

Estimate of Variance

Both baseline and termination DBPs are proposed as averages of 9 measurements, taken at 3 visits with 3 readings per visit. This procedure will reduce the variability of the BP measure, thus increasing the power of the study to detect true differences. The variance of the mean BP ($\bar{x}$) at either baseline or termination can be written as:

$$V_{(\bar{x})} = \sigma^2 = \sigma^2_p + \sigma^2_A/N + \sigma^2_e/NK$$

where: σ^2_p = between-person variance
σ^2_A = between-visit variance
σ^2_e = within-visit variance
N = number of visits = 3
K = number of measurements per visit = 3

Besides these components, the variance of the change in BP will also be affected by temporal variation, or the tracking correlation over periods of time. The variance of the change from baseline ($\bar{x}_1$) to termination ($\bar{x}_2$) can be written as:

$$V(\bar{x}_1 - \bar{x}_2) = 2\sigma^2(1-\rho)$$

where ρ = the observed tracking correlation of the BP means over an average of 18 months of follow-up for the lifestyle interventions and six months of follow-up for the supplement interventions. Thus, to estimate the variance of the change in means, we need to estimate the variance components and the tracking correlation.

1. The estimated total variances for DBP in black and white males and females have been published (101). These were combined by taking weighted averages using the race and gender distribution of the Hypertension Detection and Follow-up Program (102). These average components are:

$$\sigma^2_p = 109.11$$
$$\sigma^2_A = 26.76$$
$$\sigma^2_e = 7.42$$

Therefore, $V_{(\bar{x})}$, the estimated variance of the mean DBP at baseline or termination (averaged over three visits with three readings per visit) is 118.85.

2. A study of tracking correlation of BP in Wales (103) suggests a correlation of 0.58 for DBPs taken four years apart. This was based on a single measurement at each point. Data from an industrial population (104) suggest a one-year correlation of 0.85 for an average of 12 measurements taken at four visits with three measurements per visit. The tracking correlation observed is heavily influenced by the number of visits and measurements. The relationship of observed (ρ_{obs}) to true (ρ_{true}) correlation is:

$$\rho_{true} = \rho_{obs} \times (\sigma^2_p + \sigma^2_A/N + \sigma^2_e/NK)/\sigma^2_p$$

with the variance components defined as previously. These data suggest true four-year and one-year correlations of 0.85 and 0.91, respectively. Interpolating to 6 and 18 months, the true correlations in TOHP are estimated to be 0.92 and 0.90, respectively. Given three visits with three measurements each, we would expect to observe correlations of approximately 0.84 (6 months) and 0.83 (18 months). These figures lead to estimated variances for the change in means of 38.03 (standard error = 6.17) for 6 months and 40.41 (standard error = 6.36) for 18 months of observation.

Allocation of Subjects

Clinic-specific allocations are presented in Table 1.

Power Calculations

Power calculations assume a two-sided test with significance level 0.05 and use the following formula:

$$\text{Power} = 1 - \Phi\left[z_{1-\alpha/2} - \frac{d}{\sqrt{\frac{\sigma^2}{n_1} + \frac{\sigma^2}{n_0}}}\right]$$

where: $\Phi[\ ]$ = the area to the right of [ ] on the standard normal curve

$z_{1-\alpha/2}$ = 1.96

d = the difference in BP change between the intervention and comparison groups

σ^2 = 6.17^2 for supplements and 6.36^2 for lifestyles

n_1 = the number in the active intervention group

n_0 = the number in the control group

The estimated powers associated with the expected numbers in the proposed study design are given in Table 12. All tests will have at least .90 power to detect a 2 mm Hg change in DBP.

POWER CALCULATIONS: SBP

Estimate of Variance

The same methods used for DBP have been used to estimate the components of variance for SBP. The variance of the mean BP ($\bar{x}$) at either baseline or termination can again be written as:

$$V_{(\bar{x})} = \sigma^2 = \sigma^2_p + \sigma^2_A/N + \sigma^2_e/NK$$

where: σ^2_p = between-person variance

σ^2_A = between-visit variance

σ^2_e = within-visit variance

N = number of visits = 3

K = number of measurements per visit = 3

The variance of the difference between the baseline and termination values is a function of σ (defined above) and the tracking correlation (the variation in BP over time):

$$V(\bar{x}_1 - \bar{x}_2) = 2\sigma^2(1-\rho)$$

where: $\bar{x}_1$ = mean SBP at baseline
$\bar{x}_2$ = mean SBP at termination
ρ = the observed tracking correlation of the BP means over an average of 18 months of follow-up for the lifestyle interventions and six months of follow-up for the supplement interventions

1. Estimating the components of the variance of the mean BP at either baseline or termination

Again, using estimates from Rosner and Polk (104) and from the HDFP (102):

$$\sigma^2_p = 233.13$$
$$\sigma^2_A = 43.39$$
$$\sigma^2_e = 13.16$$

Therefore, $V(\bar{x})$, the estimated variance of the mean SBP (averaged over three visits with three readings per visit) at baseline or termination is 249.06.

2. Estimating the tracking correlation

Estimates for 4-year tracking correlations come from data from Wales (103); estimates for 1-year tracking correlations come from Rosner and Polk (104). In addition, the relation between observed and true tracking correlations is estimated by the following equation:

$$\rho_{true} = \rho_{obs} \times (\sigma^2_p + \sigma^2_A/N + \sigma^2_e/NK)/\sigma^2_p$$

For SBP, the observed and true tracking correlations are .67 and .83 for 4-years and .81 and .85 for 1-year, respectively. Interpolating to 6 and 18 months, the true correlations in TOHP are estimated to be .853 and .847. Given three visits with three measures each, we would expect to observe correlations of approximately .80 (6 months) and .79 (18 months). These figures lead to estimated variances for the change in means of 99.62

(standard error = 9.98) for 6 months of observation and 104.61 (standard error = 10.23) for 18 months of observation.

Allocation of Subjects

The same clinic-specific allocations shown in Table 1 are used.

Power Calculations

The estimated powers associated with the expected numbers are given in Table 13. All tests will have between .87 and .98 power to detect a 3 mm Hg change in SBP.

DATA ANALYSES

The data analyses will be performed by the CC, with input from other trial investigators, for review by the Data and Safety Monitoring Committee at its semi-annual meetings.

This study will allow for the evaluation of seven different interventions. For each intervention, baseline characteristics will first be examined in the intervention and comparison groups to see if randomization achieved equal allocation. The primary factors of interest are those to be affected by the trial, including DBP, body weight, dietary components, and exercise frequency. Other variables that might influence change in DBP will also be examined.

The primary outcomes of interest for the lifestyle interventions is the difference between changes in mean DBP from baseline to 18 months between the intervention and comparison groups, with the BP for each participant being determined from nine readings (three readings at each of three visits). The primary endpoint for the supplement interventions is change in DBP from baseline to six months. In the crudest level of analysis, mean change in DBP in each of the actual intervention groups with the control group will be compared in the context of the one-way analysis of variance. At a second level, mean change in DBP between each of the active intervention and control groups will be compared after controlling for clinic. This will be accomplished using multiple regression methods introducing dummy variables for

clinic and intervention group. In addition, more refined analyses will be performed to adjust for other covariates, such as mean initial DBP, age, and sex.

