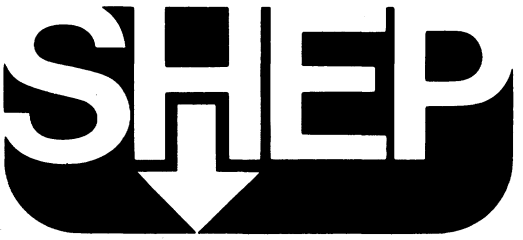

Systolic Hypertension in the Elderly Program

PROTOCOL

Revised April 17, 1985

PROTOCOL

SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

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I. INTRODUCTION

A. Background and Rationale

Isolated systolic hypertension (ISH), defined for this study as systolic pressure ≧160 mm Hg and diastolic pressure <90 mm Hg, is a common condition in the elderly. Population-based data show that the prevalence of ISH rises from approximately 8 percent in persons age 60-69 years to approximately 20 percent in persons over age 80. It has been estimated that in the U.S. more than three million persons over the age of 60 have ISH on a single measurement. These persons face an excess risk (2-3 fold) of stroke, other cardiovascular disease and death. Based on available data an annual stroke rate of 1.6 percent has been estimated in this population. Moreover, systolic hypertension may play a part in the etiology of multi-infarct dementia. Approximately half of the persons meeting the above definition of ISH on a single measurement have sustained ISH, i.e., have systolic blood pressure elevation on repeated examinations. It is the population with sustained ISH which is the subject of this study, and "ISH" as used hereafter refers specifically to this population. The size of this high-risk population is growing; the number of elderly in the United States is expected to increase by 20 percent over the next decade.

No adequate prospective evaluation has yet been completed to determine the effects of antihypertensive treatment on risks of morbidity and mortality in elderly subjects with ISH. Such treatment might have positive effects similar to those demonstrated for treating diastolic hypertension in middle-aged persons; it might also have adverse consequences. Whether one or the other of these effects predominates can most clearly be determined by carrying out a controlled clinical trial.

The Systolic Hypertension in the Elderly Program (SHEP), a multi-center study of the efficacy of antihypertensive treatment in elderly patients with ISH, will address the above issues. The primary objective of this study is to determine whether the long-term administration of antihypertensive therapy for the treatment of isolated systolic hypertension in elderly persons reduces the combined incidence of fatal and nonfatal stroke. Secondary objectives of the SHEP are to evaluate: (1) the effect of long-term antihypertensive therapy on cardiovascular morbidity and mortality in elderly people with ISH; (2) the effect of long-term antihypertensive therapy on other selected morbidity and on mortality from any cause in elderly people with ISH; (3) possible adverse effects of chronic use of antihypertensive drug treatment in this population; (4) the effect of therapy on indices of quality of life; and (5) the natural history of ISH in the placebo population.

Five thousand men and women who have ISH and are age 60 or over will be recruited, randomized into a double-blind, placebo-controlled, stepped-care treatment program, and followed for an average of five years (four to six years) (see Appendix I for sample size calculation). The study will be carried out by seventeen Clinical Centers, three laboratories for analyzing electrocardiographic, biochemical and CT scan data, and a Coordinating Center (see Appendices II and III).

B. Summary of the SHEP Pilot Study Results

To assess the feasibility of conducting a full-scale clinical trial, a pilot study was initiated in 1980. The SHEP Pilot Study had six objectives, each designed to develop and test critical components of a full-scale trial:

- To estimate and compare the yield of participants for randomization into a clinical trial from various community groups using a number of recruitment techniques.
- To estimate compliance with the visit schedule and to the prescribed double-blind treatment regimens.
- To estimate and compare the effectiveness of specified antihypertensive medications in reducing the blood pressure.
- To estimate and compare the unwanted effects of specified antihypertensive medication in an elderly population.
- To evaluate the feasibility and effectiveness of periodic behavioral assessment in this population.
- To develop and test methods of ascertaining stroke and other disease endpoints.

1. Recruitment

The feasibility of recruiting an elderly population for the study was successfully demonstrated. Each of the five clinics met its goal of at least 100 participants. Overall, 551 participants 60 years of age or over with isolated systolic hypertension were randomized within one year to the double-blind, placebo-controlled protocol.

In an unselected group of age-eligible persons not on antihypertensive treatment, the recruitment yield was approximately 1.0 percent, i.e., 1 person enrolled per 100 screened. In selected samples this yield was 4-5 percent. In the pilot SHEP, more than one-third of those screened were on antihypertensive treatment, and among those willing to be taken off therapy (up to one-third), 19 percent were randomized.

2. Compliance

Compliance with the treatment visit schedule was excellent in the pilot study. Data for the treatment visits occurring at 3, 6, 9, and 12 months showed that approximately 90 percent of treatment visits occurred within the established visit windows. When early visits and visits occurring less than one week late were included, the figure increased to 95 percent. This indicates that elderly participants were able to comply with the established visit schedule for at least a year.

The extent to which SHEP participants complied with their treatment regimens was assessed by pill-counts and self-report at each treatment visit, and by a urine test for the presence of chlorthalidone at the three-month and annual visits. The pill-count, self-report, and urinalysis data all indicated that 85-90 percent of active SHEP participants were excellent compliers with the treatment regimen throughout the first year of follow-up.

The proportion of terminations from SHEP medications was somewhat higher in the placebo group than in the active treatment group. About half of terminations were at the request of the participant. Using the life table method, the percentage of terminations after one year was estimated at 13.5 percent.

3. Effectiveness of Antihypertensive Medications

Step 1 randomization was in the ratio of 4:1 to active drug (25 mg to 50 mg chlorthalidone) or placebo. A satisfactory response to Step 1 required systolic blood pressure to fall by 20 mm Hg or to less than 160 mm Hg, whichever was lower. Those on active treatment not meeting these criteria at the three-month visit were randomized a second time to placebo, metoprolol, reserpine, or hydralazine twice daily. Placebo Step 1 participants not meeting these criteria received placebo Step 2.

A large percentage of the group randomized to chlorthalidone reached blood pressure goal, as compared with the placebo group. Three months after randomization, 75 percent of those on chlorthalidone were at goal, with the majority on the lower dosage. In contrast, only 34 percent on placebo were at or below goal, with the majority taking dose 2 of the placebo. There was little change in these percentages at six months.

At 3 months, the difference in fall of blood pressure for chlorthalidone versus placebo was 17 mm SBP and 3 mm DBP. This demonstrated that (1) the fall occurs promptly, and (2) it occurs predominantly in SBP compared to DBP.