Secondary endpoints in the trial, including changes in SBP and the development of hypertension, will also be examined. The former will be evaluated in the same manner as changes in DBP described above. The development of hypertension will be defined as either going on antihypertensive medications during the course of the trial or attaining a mean DBP greater than or equal to 95 mm Hg based on nine readings over three visits at any point in the trial.

While change in DBP from baseline to termination is the primary outcome of interest, there will also be the opportunity to examine BP measurements taken throughout the follow-up period. In particular, slopes of BP over time will be compared based on available data per participant. Slopes in different treatment groups will also be compared using analysis of variance and regression methods as discussed above. More sophisticated methods of longitudinal data will be utilized to characterize more complex changes in BP over time (105-107). In addition, BP change from baseline to the 12-month follow-up point for lifestyles interventions will also form the basis for planning for Phase II of TOHP.

The above analyses have been concerned with comparing mean change in DBP among different treatment groups. However, it is well known that effects of intervention are not uniform across all members of an actual intervention group. Furthermore, some members of the control group may seek to implement some of the intervention strategies on their own (such as weight reduction or sodium restriction). Therefore, as a secondary analysis mean changes in DBP will be examined as a function of changes in risk factors that should be affected by the interventions strategies (such as weight loss, changes in urinary sodium or potassium) regardless of treatment assignment.

Another issue that is a characteristic feature of hypertension trials performed on normotensive subjects is that some subjects have BP elevations sufficient to cause their physician to prescribe antihypertensive medication and to withdraw from the trial. These persons are crucially important to the study, since exclusion of such individuals will result in a biased estimate of effects of specific interventions. Therefore, several strategies will be employed to deal with the effects of such censored data, including the use of mean change in DBP

from entry to the relevant visit in the trial, and use of more sophisticated censored data methods to estimate what change in DBP would have occurred had such participants been left untreated and followed. For this purpose, upon untimely termination of a participant from the trial, we will obtain nine readings over three termination visits to better characterize BP changes in such persons.

Another issue that will be monitored on a regular basis is compliance of subjects with the intervention modalities. This will be analyzed by looking at changes in physiologic parameters that should be affected by the actual interventions (such as urinary sodium or potassium and body weight). Measures of compliance will be developed and assessed throughout the trial.

Finally, we will perform safety monitoring in the trial, with particular emphasis on the nutritional supplement interventions to compare side effects reported by the treated and placebo groups. Both safety and efficacy data will be analyzed every six months for purposes of review by the Data and Safety Monitoring Committee (or more frequently, if requested).

STUDY ORGANIZATION

The participating investigators and centers in the Trials of Hypertension Prevention (TOHP) collaborate through a study organization that is designed to maintain continuity of operations and effective communication among the various functional units.

Participating Units

The success of a multicenter endeavor depends upon the cooperation of the staff of each of the participating organizations in performing the tasks and responsibilities assigned to them in an efficient, effective, and timely manner. The major participating units in TOHP are listed in Appendix A.

1. Clinical Centers

   Each center responsible for recruiting, screening, enrolling and following participants is known as a clinical center and is supported by an

individual cooperative agreement with the NHLBI. The primary function of the staff at each clinical center is to carry out the provisions of the TOHP protocol. This charge involves enrolling subjects within the specified recruitment period, administering the allocated interventions, and following each subject enrolled in the study according to a specified examination schedule.

Each clinical center has a principal investigator who bears primary responsibility for the center and represents it at meetings of the TOHP Steering Committee. While the organization of each center may differ, each has at least one person, the clinic coordinator, whose primary commitment is to TOHP and who is responsible for such critical matters as:

- appointment scheduling;

- assuring the accuracy, completeness, and consistency of data reported;

- handling communications concerning study forms with the TOHP Coordinating Center, and concerning blood and urine specimens with the relevant laboratories;

- maintaining the participants' interest in the study.

2. Coordinating Center

The TOHP CC is funded through a cooperative agreement from NHLBI and is responsible for compiling and analyzing all study data and ensuring that the provisions of the protocol are carried out by all participating units. The staff includes professional personnel representing the disciplines of epidemiology, biostatistics, internal medicine, and data processing.

The CC is responsible for receiving, editing, analyzing and storing all data received from the clinical centers and central laboratory. Some of the specific functions of CC investigators and staff are:

- To work with the other study investigators in the development of study procedures, forms, and Manual of Operations;

- To coordinate communications among the centers;

- To assist in training clinic staff in study procedures;

- To coordinate certification of the clinical center staff;

- To oversee the random assignment of each study participant to one of the intervention or control regimens;

- To review all study data for completeness and accuracy;

- To monitor the performance of all participating units;

- To prepare periodic reports on the performance of the clinics;

- To analyze frequency of specified events and any adverse reactions by intervention group and to report these data to the Data and Safety Monitoring Committee;

- To prepare recruitment, technical, and statistical reports for the meetings of the Steering Committee and the Data and Safety Monitoring Committee;

- To assist in the preparation of scientific reports for publication.

3. National Heart, Lung and Blood Institute

The NHLBI has overall responsibility for the scientific and fiscal management of TOHP. The NHLBI Project Officer is a voting member of the Steering and Executive Committees of TOHP, as well as a non-voting member of the Data and Safety Monitoring Committee.

4. Central Laboratories

All urine and blood analyses except for phospholipids will be performed by Dr. John Belcher at the University of Minnesota School of Public Health in Minneapolis, which will also store additional plasma and serum samples for possible later analyses. Blood phospholipid analyses will be performed by Dr. Frank Sacks at the Channing Laboratory in Boston.

Study Administration

The administrative structure of TOHP consists of a series of committees and subcommittees which include representatives from all the participating units.

1. Steering Committee

The Steering Committee is the central governing body of TOHP. It is made up of the principal investigators, interventionists, and coordinators from each of the clinical centers as well as representatives from the CC and NHLBI. Each participating unit has one vote normally cast by the Principal Investigator. The Steering Committee meets at least semi-annually to review the progress of the trial. Each center is 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 serves as chairman of the Steering Committee.

The meetings of this group are a forum for the discussion of study problems as well as the dissemination of information. The face-to-face discussion of trial activities, along with opportunities to interact on a personal level contribute to the development of rapport among study collaborators that facilitates the operation of a multicenter clinical trial.

Subcommittees and working groups of the Steering Committee are formed as needed. There are five subcommittees of the Steering Committee that were formed initially to assist in the planning process for TOHP and have ongoing charges during the study itself. These are summarized below.