4. Side Effects

Approximately 50 percent of both the active and placebo groups reported experiencing one of the 23 symptoms asked about at each of the visits: baseline, the one month follow-up visit, the first treatment visit after starting Step 2 medications, and the 12 month visit. Few symptoms were found troublesome by more than 10 percent of either study group. Two percent of the entire study group reported symptoms that they considered as intolerable. There was little change in the frequency of most symptoms during the study, with no important differences between active and placebo groups.

Changes in serum levels of potassium, uric acid, glucose, sodium, and cholesterol were monitored. There were shifts toward lower potassium and higher uric acid in the chlorthalidone compared to the placebo group. Differences were not seen in the other laboratory measures. There were no known untoward events associated with the hypokalemia. One patient developed gout while on chlorthalidone.

The frequency of ectopic beats and other arrhythmias during the one-minute 12 lead ECG was low and comparable for the active and placebo groups.

The 12 month cumulative rate of alteration in SHEP medication prescribed as a result of side effects judged by the clinician to be potentially harmful and possibly resulting from SHEP medications in the active group was 7.1 percent compared to 4.0 percent in the placebo group. The change usually consisted of reducing the dosage level or temporarily withdrawing medications. Eight subjects had SHEP medications discontinued for such reasons and in none of these instances was there a lasting adverse effect on the participant. The most common side effects resulting in medication reduction were dizziness, weakness, GI upset, and asthma.

5. Behavioral Assessment

Behavioral assessment included quantitative scales for depression, dementia,somatic symptoms, and activity level. Interviews were completed on all 551 participants at baseline, and on 485 at the annual visit. The time required for administering the interviews appeared reasonable, they were well-accepted by the participant, and the logistics were not a problem. Thus, the behavioral evaluation is feasible for use in a multicenter collaborative trial in an elderly population.

The prevalence of behavioral problems at baseline in the SHEP cohort was quite low when compared to a population sample of elderly persons and to a group of elderly persons diagnosed as clinically depressed or demented.

The frequency of a change of one level on the behavioral scales from baseline to annual visit was examined. The majority of participants (73 percent) experienced no change on any of the four scales during the year; an unexpectedly large percentage of participants (18 percent) improved on the depression scale while only 10 percent worsened.

6. Ascertaining Stroke and Other Disease Endpoints

Methods for ascertaining stroke and other disease endpoints were developed and tested in the SHEP pilot study and were demonstrated to be feasible. The assessment of stroke usually included consultation with a neurologist.

C. Objectives of the Main Trial

1. Primary Objective

The primary objective of this collaborative clinical trial is to assess whether long-term administration of antihypertensive therapy to elderly subjects with isolated systolic hypertension reduces the combined incidence of fatal and nonfatal stroke.

2. Secondary Objectives

The secondary objectives are to evaluate:

- The effect of long-term antihypertensive therapy on cardiovascular morbidity and mortality in elderly people with ISH.
- The effect of long-term antihypertensive therapy on other selected morbidity and on mortality from any cause in elderly people with ISH.
- Possible adverse effects of chronic use of antihypertensive drug treatment in this population.
- The effect of therapy on indices of quality of life.
- The natural history of ISH in the placebo population.

These objectives have been incorporated into a list of detailed main study questions for SHEP, which are in four broad categories of (1) biologic effects of reducing systolic blood pressure, (2) major potential side effects of the drug regimen, (3) major indices of the net health effect of the treatment program, and (4) major subgroup analyses.

3. Detailed Questions:

a) Biologic effects of reducing systolic blood pressure:

1) Will treatment of isolated systolic hypertension (ISH) reduce the combined incidence of fatal and nonfatal stroke (Main trial hypothesis)?

- Will this effect be specific for hemorrhagic and lacunar stroke?
- Will treatment of ISH prolong survival, given that a stroke has occurred?
- Will treatment of ISH reduce functional impairment or depression, given survival after a stroke?
- Will treatment of ISH reduce the incidence of multi-infarct dementia (MID)?

2) Will treatment of ISH reduce the incidence of fatal or nonfatal cardiac conditions, i.e., myocardial infarction, any cardiac death (including sudden death), or left ventricular failure?

3) Will treatment of ISH reduce the incidence of fatal or nonfatal conditions included in "1" and "2" above plus: dissecting aortic aneurysm, renal insufficiency, transient ischemic attack (2 or more), angina pectoris (on 2 or more occasions), symptomatic peripheral vascular disease, or coronary bypass surgery?

b) Major potential side effects of the drug regimen:

1) Will anticipated drug effects occur more often in active than in placebo treated participants (e.g., postural hypotension or electrolyte changes)?

2) Will unanticipated drug effects be discovered by comparisons between active and placebo groups?

c) Major indices of net health effect of treatment program:

1) Will treatment reduce:
- All-cause mortality?
- All hospital admissions?
- Total hospital days (including days of inpatient rehabilitation)?
- First admissions to nursing homes?
- Days of bed-disability out of hospital?
- Days of restricted activity?
- Episodes of clinical depression?
- Levels of depressive symptoms?
- Deterioration of cognitive functioning?
- Level of functional impairment as measured by the ADL and IADL scales?
- Incidence of dementia?
- Incidence of fractures of hip, wrist and vertebrae (by history)?

2) Does treatment affect the participant's quality of life?

d) Major sub-group analyses:

For example:

1) Will the treatment of ISH reduce the frequencies of the foregoing events or conditions to a greater degree in those not on antihypertensive medication at the time of screening than in those on such medication?

2) Will the treatment of ISH reduce the frequencies of the foregoing events or conditions to a greater degree in those with evidence of prior cardiovascular disease at baseline than in those without such evidence?

3) Will the treatment program reduce the incidence of sudden cardiac death, or of cardiac death plus nonfatal myocardial infarction, in those with resting ECG abnormalities at baseline, to a lesser degree than in those with normal ECGs?

4) Will the treatment of ISH have a different effect on stroke incidence according to age, race, or sex?

D. Timetable

To carry out the objectives of this trial, three phases are planned. Phase I will consist of drafting the protocol and developing forms and an operations manual. Phase II will be the operational phase of the study, encompassing participant recruitment, intervention and follow-up. During Phase III the Coordinating Center will operate for 2.5 years after cessation of the intervention phase to permit data analysis and dissemination of results. The Clinical Centers will close six months after cessation of participant follow-up.

Phase I

- Planning and organization - July 1984 - February 1985
- Completion of protocol and operations manual - December 1984
- Review of Phase I - December 1984
- Training of Clinical Center staff - February 1985

The protocol developed during Phase I will be reviewed and approved by the SHEP Data and Safety Monitoring Board, the sponsoring institutes (NHLBI and NIA), and individual Institutional Review Boards prior to the initiation of Phase II.