The Design and Analysis Subcommittee is primarily responsible for recommending to the Steering Committee overall design features, e.g., sample

sizes, blinding, and stratification; for proposing to the CC specific data analyses for the study; for reviewing requests from investigators for data analyses and recommending priorities for analysis; and for reviewing proposals for ancillary studies and recommending approval or disapproval to the Steering Committee for their review and vote.

The Eligibility and Recruitment Subcommittee recommends 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 is also responsible for reviewing recruitment reports from the CC in order to identify problems and propose solutions on a clinic-by-clinic basis.

The Interventions Subcommittee develops intervention methods and materials, monitors compliance outcomes, and if necessary, proposes modifications of the intervention protocols for review and approval by the Steering Committee. This group also provides advice, as requested, to the Data Collection and Quality Assurance Subcommittee concerning methods for assessing adherence to the TOHP interventions.

The Data Collection and Quality Assurance Subcommittee recommends to the Steering Committee the data set to be collected from TOHP participants, including review of data forms, and is responsible for recommending to and collaborating with the CC in implementing quality assurance programs for: monitoring the performance of clinic personnel in adhering to the study protocol and Manual of Operations; certification and recertification procedures for both clinical center staff and equipment; and monitoring the quality of laboratory data.

The Publications and Presentations Subcommittee is responsible for establishing and implementing procedures for review of publications and presentations of TOHP materials and data. In addition to assuring accurate and timely presentation of pertinent information to the scientific community, an objective of the subcommittee is to encourage all investigators to have the opportunity to participate in presentation and publication of study-wide data.

In addition, at the conclusion of the planning phase, a sixth subcommittee was constituted. The Clinic Coordinators Subcommittee is composed of one

individual from each clinical center who is responsible for assisting the Principal Investigator in organizing the center staff, facilities, and tasks, as well as representatives from the CC. This group will meet in conjunction with the semiannual Steering Committee meetings and will function via correspondence and conference calls in the interim periods. Activities of this subcommittee include dissemination of information received from the CC and other trial components to appropriate clinic staff; assisting in the design and implementation of procedures for the flow of patients through the clinics and flow of data to the CC; identification and resolution of problems in organization of staff and physical facilities to maintain separation of intervention and data collection; assisting in the development of systems (such as use of case managers) to encourage high attendance and compliance rates; provision of information to the CC on a regular basis regarding the overall functioning of the clinic; and provision of input to the CC on the design and implementation of quality control monitoring and error correction procedures.

2. Executive Committee

The TOHP Executive Committee, is made up of the chairmen of the five subcommittees of the Steering Committee, the NHLBI Project Officer, the CC director, and the study chairman. This group discusses and helps to formulate and implement all Steering Committee decisions related to the conduct of TOHP within the guidelines established by the protocol.

Specific functions of the Executive Committee include:

- Resolving any operational problems that arise between Steering Committee meetings, consulting with the principal investigators if appropriate;

- Advising and assisting the CC on operational matters;

- Preliminary review of the performance of all participating centers on the basis of reports provided by the CC.

The Executive Committee meets in advance of the meetings of the Steering Committee and as necessary on other occasions.

3. Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing the initial study protocol, for assessing accumulating study data for adverse and/or beneficial intervention effects, and for seeing that risks to subjects are minimized. As part of this responsibility for minimizing risk to participants, the DSMC reviews procedures for data surveillance to assure that these are sufficient to identify the occurrence of adverse events in any intervention group. This review includes receiving monitoring reports prepared and supplied by the staff of the CC for evidence of adverse or beneficial intervention effects. After review of each report, the DSMC is responsible for making specific recommendations to the Steering Committee and the NHLBI about whether to continue the study, with or without changes in the protocol, or to stop the trial. The DSMC is also charged with advising the Steering Committee and NHLBI on whether to proceed with Phase II of TOHP. Votes at meetings are identified and recorded by individual response.

The DSMC members are appointed by the NHLBI Project Office based on consultation with the Executive Committee. The voting members represent skills in cardiovascular disease epidemiology, trial methodology, biostatistics, nutrition, behavioral science, and bioethics. The study chairman, CC director, and NHLBI Project Officer serve as non-voting members. A complete membership listing of this committee is contained in Appendix B.

Members of the DSMC are expected:

- To acquire a detailed knowledge of the TOHP design and goals;

- Attend two meetings of the DSMC each year, with additional meetings as needed during periods of active decision making;

- To study data monitoring reports and other material submitted by the CC or the Data Collection and Quality Assurance Subcommittee;

- To suggest analyses to be included in data monitoring reports;

- To communicate in a timely way with the Institute and principal investigators, with an emphasis on two-way communications.

Members of the DSMC may be invited to attend meetings of the Steering Committee at the discretion of the Steering Committee Chairperson.

4. Study Chairman

The study chairman, appointed by the NHLBI Project Office, has a major responsibility for the scientific direction of TOHP and proper implementation of the decisions made by the Steering Committee. He is informed on all aspects of study operations and takes action as necessary to insure the smooth operation of the trial. He also serves as chairman of the Executive Committee and the Steering Committee for the trial.

ANCILLARY STUDIES

An ancillary study is a research study, the principal investigator of which is at least a TOHP co-investigator and which must be approved by the principal investigator. An ancillary study is characterized by one or more of the following:

1. Observations/procedures supplemental to the TOHP protocol are implemented in all or a subgroup of participants according to a set protocol;

2. Additional work by or information from the TOHP coordinating center on screenees or participants is required; or

3. Investigative work on the methodology of TOHP is involved.

Ancillary studies are encouraged, for they can enhance the value of TOHP and insure the continued interest of the many capable investigators involved.

Request for Approval of an Ancillary Study

An investigator who wishes to undertake an ancillary study must prepare a formal research proposal describing the proposed study. This proposal should

contain statements on objectives, background, methods of study and feasibility, as outlined in the next section.

These proposals for ancillary studies are to be submitted to the Design and Analysis Subcommittee for preliminary review. Copies of the proposal should be made available to all members of the subcommittee one week prior to the meeting at which it is to be considered. The primary objective is to review the compatibility of the ancillary study with the existing study and its priorities. Any proposed procedure that would interefere with one or more of the procedures of the TOHP protocol or would result in a decrease in the compliance of the participants in TOHP is sufficient reason for the disapproval of the proposed ancillary study. Questions on the proposal are referred back to the applicant for amplification, clarification, or withdrawal of the request. The Design and Analysis subcommittee will make a recommendation to the Steering Committee on approval or disapproval of the proposed study. A proposal that has received conditional approval must be resubmitted to the Design and Analysis Subcommittee for final consideration.

Those proposals that are judged compatible with the TOHP protocol are submitted to the Data and Safety Monitoring Committee (DSMC) for review. After this final review of the proposal, the NHLBI project office will prepare a statement of the DSMC's consensus, including anyreservations or objections, and forward it to the investigator who requested approval of the ancillary study.