Phase II

- Begin recruitment of participants - March 1985
- Completion of recruitment - February 1987
- Completion of follow-up - February 1991

Phase III

- Close out of Clinical Centers - August 1991
- Completion of data analysis - August 1993

II. DETAILED PROTOCOL FOR THE SHEP

A. Recruitment of the Study Cohort

Recruitment efforts will be carried out at both the national and local level. At the national level endorsements will be sought from major organizations in medicine and aging. A national press release has been developed and has appeared in the Journal of the American Medical Association, March 22/29, 1985 (Vol. 253, No. 12). In particular, a supplementary resource for identifying age-eligible potential screenees for postal contact may be provided by area-specific lists of names and addresses of Medicare beneficiaries (i.e., covered persons age 65 and over). These will be obtained through the cooperation of the Health Care Finance Administration, U.S. Department of Health and Human Services. At the local level, area physicians, local government agencies, medical societies and hospitals will be contacted. A set of slides and brochures has been prepared and a logo has been developed for use in presentations to local providers, directors of organizations dealing with the elderly, and potential participants. Other local efforts to aid recruitment may include driver's license listings, voter registration listings, church and city directories, and commercial mailing lists. Techniques for recruiting will include: screening at community locations (e.g., senior housing developments, senior centers, health fairs, shopping centers and churches); door-to-door screening in areas where the elderly are highly prevalent; systematic telephoning; mailings based on listings of age-eligibles; physician referrals; medical record reviews; news releases; advertisements in newspapers, fliers, posters and TV; and other miscellaneous techniques.

B. Screening Phase

1. Initial Contact

All participants will have an Initial Contact which may take place in a SHEP clinic or at a location in the community convenient to the population being recruited. Several optional activities may precede the Initial Contact, such as telephone calling, which may be useful in screening out participants who are not likely to be eligible. The Initial Contact will serve primarily to eliminate persons who are clearly not eligible by age and blood pressure; informed consent will be obtained for this contact, if locally required. For everyone who participates at this visit, the following information will be obtained: date of birth, whether medication for high blood pressure is currently being taken, and a single blood pressure reading, taken in the sitting position with a standard sphygmomanometer. Participants must be 60 years of age or older for further consideration.

Persons not on antihypertensive medication whose single SBP is less than 150 mm Hg will not be evaluated further. (If such a person has a single DBP greater than 90 mm Hg, extra blood pressure readings may be taken for the participant's benefit, but this is not required.) If the first reading is 150 mm Hg SBP or greater, then two additional measurements will be taken. In order to be eligible for further screening, the average SBP of these second and third measurements must be at least 160 mm Hg but less than 220 mm Hg, and the average DBP must be less than 100 mm Hg (see Table 1 for a summary of blood pressure eligibility criteria).

For individuals who are on antihypertensive medications, three blood pressure readings will be taken, regardless of SBP level on the first reading. The average of the second and third SBP readings must be at least 130 and less than 220 and DBP less than 85 mm Hg in order to qualify that person for further evaluation.

For participants who do not meet the age and blood pressure criteria, no further information will be sought. For those who meet the criteria, other causes for exclusions will be queried: (a) an anticipated change of residence of more than 50 miles in the next year; (b) a cardiac pacemaker currently in use; (c) myocardial infarction or coronary artery bypass surgery in the past six months; (d) treatment with anticoagulants or insulin; or (e) stroke with apparent residual effects.

Participants who are not on antihypertensive medication and who are still eligible will be invited back to Baseline Visit 1 in 7-10 days, or as soon as possible. They will be asked to provide their names, addresses and telephone numbers, will receive a short orientation to the study, and will be given take-home forms to obtain further demographic and medical information, including medication history. They may also be given a consent form for Baseline Visit 1 and Baseline Visit 2 to take home and review, depending on local requirements.

TABLE 1

SHEP BLOOD PRESSURE ELIGIBILITY CRITERIA*

	Not On Antihypertensive Medications	On Antihypertensive Medications
Initial Contact:	SBP 160-219 mm Hg DBP <100 mm Hg	SBP 130-219 mm Hg DBP <85 mm Hg
Drug Evaluation Visit 1		SBP 130-219 mm Hg DBP <85 mm Hg
Drug Evaluation Visit 2†		SBP 160-219 mm Hg DBP <100 mm Hg
Baseline Visit 1	SBP 150-219 mm Hg DBP <95 mm Hg	
Baseline Visit 2	SBP 150-219 mm Hg‡ DBP <95 mm Hg and average of BL1 and BL2: SBP 160-219 mm Hg DBP <90 mm Hg	

*mean of second and third readings in the series for DBP and SBP values at Initial Contact and all Drug Evaluation visits; mean of two sitting determinations at Baseline Visits 1 and 2.

†or subsequent visit in evaluation period, up to 8 weeks after withdrawal of antihypertensive medications; participants with SBP less than 160 mm Hg should continue to be followed until SBP is in eligible range, SBP or DBP rise above eligible levels, or the 8-week evaluation period ends.

‡allow one more visit to qualify if SBP ≥220.

Participants who are receiving medicine for high blood pressure and who are still eligible will also be asked if they would be willing to allow their personal physician (if any) to be contacted to discuss possible antihypertensive medication changes. Those who agree to participate will be given an appointment for Drug Evaluation Visit 1 (DEV1). However, drug discontinuation could take place at the Initial Contact, providing that medical care of the participant is under the direction of a SHEP physician or the treating physician is contacted and gives permission during the Initial Contact, and that the participant meets the requirements for withdrawal discussed in Section II.B.2 following.

2. Withdrawal of Antihypertensive Medications

A participant will be a candidate for withdrawal if at the Initial Contact the average of the second and third SBP readings is at least 130 and less than 220 and DBP less than 85 mm Hg. All drug evaluation visits must take place in the clinic. The primary purpose of DEV1 is to evaluate whether the participant can be safely taken off medication. Any participant will be excluded from further study if withdrawal from medications is medically contraindicated, including any case in which medication has been prescribed for known diastolic hypertension. Informed consent is required specifically for withdrawal from medications. Three blood pressure determinations will be taken with a standard sphygmomanometer. Drug withdrawal may begin if at the Drug Evaluation Visit 1, the average of the second and third SBP readings is at least 130 and less than 220 and DBP less than 85 mm Hg. Several visits may be necessary in the SHEP clinician's judgement, to withdraw medications completely. During the drug withdrawal period, if SBP is at least 220 or DBP is 100 mm Hg or greater, the participant is ineligible and must be referred back to the usual source of care or original medications restarted. Those who are taken off antihypertensive medications completely will be given another appointment to be seen in two weeks. At that visit or any subsequent interim visit in the following two to six weeks, if the average of the second and third systolic blood pressure readings is at least 160 and less than 220 mm Hg, and the average DBP less than 100 mm Hg, the participant is eligible for Baseline Visit 1. If SBP is at least 220 or DBP is 100 mm Hg or greater, the participant is ineligible and must be referred back to the usual source of care or medication must be restarted. Participants may have blood pressure medications discontinued for up to eight weeks in order to establish blood pressure eligibility. Individuals who do not qualify at this time because their blood pressure is not high enough should be referred back to their usual source of care. If they remain off of antihypertensive medications and subsequently reach blood pressure levels eligible for the SHEP, they may be re-screened.

C. Baseline Phase

This phase, consisting of Baseline Visits 1 and 2 for each participant, permits eligibility for inclusion in the trial to be established, orientation to the program to be accomplished, and baseline data to be acquired. At all clinic visits, blood pressure will be measured with a Random-Zero device. Systolic pressure will be defined as the pressure at the first recognized Korotkoff sound. Diastolic pressure will be defined as the pressure at the fifth phase or last Korotkoff sound heard. After determining peak inflation pressure, two readings will be taken in the seated position, with a Random-Zero sphygmomanometer. In addition, two determinations of blood pressure will be made in the standing position. All decisions regarding eligibility and management will be based on the average of the two recorded values for the sitting determinations.

1. Baseline Visit 1

A participant will remain eligible if the average systolic blood pressure is at least 150 and less than 220 mm Hg and the average diastolic pressure is less than 95 mm Hg. In addition to the blood pressure determinations and review and completion of the take-home medical and medication histories, an ECG and two-minute rhythm strip, physical exam, and urinalysis will be performed. For those participants with a history of kidney disease, or proteinuria or hematuria with dipstick urinalysis, a non-fasting blood sample may be drawn at the discretion of the SHEP clinic physician for the purpose of locally determining serum creatinine.

A list of mandatory exclusions follows:

1) ECG evidence of:
   a) atrial fibrillation or flutter,
   b) second or third degree A-V block,
   c) multifocal VPBs, VPBs in pairs or runs, or VPBs more frequent than 10 percent of beats,
   d) bradycardia (<50 beats/minute).
2) Permanent pacemaker, judging by history and/or ECG.
3) History of stroke with residual paresis or other major neurological disability.
4) Suspect or established significant renal dysfunction.
5) Alcohol abuse (history of treatment for alcoholism, history of six or more drinks per day, or alcoholic liver disease).
6) History of coronary bypass surgery or myocardial infarction within the past six months.
7) Active treatment with insulin, anticoagulants, or drugs having antihypertensive activity (e.g.: beta-blockers, calcium channel blockers, diuretics, sympatholytics, etc.).
8) Congestive heart failure that is not adequately controlled.
9) Malignant neoplasm (other than non-melanomatous skin cancers) or other life-threatening disease.

10) Contraindications to chlorthalidone.

11) Contraindications to both atenolol and reserpine.

12) Peripherial arterial disease and evidence of ischemic tissue injury or loss.

13) Dementia, judged clinically.

14) Residence in nursing home requiring skilled nursing care.

15) History of transient ischemic attack (TIA) and carotid bruit in the appropriate location.

16) Two TIA's in the same location.

17) Malignant hypertension, past or present.

18) Treatment for known diastolic hypertension.

Other exclusions are possible if the physician feels that the individual's participation in a long-term study would be seriously impaired.

2. Baseline Visit 2

To remain eligible a participant must have an average systolic blood pressure of at least 150 and less than 220 mm Hg, and an average diastolic blood pressure less than 95 mm Hg based on determinations taken at Baseline Visit 2. In addition, the average of the first and second Baseline Visit SBPs must be at least 160 and less than 220, and DBP less than 90 mm Hg. Those participants with SBP of 220 mm Hg or greater will be allowed one more clinic visit within one week to qualify. For participants who are eligible, the average of the blood pressures at the first and second Baseline Visits is designated the "baseline blood pressure." An abbreviated SHORTCARE form, a behavioral assessment instrument for dementia and depression, will be administered, and persons who reach a criterion score for dementia will be referred to a study physician for further evaluation on eligibility. A detailed side effects history will be taken. Individuals who are still eligible and, after orientation to the study, agree to participate by signing the consent form, will be randomized by telephone with the Coordinating Center. Randomized participants will then have a blood specimen drawn after a 12-hour fast, receive some general information on diet, smoking and exercise, will be asked about activities of daily life, and then will be given their SHEP medications. Participants in six Clinical Centers will receive further behavioral evaluation.

3. Randomization

Participants will be randomized to either the active or placebo treatment regimen in a ratio of 1:1, stratified by Clinical Center and medication status at Initial Contact. Restricted randomization will be used to ensure sample sizes will be about equal in the active and placebo treatment groups during the course of the recruitment period. It is felt that with such a large sample randomization should produce comparable study groups with respect to baseline prognostic factors. Small imbalances can be taken into account at the time of analysis using appropriate statistical methods.

D. Treatment Program

1. Double-Blind Stepped Care Program

Approximately 300 participants will be randomized at each center to either chlorthalidone or matching placebo in a double-blind manner. The baseline systolic blood pressure will be used to establish goal blood pressure for each participant. For individuals with a baseline systolic blood pressure above 179 mm Hg, the goal will be 159 mm Hg. For those at 160 to 179 mm Hg, the goal will be a reduction of 21 mm Hg.

The objective of the treatment program is to use the minimal amount of medication that will keep systolic blood pressure at or below goal. Both the dosages and the selection of drugs will be stepped up until either goal or the maximum allowable dose of medication has been reached. Intolerable side effects or potentially serious blood chemistry changes (collectively termed "adverse effects") may require either stopping short of maximum dosage or prescription of a different study drug.

All randomized participants will be started on a low dose of chlorthalidone (12.5 mg/day) or matching placebo. Following randomization, a participant should return in four weeks for a first visit, and then again four weeks later. If at or below SBP goal at eight weeks, the participant will return at the regularly scheduled quarterly visit. If goal has not been reached at the end of eight weeks, the dosage will be increased to 25 mg/day of chlorthalidone or matching placebo. The participant continues to return at four-week intervals for blood pressure checks. If, at 16 weeks, the participant is still above goal on 25 mg/day of the Step 1 drug, the Step 2 drug, atenolol 25 mg/day or matching placebo, will then be prescribed. The same type of visit sequence will apply to persons on Step 2 drugs: two visits at four-week intervals, with dosage increase to atenolol 50 mg/day or matching placebo at eight weeks for persons not at goal.