Form of Protocol for an Ancillary Study

A proposal for an ancillary study that is submitted to Design and Analysis should include information on the following areas:

A. Objectives
B. Background
C. Methods of Study
D. Effects on TOHP
    1. Financial
    2. Logistic/Study Flow
    3. Scientific
    4. Compliance

E. Source of Support
F. Investigators and Clinics Involved
G. Length of Time Required for Procedures
H. Other Ancillary Studies that Clinics are Involved In

Some ancillary studies may require the CC to perform statistical analyses or make available to the investigator data that are not already available. In either or both cases, the proposal should be accompanied by a statement from the CC indicating the commitment of its services to the study.

If additional funding is requested, a proposed budget following the usual NIH format must be submitted.

Funding of an Ancillary Study

If no additional funds are required, the investigator may proceed with the ancillary study as soon as written approval from the project office has been received. If additional funds are requested in the proposal, the project officer will submit a written summary of the decisions of the Steering Committee to the investigator.

Publication and/or Presentation of Ancillary Study Results

All manuscripts or presentations for scientific meetings that are based on ancillary studies making use of data collected according to the TOHP protocol must be reviewed and approved by the Publications and Presentations Subcommittee before publication or presentation.

PROTOCOL CHANGES

Any change to the protocol must be submitted in writing to the Steering Committee and approved by a two-thirds majority of all voting members (one vote for each PI, NHLBI Project Officer, and Coordinating Center Director). Alternatively, any protocol change which arises in the course of a Steering Committee meeting and is thus not in written form requires unanimous approval.

REFERENCES

1. US DHHS. Health United States. Public Health Service, National Center for Health Statistics, DHHS Publ No (PHS) 85-1232. Hyattsville, MD: 1984.

2. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. Final report of the Pooling Project. J Chron Dis 1978; 31:201-62.

3. Kaplan NM. Clinical Hypertension. 4th edition. Baltimore: Williams and Wilkins, 1986.

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. JAMA 1967; 202:1028-34.

5. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970; 213:1143-52.

6. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction of mortality of persons with high blood pressure, including mild hypertension. JAMA 1979; 242:2562-71.

7. Australian National Blood Pressure Study Management Committee. The Australian therapeutic trial in mild hypertension. Lancet 1980; 1:1261-7.

8. Helgeland A. Treatment of mild hypertension. a five-year controlled drug trial. The Oslo Study. Am J Med 1980; 69:725-32.

9. Amery A, Birkenhager W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; 1:1349-54.

10. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. Br Med J 1985; 291:97-104.

11. Aagaard GN. Drug therapy. III. Treatment of uncomplicated hypertension. Northwest Med 1970; 99(2).

12. Physicians' Desk Reference. 36th edition. Oradell, NJ: Medical Economics Company, 1982.

13. Berchtold P, Sims EAH, Brandau K (eds). Obesity and Hypertension. Int J Obesity 1981; 5(Suppl 1).

14. Berchtold P, Jorgens V, Finke C, Berger M. Epidemiology of obesity and hypertension. Int J Obesity 1981; 5(Suppl 1):1-7.

15. Chiang BN, Perlman LV, Epstein FH. Overweight and hypertension. A review. Circulation 1969; 39:403-21.

16. Sims EAH, Berchtold P. Obesity and hypertension: mechanisms and implications for management. JAMA 1982; 247:49-52.

17. Reisin E, Frohlich ED, Messerli FH, et al. Cardiovascular changes after weight reduction in obesity hypertension. Ann Intern Med 1983; 98:315-9.

18. Fletcher AP. The effect of weight reduction upon the blood-pressure of obese hypertensive women. Q J Med 1954; 23:331-45.

19. Dahl LK, Silver L, Christie RW. The role of salt in the fall of blood pressure accompanying reduction in obesity. N Engl J Med 1958; 258:1186-92.

20. Tyroler HA, Heyden S, Hames CG. Weight and hypertension: Evans County studies of blacks and whites. In: Paul O (ed). Epidemiology and Control of Hypertension. Miami: Symposium Specialists, 1975: 177-204.

21. Ramsay LE, Ramsay MH, Hettiarachchi J, Davies DL, Winchester J. Weight reduction in a blood pressure clinic. Br Med J 1978; 2:244-5.

22. Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B. Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. N Engl J Med 1978; 298:1-6.

23. Stamler J, Farinaro E, Mojonnier LM, Hall Y, Moss D, Stamler R. Prevention and control of hypertension by nutritional-hygienic means: long-term experience of the Chicago Coronary Prevention Evaluation Program. JAMA 1980; 243:1819-23.

24. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med 1981; 304:930-3.

25. Fagerberg B, Andersson OK, Isaksson B, Bjorntorp P. Blood pressure control during weight reduction in obese hypertensive men: separate effects of sodium and energy restriction. Br Med J (Clin Res) 1984; 288:11-4.

26. Maxwell MH, Kushiro T, Dornfeld LP, Tuck ML, Waks AU. Blood pressure changes in obese hypertensive subjects during rapid weight loss: comparison of restricted versus unchanged salt intake. Arch Intern Med 1984; 144:1581-4.

27. Berchtold P, Jorgens V, Kemmer FW, Berger M. Obesity and hypertension: cardiovascular response to weight reduction. Hypertension 1982; 4(Suppl III):50-5.

28. Kaplan NM. Non-drug treatment of hypertension. Ann Intern Med 1985; 102:359-73.

29. Chapman CB, Gibons TB. The diet and hypertension: a review. Medicine 1949; 29:29-69.

30. Allen FM, Sherrill JW. The treatment of arterial hypertension. J Metab Res 1922; 2:429-545.

31. Parijs J, Joossens JV, Van der Linden L, Verstreken G, Amery AKPC. Moderate sodium restriction and diuretics in the treatment of hypertension. Am Heart J 1973; 85:22-34.

32. Morgan T, Adam W, Gillies A, Wilson M, Morgan G, Carney S. Hypertension treated by salt restriction. Lancet 1978; 1:227-30.

33. Carney S, Morgan T, Wilson M, Matthews G, Roberts R. Sodium restriction and thiazide diuretics in the treatment of hypertension. Med J Aust 1975; 1:803-7.

34. Parfrey PS, Wright P, Goodwin FJ, et al. Blood pressure and hormonal changes following alteration in dietary sodium and potassium in mild essential hypertension. Lancet 1981; 1:56-63.

35. Amery A, Bulpitt C, Fagard R, Staessen J. Does diet matter in hypertension? Eur Heart J 1980; 1:299-308.

36. Kempner W. Treatment of hypertensive vascular disease with rice diet. Am J Med 1948; 4:545-77.

37. Dole VP, Dahl LK, Cotzias GC, Dziewiatkowski DD, Harris C. Dietary treatment of hypertension. II. Sodium depletion as related to therapeutic effect. J Clin Invest 1951; 30:584-95.

38. Watkin DM, Froeb HF, Hatch FT, Gutman AB. Effects of a diet in essential hypertension. II. Results with unmodified Kempner rice diet in 50 hospitalized patients. Am J Med 1950; 9:441-93.