Participants in whom contraindications exist to atenolol at the point of Step 2 initiation, or intolerable side effects to atenolol develop, will receive reserpine in doses of 0.05 or 0.1 mg/day as a secondary Step 2 drug in an analogous manner.

In summary, if a participant is above goal at two consecutive monthly visits, he or she will be stepped up to an increased dose or the next step drug until at the maximum step and dose. Other reasons for stepping up medications would be if a participant is at escape blood pressure (defined below), or if it is otherwise necessary in the clinician's judgment.

If at any visit the participant reports being prescribed any antihypertensive agent by a non-SHEP physician, the SHEP physician will contact the prescribing physician, review the SHEP study, and discuss whether the participant may discontinue that drug. If the prescribing physician declines, the SHEP medications may be reduced or stopped if it is necessary in the judgement of the SHEP physician.

2. Blood Pressure Escape Criteria

An escape blood pressure is defined as an SBP or DBP alert level that indicates a special action; SBP and DBP escape criteria are outlined in Tables 2 and 3.

An average SBP reading of 240 mm Hg or above on a single visit qualifies as an escape pressure, and individual therapy should be initiated. For participants not on maximum study medications (i.e., not on Step 2, Dose 2), an average SBP of 220-239 mm Hg requires a return in two weeks; if the SBP is still 220-239 mm Hg, the next drug dose or step should be initiated. If the participant is on maximum drug dosage and the average SBP is 220-239 mm Hg on two visits two weeks apart, then this participant should be regarded as a treatment failure and put on individual, open-label antihypertensive therapy. Unblinding as to initial randomization to active or placebo therapy will be discouraged for participants requiring open-label antihypertensive therapy.

An average DBP of 115 mm Hg or above at a single visit requires prompt individual open-label therapy. If the average DBP is 95-114 and the participant is not on the maximum dosage of study drugs, the participant should return in one to two weeks; if still elevated, the next dose step should be initiated and and the participant should return again in one to two weeks, with the process repeating until the participant's DBP responds or the maximum dosage of protocol drugs is reached. If the DBP remains elevated on maximum dosage of study medication, individual open-label therapy should be prescribed.

If the participant is not on the maximum dose of study medications and the DBP is 90-94 mm Hg on two consecutive monthly visits, the next drug dose or step should be prescribed. This process will be repeated until DBP is below 90 mm Hg or the maximum dose of study medications is reached. If the participant is on the maximum dose of study medications, and the DBP is 90-94 mm Hg at three consecutive monthly visits, individual non-pharmacologic therapy or open-label drugs should be initiated.

If escape criteria are attained, the SHEP protocol medications should be stopped, and therapy adjusted according to the clinician's best judgment. These patients should still be followed in the SHEP clinic, according to the visit schedule described herein for all SHEP participants, and should receive all evaluations required at those visits.

TABLE 2

SHEP SYSTOLIC BLOOD PRESSURE ESCAPE CRITERIA

Situation	SBP Level	Action
1. Anytime	≧240 mm Hg	Individual open-label therapy should be initiated.
2. Participant not on maximum dosage of study drugs	220-239 mm Hg	Return in two weeks; if SBP remains above 220 mm Hg, move to next drug dose or step.
3. Participant on maximum dosage of study drugs	220-239 mm Hg	Return in two weeks; if SBP remains above 220 mm Hg, individual open-label therapy should be initiated.

TABLE 3

SHEP DIASTOLIC BLOOD PRESSURE ESCAPE CRITERIA

Situation	DBP Level	Action
1. Any time	≧115 mm Hg	Individual open-label therapy should be initiated
2. Participant not on maximum dosage of study drugs	95-114 mm Hg	Return in 1-2 weeks; if DBP remains 95-114, move to next drug dose or step; return in 1-2 weeks and repeat step-up until DBP is less than 95 or maximum dose of study drugs reached
3. Participant not on maximum dosage of study drugs	90-94 mm Hg	On two consecutive monthly visits; move to next drug dose or step; repeat until DBP <90 or maximum dose of study drugs reached
4. Participant on maximum dosage of study drugs	95-114 mm Hg	Return in one to two weeks; if DBP still 95-114, initiate individual open-label therapy
5. Participant on maximum dosage of study drugs	90-94 mm Hg	On three consecutive monthly visits; initiate open-label drug or nonpharmacologic therapy

3. Possible Adverse Effects

If conditions occur that may be harmful and are considered drug-related ("adverse effects") (e.g., postural hypotension symptoms, depression, asthma or bronchospasm, Raynaud's phenomenon, serious lethargy, etc.), the medication thought to be associated with that adverse effect may be stepped down to progressively lower levels (or immediately if warranted by severity of adverse effects), ultimately reaching every-other-day dosage of Step I drug. If clinically advisable, medication may be discontinued. Whenever medication is reduced or discontinued, consideration will be given to carefully re-starting study medication if the blood pressure is above goal and the participant is willing.

If SBP falls to 110 mm Hg or below, drugs may be stepped down to the next lower step or dose at the discretion of the SHEP clinician. If SBP is above goal at any subsequent visit, drugs will be stepped up again.

Potassium supplementation is indicated if, on two consecutive scheduled visits, serum potassium is less than 3.5 meq/l. If it is between 3.2 and 3.5 meq/l once, potassium should be re-checked on the next scheduled visit. If the potassium is less than 3.2 meq/l, the participant should be recalled within one week of notification for a local re-check of the potassium level.

Oral potassium supplementations will be Micro-K in 10 meq tablets. The suggested dosage schedule for Micro-K is:

1) 2 tablets once per day to start (20 meq)
2) 3 tablets once a day if needed (30 meq)
3) 2 tablets two times a day if needed (40 meq)

For any participant, if the serum uric acid level rises above 9.9 mg/dl, a uric acid-lowering agent may be added to the regimen; such action is required for participants with a history of acute gout.

4. General Lifestyle Advice

Standardized general information on nutrition, smoking and exercise will be given to all participants. Moderation of salt intake in favor of foods high in potassium will be recommended. Avoidance or reduction of obesity, and regular gradual exercise will be advised.

E. Behavioral Evaluation

The objectives of the behavioral evaluation component of the SHEP are:

1) to define the level of cognitive functioning and affective functioning, activities of daily living, and nature of social supports at baseline, and

2) to measure changes in these variables over time in relation to treatment assignment and blood pressure levels.

In a pre-test, this component usually took no more than 60 minutes to administer, could be administered by persons other than behavioral scientists, and was generally well-received by the participants.

The entire battery includes:

1) SHORTCARE (reduced to those items required for detecting clinically significant depression and dementia)

2) Center for Epidemiologic Studies-Depression Scale (CES-D)

3) Activities of Daily Living (ADL)

4) Social Network Questionnaire (social support)

5) Behavioral Evaluation-Part II, consisting of :

- questions on anger
- Trailmaking Test (visual-spatial ability, set-shifting)
- Digit-Symbol Substitution (visual-spatial ability, set-shifting, attention, memory)
- Addition Test
- Finding A's Test
- Boston Naming Test (language)
- Delayed Recognition Span Test (memory)
- Quality of Life
- Activities Scale
- Letter Sets Test

The SHORTCARE is the instrument used to screen systematically for clinically significant depression and dementia. It will be administered along with the CES-D at baseline prior to randomization, quarterly during the first year of follow-up, and at all annual visits. If a participant reaches criterion score for dementia on the SHORTCARE prior to randomization, that person will be referred back to a physician for judgment as to that person's eligibility for the trial, in light of what is already known about that person. Participants reaching depression criterion score at two consecutive visits will be referred for diagnostic evaluation. At all evaluations, persons reaching criterion score for dementia will be referred for diagnostic evaluation.

The Activities of Daily Living Questionnaire will be administered at the Baseline Visit 2 and annually, and the Social Network Questionnaire will be administered at the one-month clinic visit and annually.

The Behavioral Evaluation-Part II will be administered at baseline (after randomization), and at all annual visits by six of the seventeen SHEP Clinical Centers.

F. Follow-up Procedures

1. One-Month, Two-Month, and Quarterly Visits (Required)

All participants are required to be seen in the clinic at one month, two months, and quarterly after the date of randomization. All of these required visits will include measurement of blood pressure, heart rate and weight, a general interval history that includes screening questions for stroke and other endpoints, and the use of concomitant medications. A pill count and compliance self report will be done at visits following a medication change and every six months. If positive responses are obtained from the general interval history, a complete side effects questionnaire will be administered, including a brief physical exam for positive responses to selected items. The SHORTCARE and CES-D sections of the behavioral evaluation will be administered at the quarterly visits during the first year of follow-up. Additional procedures will include a serum potassium determination at the next visit after starting or increasing a Step I drug.

2. Annual Visits

The annual visits (at each anniversary of the date of randomization) will include all procedures in the one-month, two-month and quarterly visits, plus a more comprehensive history and physical examination, complete side effect questionnaire for all participants, a brief neurologic exam, and the complete behavioral evaluation. Blood chemistries (fasting at Baseline, Year 1 and Final Annual), urine chlorthalidone (blinded), dipstick urinalysis, hematology, and a 12-lead resting ECG and two-minute rhythm strip will be included at annual visits as specified below.

3. Other Visits

Other visits may be scheduled at the SHEP clinic for various reasons: (a) the participant is above goal SBP; (b) the participant is at escape SBP or DBP levels; (c) serum potassium is not in the normal range; (d) it is necessary in the clinician's judgment; or (e) it is requested by the participant. These visits will include, at a minimum, measurement of blood pressure and pulse; other procedures indicated will depend on the reason for the visit.

4. Laboratory and ECG Procedures

The SHEP study will use the procedures listed below in the frequencies indicated:

Procedures	Frequency
Serum chemistries: Alkaline phosphatase Blood urea nitrogen Calcium Creatinine Glucose SGOT Sodium Uric acid	Baseline and Annual
Serum potassium	Baseline, one month, annual plus visit after Step 1 dose is increased
Total serum cholesterol, HDL cholesterol, and triglycerides	Baseline, Year 1, Final Annual
Hb/Hct, WBC (local)	Baseline and Annual
Qualitative test for urine chlorthalidone	Year 1, Year 4
Dipstick urinalysis (local)	Baseline and Annual
ECG and two-minute rhythm strip	Baseline, Year 2, and Final Annual

G. Morbidity and Mortality Surveillance

1. Endpoint Evaluation

The major hypothesis will include all strokes, fatal and nonfatal. One event per patient will be permitted for primary analytic purposes, but data will be collected on all events for other analyses. All events will be adjudicated as either present or absent.

Three categories of events will be classified: strokes (fatal and nonfatal), non-stroke cardiovascular events and conditions (fatal and nonfatal), and other events. These events are listed below:

I. Stroke - fatal and nonfatal

Atherosclerotic	Intraparenchymal hemorrhage
Embolic	Subarachnoid hemorrhage
Lacunar	Other hemorrhage
Other ischemic	Unknown

II. Non-stroke cardiovascular events and conditions--fatal and nonfatal

Acute myocardial infarction	Coronary bypass surgery
Sudden death	Carotid surgery
Left ventricular failure	Other arterial surgery
Other cardiovascular death	Peripheral vascular disease
Renal dysfunction	Left ventricular hypertrophy
Transient ischemic attack	Significant ventricular arrhythmia
Angina	Aortic aneurysm

III. Other events

Noncardiovascular death	Depression
Hospitalizations for reasons other than above	Dementia--multi-infarct other
Intermediate or skilled nursing home admission	Fractures

2. Acute Evaluation of Stroke

Stroke is defined as a neurological condition with a rapid onset of a persistent neurologic deficit attributed to an obstruction or rupture of the arterial system which is not known to be secondary to brain trauma, tumor, infection or other cause. The deficit must last more than 24 hours unless death intervenes or there is a demonstrable lesion compatible with an acute stroke on a CT scan. The steps in ascertaining that a stroke may have occurred in SHEP will be suspicion through a scheduled clinic examination, or through interim ascertainment of hospitalization or death. All strokes should be reviewed in the acute phase by a consulting neurologist if possible. All suspected strokes will be coded by the Endpoint and Toxicity Subcommittee. Specific stroke criteria are listed in Appendix IV.

An attempt will be made to categorize strokes as thrombotic, embolic or hemorrhagic, including subtypes (see Appendix IV), but this subdivision is not relevant to the primary analysis of events. It would, however, be necessary for addressing a subhypothesis relating to type-specific effects of antihypertensive therapy in ISH.

Since the CT scan is such an important test to confirm stroke or rule out other diseases, an effort will be made to obtain CT scans on all SHEP participants with suspected stroke. If the participant is seen in the hospital by a consulting neurologist, the neurologist can suggest a CT scan be done early if none has yet been done. If the participant had an early CT scan and it was normal, the neurologist may obtain a follow-up CT scan. If the participant has been discharged from the hospital and no CT scan was done, or no lesion was demonstrated, it is proposed that a CT scan be done with the participant's permission.

The CT scans will be collected by each Clinical Center and sent to a central reading location. Information about the type of machine and the slice thickness is requested. The reading of the CT scans will be accomplished by a reader(s) using a standardized protocol. The reader(s) would be blinded to the clinical opinion or presumed location of the stroke. The results of the readings would be used, along with other available information, by the Endpoint and Toxicity Subcommittee in the determination of whether or not a stroke occurred.