39. Magnani B, Ambrosioni E, Agosta R, Racco F. Comparison of the effects of pharmacological therapy and a low sodium diet on mild hypertension. Clin Sci Mol Med 1976; 51(Suppl 3):625s-6s.

40. MacGregor GA, Markandu ND, Best FE, et al. Double-blind randomized crossover trial of moderate sodium restriction in essential hypertension. Lancet 1982; 1:351-5.

41. Watt GCM, Edwards C, Hart JT, Hart M, Walton P, Foy CJW. Dietary sodium restriction for mild hypertension in general practice. Br Med J (Clin Res) 1983; 286:432-6.

42. Richards AM, Nicholls MG, Espiner EA, et al. Blood pressure response to moderate sodium restriction and to potassium supplementation in mild essential hypertension. Lancet 1984; 1:757-61.

43. Silman AJ, Locke C, Mitchell P, Humpherson P. Evaluation of the effectiveness of a low sodium diet in the treatment of mild to moderate hypertension. Lancet 1983; 1:1179-82.

44. Beard TC, Cooke HM, Gray WR, Barge R. Randomized controlled trial of a no-added-sodium diet for mild hypertension. Lancet 1982; 2:455-8.

45. Oliver G, Schafer EA. The physiological effects of extracts of the suprarenal capsules. J Physical (London) 1895; 18:230-76.

46. Frohlich ED. The adrenergic nervous system and hypertension - state of the art. Mayo Clin Proc 1977; 52:361-8.

47. Julius S. Borderline hypertension. An overview. Med Clin North Am 1977; 61:494-511.

48. Patel C, Marmot MG, Terry DJ. Controlled trial of biofeedback-aided behavioural methods in reducing mild hypertension. Br Med J (Clin Res) 1981; 282:2005-8.

49. Glasgow MS, Gaarder KR, Engle BT. Behavioral treatment of high blood pressure. II. Acute and sustained effects of relaxation and systolic blood pressure biofeedback. Psychosom Med 1982; 44:155-70.

50. Peled-Ney R, Silverberg DS, Rosenfeld JB. A controlled study of group therapy in essential hypertension. Isr J Med Sci 1984; 20:12-5.

51. Engel BT, Glasgow MS, Gaarder KR. Behavioral treatment of high blood pressure. III. Follow-up results and treatment recommendations. Psychosom Med 1983; 45:23-9.

52. Luborsky L, Crits-Christoph P, Brady JP, et al. Behavioral versus pharmacological treatments for essential hypertension - a needed comparison. Psychosom Med 1982; 44:203-13.

53. Patel C, Marmot MG, Terry DJ, Carruthers M, Hunt B, Patel M. Trial of relaxation in reducing coronary risk: four year follow up. Br Med J 1985; 290:1103-6.

54. Addison W. The uses of sodium chloride, potassium chloride, sodium bromide and potassium bromide in cases of arterial hypertension which are amenable to potassium chloride. Can Med Assoc J 1928; 18:281-5.

55. Smith SJ, Markandu ND, Sagnella GA, Poston L, Hilton PJ, MacGregor GA. Does potassium lower blood pressure by increasing sodium excretion? A metabolic study in patients with mild to moderate essential hypertension. J Hypertens 1983; 1(Suppl 2):27-30.

56. Sealey JE, Clark I, Bull MB, Laragh JH. Potassium balance and the control of renin secretion. J Clin Invest 1970; 49:2119-27.

57. Chen WT, Brace RA, Scott JB, Anderson DK, Haddy FJ. The mechanism of the vasodilator action of potassium. Proc Soc Exp Biol Med 1972; 140:820-4.

58. Iimura O, Kijima T, Kikuchi K, et al. Studies on the hypotensive effect of high potassium intake in patients with essential hypertension. Clin Sci 1981; 61(Suppl):77s-80s.

59. Yamori Y, Kihara M, Nara Y, et al. Hypertension and diet: Multiple regression analysis in a Japanese farming community. Lancet 1981; 1:1204-6.

60. Sasaki N. High blood pressure and the salt intake of the Japanese. Jap Heart J 1962; 3:313-6.

61. Langford HG. Dietary potassium and hypertension: epidemiologic data. Ann Intern Med 1983; 98:770-2.

62. Dawber TR, Kannel WB, Kagan A, Donabedian RK, McNamara PM, Pearson G. Environmental factors in hypertension. In Stamler J, Stamler R, Pullman TN, (eds). The Epidemiology of Hypertension. New York: Grune and Stratton, 1967: 255-88.

63. Parfrey PS, Conder K, Wright P, et al. Blood pressure and hormonal changes following alteration in dietary sodium and potassium in young men with and without a familial predisposition to hypertension. Lancet 1981; 1:113-7.

64. Skrabal F, Auback U, Hortnagl H, et al. Effect of moderate salt restriction and high potassium intake on pressor hormones, response to nonadrenalin and baroreceptor function in man. Clin Sci 1980; 59:157s-60s.

65. Pak CYC. Overview: calcium and hypertension. In: Horan MJ, Blaustein M, Dunbar JB, Kachadorian W, Kaplan NM, Simopoulos AP (eds). NIH Workshop on Nutrition and Hypertension. New York: Biomedical Information Corporation, 1985: 155-65.

66. Belizan JM, Villar J. The relationship between calcium intake and edema-proteinuria, and hypertension-gestosis: an hypothesis. Am J Clin Nutri 1980; 33:2202-10.

67. Belizan JM, Villar J, Zalazar A, Rojas L, Chan D, Bryce GF. Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women. Am J Obstet Gynecol 1983; 146:175-80.

68. Belizan JM, Villar J, Pineda O, et al. Reduction of blood pressure with calcium supplementation in young adults. JAMA 1983; 249:1161-5.

69. McCarron DA, Morris CD, Cole C. Dietary calcium in human hypertension. Science 1982; 217:267-9.

70. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984; 224:1392-8.

71. McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension: a randomized, double-blind, placebo-controlled crossover trial. Ann Intern Med 1985; 103:825-31.

72. Sacks FM, Rosner B, Kass EH. Blood Pressure in vegetarians. Am J Epidemiol 1974; 100:390-8.

73. Rouse IL, Armstrong BK, Beilin LJ. The relationship of blood pressure to diet and lifestyle in two religious populations. J Hypertension 1983; 1:65-71.

74. Marier JR. Quantitative factors regarding magnesium status in the modern-day world. Magnesium 1982; 1:3-15.

75. Resnick LM, Gupta RK, Laragh JH. Intracellular free magnesium in erythrocytes of essential hypertension: relation to blood pressure and serum divalent cations. Proc Natl Acad Sci USA 1984; 81:6511-5.

76. Resnick LM. Dietary magnesium manipulation in the management of hypertension. Presented at Nutritional Management of Hypertension: a workshop under the auspices of the Canadian Hypertension Society, Harrison, BC, September 7, 1985.

77. Cholst IN, Steinberg SF, Topper PJ, Fox HE, Segre GV, Bilezekian JP. The influence of hypermagnesemia on serum calcium and parathyroid hormone levels in human subjects. N Engl J Med 1984; 310:1221-5.