3. Review and Adjudication Process

The following events require special notification to the Coordinating Center and review and adjudication by the Endpoint and Toxicity Subcommittee:

- any death
- stroke
- acute myocardial infarction
- transient ischemic attack
- left ventricular failure

The Coordinating Center will work to ensure that all information required by the Endpoint and Toxicity Subcommittee has been assembled and arranged prior to each of its scheduled meetings. Should any of this information not be received after a specified interval, the Coordinating Center will contact the Clinical Center. The material provided to the subcommittee will be screened to exclude potentially unblinding content not essential for establishing a diagnosis.

In the case of a death, the Coordinating Center will expect to receive initial notification within 48 hours of ascertainment of the fact of death by the local SHEP clinic. A death certificate, narrative histories from the personal physician and next-of-kin, and, if available, a hospital summary and autopsy report will be required. Timeliness of receipt of these essential documents will be monitored closely.

Morbid events may be ascertained through a routine physical examination, interval medical history, and/or examination by a neurologist in the case of possible stroke. The Clinical Centers will be responsible for the timely initial notification of the event, as required, and collection and transmission of other information pertinent to the event, such as hospital discharge summaries, in addition to routinely collected study forms.

4. Lost to Follow-up--NDI and SSA

Although efforts will be made during the study to minimize losses to follow-up, at the end of the follow-up period there will be a small number of persons for whom vital status cannot be ascertained through local Clinical Center efforts. Detailed efforts will be made, for example, through the National Death Index and Social Security Administration, to ascertain vital status for these participants, and will be undertaken by the Coordinating Center in conjunction with the Clinical Centers concerned.

H. Safeguards

1. Informed Consent

Informed Consent will be obtained for (1) the screening phase of the study, (2) withdrawal of antihypertensive medications, if applicable, and (3) randomization into the trial. Individuals who are eligible to participate will be informed of the nature of the study and that they will have equal chances of being treated either by active drugs or by placebo. Materials will be developed that will explain to the potential participant the benefits and risks of the SHEP, all protocol procedures, the right to withdraw from the study at any time without penalty, alternative treatments (if any), the confidentiality of all personal information, and a statement regarding compensation if research related injury should occur. Participants will be asked for their permission to use their Medicare number (or, if unknown, Social Security number) in making inquiries of the Medicare agency regarding hospitalizations. They will be told that this will in no way affect their Medicare coverage. In addition, the participant will be given ample opportunity to raise questions. Consent will also be required to collect medical records for events occurring during the trial.

2. Care of Participants in the Event of Possible Adverse Reactions or Acute Illness

Participants will be monitored closely for possible adverse reactions and will be advised to contact the Clinical Centers if they suspect such a reaction. Each suspected adverse reaction should be carefully reviewed by the physician(s) at the Clinical Center. Actions to be taken with respect to the drug regimen are outlined in Section II.D.2, above.

Each Clinical Center should have a physician on call at all times to make appropriate referral in the case of emergencies. In the event of such an emergency, or if a specific clinical need arises, a pharmacist or other individual not directly involved in SHEP will have access to a list to be used in patient unblinding. (This must be provided for by all Clinical Centers on a continuous, 24-hour basis throughout the course of the SHEP.) Once the emergency or acute episode is over, a participant may be restarted on medication if appropriate.

To avoid unnecessary unblinding, the Principal Investigator of each SHEP Clinical Center (or a designated Co-Investigator) will, except in extreme emergencies, discuss the need for unblinding with the participant's attending physician. If unblinding is thought to be necessary, the Principal Investigator will instruct the pharmacist to release the information to the attending physician. The attending physician alone will be unblinded and will be instructed to keep the data confidential if possible. All unblinding will be discussed with the Coordinating Center prior to taking any such action, when possible. Again, a participant may be restarted on his or her original drug regimen, if the SHEP physician feels it is appropriate and the participant agrees.

I. Distributed Data Entry System

The SHEP study will use a distributed data entry system. Remote data entry via microcomputers at each Clinical Center will provide the means for consolidating collection, entry, verification and validation of the data prior to transmission to the Coordinating Center.

Important features anticipated from the use of distributed data processing are reduction in error rates, potential for more complete data and promotion of timeliness of the data on the computer masterfile.

The study data will be collected on an array of paper forms designed to meet the needs and requirements of the SHEP, as outlined in this Protocol: screening, clinical data, laboratory investigations, follow-up, endpoints, and others.

At the end of each clinic day, the data collected will be stored locally on a microcomputer. This system will include a keyboard, video display screen, storage device (floppy disks), a printer and a modem for telephone communications. Software will include custom programs for interactive data entry, verification, and validation, range and consistency checks. The layout of each form type will be displayed on the screen as the operator is queried or prompted through each data item in the required sequence.

After each form has been entered, validated and verified, the data will be stored on disk for periodic transmission via telephone line to the Coordinating Center.

Copies of paper forms will be collected by the Coordinating Center for baseline visits, required follow-up visits and procedures, endpoint reports with ancillary documentation, and reports of unblinding. Periodically, random samples of paper forms will be selected for comparison with the SHEP computerized data base. In addition, paper forms not collected by the Coordinating Center will be compared during periodic site visits.

J. Training

After the Protocol and Manual of Operations have been developed, but before the first participant is screened, Clinical Center staff members will be trained in the standardized collection and preparation of study data. These centralized training sessions will be held in February 1985. The Manual of Operations and the Training Manuals will be the basic tools in this training. These sessions will cover the following areas:

1. Data collection:

Forms will be developed in order to facilitate data collection. Training sessions will be held centrally, with each form and procedure being reviewed in detail with the respective portions of the Manual of Operations being used as training material. Specialized training/ orientation sessions will also be held for those staff members involved in completing special study procedures and forms, e.g., neurological evaluation, mortality/morbidity review documents, recording of ECGs, and collection of serum specimens.

2. Blood pressure observation:

Coordinating Center personnel will supervise centralized training sessions in blood pressure monitoring, using established blood pressure training and certification methods. Two persons from each Clinical Center will be centrally trained and certified; these staff members will be provided with full sets of the training materials needed to reproduce the same certification program for field and clinical staff at their own Clinical Centers. All SHEP blood pressure observers will be recertified annually. This training/recertification/monitoring system will do much to ensure that standardized high-quality blood pressure measurement continues throughout the SHEP.

3. Behavioral evaluations:

The Behavioral Assessment Subcommittee will develop training procedures for behavioral evaluation and will oversee such activities. Special emphasis will be placed on techniques for minimizing anxiety during these evaluations. Provisions will be made for periodic retraining during the trial.