78. Smith WO. Magnesium deficiency in the surgical patient. Am J Cardiol 1963; 12:667-70.

79. Kobayashi JA. Geographical relationship between the chemical nature of river water and death rate from apoplexy. Ber Ohara Inst Lansw Biol 1957; 11:12-21.

80. Schroder HA. Relation between mortality from cardiovascular disease and treated water supplies. Variations in states and 163 largest municipalities in U.S. JAMA 1960; 172:1902-8.

81. Seelig MS. Magnesium Deficiency in the Pathogenesis of Disease. New York: Plenum, 1980: 17-21.

82. Durlach J, Bara M, Guiet-Bara A. Magnesium level in drinking water and cardiovascular risk factor: a hypothesis. Magnesium 1985; 4:5-15.

83. Altura BM, Altura BT. Interactions of Mg and K on blood vessels - aspects in view of hypertension. Magnesium 1984; 3:175-94.

84. Mader IJ, Iseri LT. Spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany due to hypersecretion of corticosterone-like mineralocorticoid. Am J Med 1955; 19:976-88.

85. Weaver K. A possible anticoagulant effect of magnesium in pre-eclampsia. In: Cantin M, Seelig MS (eds). Magnesium in Health and Disease. New York: Spectrium, 1980: 833-8.

86. Hall RCW, Joffe JR. Hypomagnesemia. Physical and psychiatric symptoms. JAMA 1973; 224:1749-51.

87. Mordes JF, Swartz R, Orky RA. Extreme hypermagnesemia as a cause of refractory hypotension. Ann Intern Med 1975; 83:657-8.

88. Dyckner T, Wester PO. Effect of magnesium on blood pressure. Br Med J 1983; 286:1847-9.

89. Cappuccio FP, Markandu ND, Beynon GW, Shore AC, Sampson B, MacGregor GA. Lack of an effect of oral magnesium on high blood pressure: a double-blind study. Br Med J 1985; 291:235-8.

90. Bang HO, Dyerberg J, Njorn N. The composition of food consumed by Greenland Eskimos. Acta Med Scand 1976; 200:69-73.

91. Dyerberg J, Bang HO. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet 1979; 2:433-5.

92. Dyerberg J, Bang HO, Stofferson E, Moncada S, Vane Jr. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978; 2:111-9.

93. Scherhag R, Kramer HJ, Dusing R. Dietary administration of eicosapentaenoic and linolenic acid increases arterial blood pressure and suppresses vascular prostacyclin synthesis in the rat. Prostaglandins 1982; 23:369-82.

94. Gerber JG. Indomethacin-induced rises in blood pressure. Ann Intern Med 1983; 99:555-8.

95. Cleve DM, Stoll JS. Renal syndromes associated with nonsteroidal anti-inflammatory drugs. N Engl J Med 1984; 310:563-72.

96. Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC. Platelet function, thromboxane formation and blood pressure control during supplementation of the western diet with cod liver oil. Circulation 1983; 67:504-11.

97. Terano T, Hirai A, Hamazaki T, et al. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. Atherosclerosis 1983; 46:321-31.

98. Kobayashi S, Hirai A, Terano T, Hamazaki T, Tamura Y, Kumagai A. Reduction in blood viscosity by eicosapentaenoic acid. Lancet 1981; 1:197.

99. Mortensen JZ, Schmidt EB, Nielsen AH, Dyerberg J. The effect of n-6 and n-3 polyunsaturated fatty acids on hemostasis, blood lipids and blood pressure. Thromb Haemost 1983; 50:543-6.

100. Singer P, Jaeger W, Wirth M, et al. Lipid and blood pressure-lowering effect of mackerel diet in man. Atherosclerosis 1983; 49:99-108.

101. Rosner B, Polk BF. Predictive values of routine blood pressure measurements in screening for hypertension. Am J Epidemiol 1983; 117:429-42.

102. Hypertension Detection and Follow-up Program Cooperative Group. Variability of blood pressure and the results of screening in the Hypertension Detection and Follow-up Program. J Chron Dis 1978; 31:651-67.

103. Rosner B, Hennekens CH, Kass EH, Miall WE. Age-specific correlation analysis of longitudinal blood pressure data. Am J Epidemiol 1977; 106:306-13.

104. Rosner B, Polk BF. The instability of blood pressure variability over time. J Chron Dis 1981; 34:135-9.

105. Laird NM, Ware JH. Random effect models for longitudinal data. Biometrics 1982; 38:963-74.

106. Cook NR, Ware JH. Design and analysis methods for longitudinal research. Am Rev Public Health 1983; 4:1-23.

107. Rosner B, Munoz A. The use of autoregressive models in the analysis of longitudinal data in epidemiologic studies. Stat in Medicine, 1985.

Table 1
ALLOCATION OF TOHP PARTICIPANTS, BY CLINIC

ACTUAL NUMBERS RANDOMIZED INTO LIFESTYLES AND SUPPLEMENTS STAGE 1

CLINIC	Sodium Reduction	Weight Reduction	Stress Management	Lifestyle Control	Calcium	Magnesium	Placebo
Baltimore	66	60	--	82	22	20	21
Birmingham	--	63	66	89	--	--	--
Davis	69	45	--	83	51	48	50
East Boston	--	--	--	--	23	22	22
Jackson	49	42	--	67	17	14	16
Memphis	47	--	50	63	21	22	22
Newark	63	--	66	85	--	--	--
Pittsburgh	--	--	--	--	92	90	91
Portland	--	66	60	83	--	--	--
St. Louis	33	32	--	37	11	11	12
TOTALS	327	308	242	589	237	227	234

ESTIMATED NUMBERS IN SUPPLEMENTS STAGE 2*

CLINIC	Potassium	Fish Oil	Placebo
Baltimore	25	23	22
Davis	43	41	42
East Boston	20	19	19
Jackson	14	12	14
Memphis	18	19	19
Pittsburgh	78	76	77
St. Louis	9	9	10
TOTALS	207	199	203

* This reflects rerandomizing 85% of Stage 1 participants plus 6 additional in each group at Baltimore

Table 2
DATA COLLECTION SCHEDULE FOR LIFESTYLE INTERVENTIONS

	Screening Visits (10-30 days apart)			Status Review Visit	Follow-Up Visits Months Post-Randomization 3	6	12	18	Termination Visits (7-30 days apart)		
	SV1	SV2	SV3	SRV	F01	F02	F09	F16	F19	F20	F21
Blood Pressure	X	X	X		X	X	XXX	XXX	X	X	X
Height	X										
Weight	X		X		X	X	X	X	X		
Medical History (Health Experience Form)	X						X	X	X		
Demographic Information	X										
Participant Information	X						X				
Physical Activity Form		X					X	X			
Lazarus' Hassles Scale		X				X		X			
General Well Being Scale		X				X		X			
Multidimensional Health Locus of Control		X				X		X			
Treatment Evaluation Scale*				X		X		X			
Health Habits Questionnaire			X					X			
24-Hour Diet Recall			X			X		X			
Blood Sample			X				X	X			
24-Hour Urine Sample			X	X		X	X	X			

* Administered to all participants except controls for the lifestyle interventions

Table 3
DATA COLLECTION SCHEDULE FOR SUPPLEMENTS INTERVENTIONS

	-- Stage 1 --								Re-eligibility Screening			-- Stage 2 --				
	SV1	SV2	SV3	SRV	F01	F02	F03	F04	F05	F06	F07	F08	F12	F13	F14	F15
Blood Pressure	X	X	X		X	X	X	X	X	X	X		X	X	X	X
Height	X															
Weight	X		X		X	X			X		X		X	X		
Medical History (Health Experience)	X					X			X					X		
Demographic Information	X															
Participant Information	X								X							
Physical Activity Form		X				X				X				X		
Lazarus' Hassles		X				X				X				X		
General Well Being		X				X				X				X		
Health Locus		X				X				X				X		
Treatment Eval				X		X						X		X		
Health Habits Questionnaire			X			X					X			X		
24-hr Diet Recall			X			X					X			X		
Blood Sample			X		X	X					X		X	X		
24-hr Urine			X	X	X	X					X		X	X		
Pill Count				X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4

BLOOD AND URINE TESTS FOR LIFESTYLE INTERVENTIONS

		FOLLOW-UP VISITS			
	SV3	SRV	6-Month	12-Month	18-Month
BLOOD					
Serum calcium	x[a]				
Serum glucose	x[a]				
Serum creatinine	x[a]				
Serum potassium	x[a]				
Total cholesterol	x[a]				
Plasma and serum samples[b]	x				
Plasma sample for possible lipid analyses	x[c]			x[c]	x[c]
URINE					
Creatinine	x	x	x	x	x
Sodium	x	x	x	x	x
Potassium	x	x	x	x	x
Cortisol and catecholamines	x[d]	x[d]	x[d]		x[d]

[a] For eligibility (local laboratory)

[b] To be collected and stored for possible future analyses

[c] At SV3 only, to be collected and stored for all lifestyle participants at clinics offering weight loss. At the 12 and 18 month follow-up visits, to be collected and stored for weight loss and high weight control groups only (central laboratory)

[d] To be collected and stored at the central lab for all lifestyle and control participants, with a sample of sodium, stress, and control groups to be analyzed, pending availability of funds

Table 5

BLOOD AND URINE TESTS FOR SUPPLEMENTS INTERVENTIONS

	Stage 1 (Calcium and Magnesium)				Stage 2 (Potassium and Fish Oil)		
			FOLLOW-UP VISITS		New Baseline	FOLLOW-UP VISITS	
	SV3	SRV	3-Month	6-Month	EL3	3-Month	6-Month
BLOOD							
Serum calcium	x[a]				x[a]		
Serum glucose	x[a]						
Serum creatinine	x[a]				x[a]		
Serum potassium	x[a]				x[a]		
Serum magnesium	x		x[d]	x[d]			
Total cholesterol	x[a]				x[a]		
Plasma and serum samples*	x						
Plasma fatty acid phospholipids					x	x[c]	x[c]
Plasma sample for possible lipid analyses					x	x[b]	x[b]
URINE							
Creatinine	x	x	x	x	x	x	x
Sodium	x	x	x	x	x	x	x
Potassium	x	x	x	x	x	x	x
Magnesium	x	x	x[d]	x[d]			
Calcium	x	x	x[e]	x[e]			

[a] For eligibility (local laboratory)
[b] Fish oil and control groups only
[c] 50% sample of fish oil and control groups only
[d] Magnesium and control groups only
[e] Calcium and control groups only
* To be collected and stored for possible future analyses

Note: All of the above plasma and serum samples are drawn on all participants in the supplements intervention; analyses for specific assays are performed on all or a sample of participant as described in the footnotes.

Table 6

OUTLINE OF THE LOW-SODIUM INTENSIVE INTERVENTION SESSIONS

SESSION	THEME
Individual	Welcome
Group 1	'First Taste'
Group 2	'The Big Picture'
Group 3	'Starting Early'
Group 4	'New Approaches to Lunch'
Group 5	'The Best Meal of the Day'
Individual	Problem Solving
Group 6	'Sodium and Social Life'
Group 7	'Putting it all Together'
Group 8	'Keeping up with a New Lifestyle'
Monthly Maintenance Sessions	

Table 7

SCHEDULE OF INDIVIDUAL AND GROUP CONTACTS IN THE LOW SODIUM INTERVENTION

Screening			Randomization	Intensive Intervention Phase								
			Weeks:									
SV1	SV2	SV3	SRV	1	2	3	4	5	6	7	8	9	10
			IND1					IND2					
				GP1	GP2	GP3	GP4		GP5		GP6		GP7

IND = Individual contact
GP = Group contact

'TRANSITION'			MAINTENANCE								END
Months:											
3	4	6	8	10	12	14	16	18	20	22	24
IND					IND						IND
		GP	GP		GP	GP		GP	GP		GP
M	M	M	N	N		N	N		N	N	

[----------individualized telephone or in-person follow-up as needed----------]

IND = individual contact
GP = group contact
N = newsletter
M = transitional mailing

TOTALS: Minimum in-person contacts: Individual = 5; Group = 14

Table 8

DATA COLLECTION SCHEDULE FOR 24-HOUR AND OVERNIGHT URINES
FOR THE SODIUM INTERVENTION

Phase 1: Intensive Intervention

SCREENING			RANDOMIZATION	INTENSIVE INTERVENTION PHASE (Group Meeting Number)									
SV1	SV2	Sv3	SRV	1	2	3	4	5	6	7	8	9	>10
		U*°	U*°					U#	U#	U#			U#

Phase 2: Long Term Intervention

Phase 2A 'TRANSITION'			Phase 2B MAINTENANCE		
Months 6	9	12	15	18	
U*°	U#	U*°	U#	U*°	

* 24 hour urine; the overnight component will be collected separately and analyzed locally.

\# Overnight urine (local laboratory)

° Urine specimens collected trial wide.

Table 9

OUTLINE OF INTENSIVE INTERVENTION SESSIONS FOR WEIGHT LOSS INTERVENTION

Session 1

Weight loss and blood pressure
Introduction to keeping food diaries - portion size, describing food items
Introduction to exercise and the exercise graph
Keeping the weight graph
Building group cohesiveness

Session 2

Counting calories - fat, alcohol and sugar
Portion sizes
Exercise calories - burning fat vs. burning sugar, bonus exercise/step losing
Goal setting and action plans - didactic: weight, calorie and exercise goals
Individual planning (small group meeting)

Session 3

Counting calories - Cutting calories: substitutions, elimination, reducing portion size
Exercise and appetite/the rewards of exercise
Review of goal setting and action planning
Individual planning

Session 4

Food purchasing/shopping: Planning - nutrition, behavior
First supervised exercise: how to measure exercise intensity/pulse counting, effort/speed /duration = exercise dosage
Individual planning

Session 5

Situational triggers (small food topic to be selected): behavior change topic individual planning, supervised weight loss/exercise/body composition
Exercise planning/objectives
Supervised exercise
Individual Planning

Session 6

Eating Out I
Situational triggers continued, especially social triggers
Individual planning
Supervised exercise

Session 7

Eating Out II
Building social support
Individual planning
Supervised exercise
Advanced exercise calculations

Session 8

Introduction of "Diet Exchange" Program
Exercise exchange system - self-scoring of exercise records
Individual planning
Supervised exercise

Session 9

Review of First Food Exchange Diaries
Healthy Eating (U.S. Dietary Goals)
Individual Planning
Supervised Exercise

Session 10

Food Exchange Scoring System
Self-reinforcement techniques
Individual Planning
Supervised Exercise

Sessions 11-14

Outlines to be developed. All of these sessions will include:
Individual Planning
Supervised Exercise

Table 10

FINAL TOHP STRESS MANAGEMENT PROGRAM COMPONENT SEQUENCING

MONTH	SESSION	TYPE		
			Weekly Sessions	
M01	01	I	Individual orientation & intervention data collection	
M01	02	G	Group building + Slow-Paced Breathing	
M01	03	G	Bernstein & Borkovec Progressive Muscle Relaxation (B&B PMR) #1	
M01	04	G	B&B PMR #2: Emphasis on minimal tension & applications	
M02	05	G	Relaxation using Imagination	
M02	06	G	Applied Relaxing Imagination: Desensitization	
M02	07	G	Applied Relaxing Imagination: Positive Covert Rehearsal	M1
M02	08	G	Clinically Standardized Meditation (CSM)	
			Biweekly Sessions	
M03	09	G	Time Management #1	
M03	10	G	Active Listening Training	M2
M04	11	G	Active Listening + Assertiveness Training #1	
M04	12	G	Changing Stressful Thinking Patterns #1	
			Monthly Sessions	
M05	13	G	Changing Stressful Thinking Patterns #2	
M06	14	I	Individual session. Focus: Long term maintenance & applied skills	
M07	15	G	Long Term Maintenance of Stress Management Activities	
M08	16	G	Positive Cognitive Coping Strategies	
M09	17	G	Time Management #2	M3
M10	18	G	Active Listening + Assertiveness Training #2	
M11	19	G	Anger Management #1	M4
M12	20	G	Anger Management #2	
			Bimonthly Sessions	
M14	21	G	General Problem Solving Session #1	M5
M16	22	G	General Problem Solving Session #2	M6
M18	23	G	General Problem Solving Session #3	M7

Type: G or I: Type of session, group or individual
M1, etc.: Represents 10 min. segment on long term maintenance

Table 11

DOSAGES AND NUMBER OF DAILY PILLS REQUIRED FOR TOHP SUPPLEMENTS INTERVENTIONS

Supplement	Dosage/Day	Dosage/Pill	Pills/Day
Calcium carbonate	1000 mg	500 mg	2
Magnesium diglycine	360 mg	60 mg	6
Potassium	60 mmoles	20 mmoles	3
Fish oil*	3000 mg	500 mg	6

* 1000 mg capsule of Promega contains 500 mg of fish oil.

Table 12

SAMPLE SIZE AND POWER ESTIMATES: DBP

Intervention	Size of Comparison		Average Expected Follow-up	Δ for 80% Power (mm Hg)	Δ = 2 mm Hg
	Active	Control			
Sodium Restriction	327	416	18 months	1.32	.99
Weight Reduction	308	232	18 months	1.55	.95
Stress Management	242	319	18 months	1.66	.92
Calcium	237	234	6 months	1.60	.94
Magnesium	227	234	6 months	1.61	.94
Potassium	207*	203*	6 months	1.70	.91
Fish oil	199*	203*	6 months	1.72	.90

* Estimated numbers based on rerandomizing 85% of Stage 1 participants plus 6 additional in each group at Baltimore

Table 13
SAMPLE SIZE AND POWER ESTIMATES: SBP

Intervention	Size of Comparison		Average Expected Follow-up	Δ for 80% Power (mm Hg)	Δ = 3 mm Hg
	Active	Control			
Sodium Restriction	327	416	18 months	2.12	.98
Weight Reduction	308	232	18 months	2.49	.92
Stress Management	242	319	18 months	2.68	.88
Calcium	237	234	6 months	2.50	.92
Magnesium	227	234	6 months	2.59	.91
Potassium	207*	203*	6 months	2.70	.88
Fish oil	199*	203*	6 months	2.75	.87

* Estimated numbers based on rerandomizing 85% of Stage 1 participants plus 6 additional in each group at Baltimore

APPENDIX A

Participating Units

PARTICIPATING UNITS

Clinical Centers

East Boston Neighborhood Health Center
East Boston, Massachusetts
PI: James Taylor, MD

Kaiser Permanente Center for Health Research
Portland, Oregon
PI: Thomas Vogt, MD

New Jersey Medical School
Newark, New Jersey
PI: Normal Lasser, MD

St. Louis University
St. Louis, Missouri
PI: Jerome Cohen, MD

The Johns Hopkins University
Baltimore, Maryland
PI: Paul Whelton, MD

University of Alabama
Birmingham, Alabama
PI: Albert Oberman, MD

University of California
Davis, California
PI: Nemat Borhani, MD

University of Mississippi
Jackson, Mississippi
PI: Herbert Langford, MD

University of Pittsburgh
Pittsburgh, Pennsylvania
PI: Lewis Kuller, MD

University of Tennessee
Memphis, Tennessee
PI: William Applegate, MD

Coordinating Center

Harvard Medical School
Brigham and Women's Hospital
Brookline, Massachusetts
PI: Charles Hennekens, MD

Project Office

National Heart, Lung & Blood Institute
Bethesda, Maryland
PI: Jeffrey Cutler, MD

Central Laboratories

University of Minnesota
Minneapolis, Minnesota
PI: John Belcher, PhD

Channing Laboratory
Harvard Medical School
PI: Frank Sacks, MD

APPENDIX B

Data and Safety Monitoring Committee

DATA AND SAFETY MONITORING COMMITTEE

Members

Jeremiah Stamler, MD (Chairman)
Northwestern University

W. Stewart Agras, MD
Stanford University

Marianna Fordyce-Baum, PhD
University of Miami

C. Morton Hawkins, ScD
University of Texas

Theodore Kotchen, MD
University of Kentucky

Laurence McCullough, PhD
Georgetown University

Ronald Prineas, PhD
University of Miami

Ex-Officio Members

Herbert Langford, MD
Chairman, Steering Committee
University of Mississippi

Charles H. Hennekens, MD
Director, Coordinating Center
Harvard Medical School

Jeffrey Cutler, MD
Project Officer
National Heart, Lung & Blood Institute