4. Data entry, validation and transmission:

Special training sessions will be held at the Coordinating Center for appropriate Clinical Center personnel in data entry, validation and transmission by using both the hardware and the software to be used in the SHEP. Easy-to-understand documentation for each procedure and each form will be developed concurrently with the distributed data processing system and used as a basis for the training sessions. The training materials will contain clear, realistic examples of each step in each process (entry, validation, transmission) including specific instructions regarding out-of-range and unavailable data. These sessions will also include training in other edit procedures. Communication with the Coordinating Center personnel via the micro-computer system or telephone will be encouraged at all times for questions or suggestions on the system and to ensure the clarity and conciseness of reports produced.

In addition to central sessions which may be held periodically during the course of the study to provide training on revised procedures and to reinforce earlier training, the personnel of the Coordinating Center and other appropriate SHEP staff will site visit Clinical Centers to review any problem areas which may develop and to help train new personnel if necessary. It is proposed that central training sessions be held twice a year at different Clinical Centers, possibly in conjunction with Steering Committee meetings. Much informal training is accomplished by giving coordinators the opportunity to share problems and exchange solutions.

K. Quality Control

There are basically five areas of quality control (QC) in this trial:

- Clinical Centers
- ECG Reading Center, Central Laboratory, and CT Scan Reading Center
- Coordinating Center
- Project Office/Steering Committee
- Data and Safety Monitoring Board

1. Clinical Centers

Comprehensive training sessions will provide the basis for all Clinical Centers to carry out properly all study procedures and data collection. These training sessions are briefly described in Section II.J of this Protocol. Specific QC activities to be carried out at the Clinical Center level include:

a) Certification/recertification of field and clinic staff in study procedures, by centrally-trained supervisors.

b) Regular observation and monitoring of specific clinical procedures.

c) Scheduling and monitoring of regular equipment maintenance.

d) Reporting of quality control concerns/problems to Coordinating Center personnel for prompt resolution.

e) Monitoring and editing of study data through the distributed data processing system.

Clinical Center staff will be encouraged to communicate with the Coordinating Center for any questions of interpretation of procedures or criteria.

2. ECG Reading Center, CT Scan Reading Center, and Central Laboratory

External quality control of the ECG and CT Scan Reading Centers will be accomplished by submitting randomly selected ECGs and CT Scans to the appropriate center for re-reading. This set of quality control ECGs and CT Scans will be blinded at the Coordinating Center each time they are cycled through the system to ensure an unbiased and representative check on the quality of the coding process.

External quality control will be conducted for the serum determinations and urine chlorthalidone analyses at the Central Laboratory. Specially prepared samples will be cycled through the Central Laboratory in a blinded fashion. The data from these samples will be analysed at the Coordinating Center for consistency and system drift over time. Also, the Central Laboratory will complete the CDC lipid standardization program.

In addition, internal quality control procedures are carried out at the ECG Center and Central Laboratory. Results of these procedures will be obtained as a supplement to other quality control procedures.

3. Coordinating Center

During the first year of recruitment and follow-up, the Coordinating Center, with other study personnel, will hold site visits at each Clinical Center to ensure that study procedures are understood and carried out correctly. Thereafter, site visits will be performed if consistent departures from the protocol and Manual of Operations are detected for any center. Retraining and/or recertification will occur as needed during these visits. Consistent departures across all centers may precipitate changes in procedures and/or special retraining sessions. It is the responsibility of Coordinating Center personnel to review on a timely basis reports prepared to monitor such items, to initiate procedures to remedy departures as soon as possible, and, if necessary, perform site visits at the Clinical Centers, as well as to perform follow-up evaluations of actions taken.

Monitoring of study data will take place at the Coordinating Center. These activities include inventory, validation, data control (e.g., filing, manual editing, special coding efforts), some data entry, and report generation. Some of the monitoring and quality control reports will be transmitted to the Clinical Centers for immediate action and attention. Other quality control and monitoring reports will be generated for the Project Office/Steering Committee and Data and Safety Monitoring Board.

4. Project Office/Steering Committee

During the recruitment period of Phase II, weekly reports will be provided to the Project Officer and NIA on recruitment activities by each Clinical Center.

During all phases, monitoring reports and analyses will be generated for the Project Officer, NIA, and other investigators to monitor data quality, Clinical Center performance, protocol adherence, and adverse reactions.

Annual reports will, among other items, summarize the year's quality control activities.

5. Data and Safety Monitoring Board

The Data and Safety Monitoring Board will periodically review and evaluate study progress including data on recruitment, quality control, compliance, adverse effects, and fatal and nonfatal events. During Phase II, unblinded data will be available to this group only.

L. Data Analysis

The primary endpoint of the SHEP is fatal plus nonfatal stroke. The primary response variable is the time from randomization to development of a stroke. Consequently, life tables and survival analysis techniques will be employed to compare the rate of stroke in the active treatment group with the placebo group. All randomized participants will remain in their originally assigned groups for purposes of analysis, regardless of subsequent medication changes (e.g., termination of SHEP medications or initiation of open-label antihypertensive therapy).

Life tables will be calculated for each treatment group to determine the incidence rates of stroke at each year of follow-up. Statistical tests will be used to compare the 5-year incidence rates.

A comparison of 5-year rates does not consider, however, the pattern of incidence over the entire follow-up period. To this end, two-sample non-parametric procedures such as the log-rank test or the proportional hazards (ph) regression model will be used to compare the incidence curves. These methods are more powerful than a simple comparison of rates at a fixed time point. The ph model will be particularly important in assessing the efficacy of the study medication after multivariate adjustment of any baseline differences between treatment groups with respect to the potential risk factors (covariates). Other analyses will be employed to test previously-defined sub-hypotheses.

During the trial, endpoint data will be monitored and submitted to the Data and Safety Monitoring Board to permit early termination of the study should the data warrant. Multiple testing procedures would be employed to aid in such a decision.

M. Publication and Presentation Policy

This section of the SHEP Protocol is being developed and will be acceptable to and voted on by the SHEP Steering Committee.

N. Ancillary Study Policy

Individual investigators are encouraged to carry out ancillary studies. Such ancillary studies enhance the value of the Systolic Hypertension in the Elderly Program and ensure the continued interest of the investigators. Nevertheless, to protect the integrity of the SHEP, such ancillary studies must be reviewed and approved by the Scientific Review and Ancillary Studies Subcommittee and the Steering Committee before their inception. This review will be primarily to determine that the ancillary study will not compromise, complicate, or jeopardize the conduct of the SHEP protocol. Review of proposed ancillary studies for scientific merit is not the primary responsibility of this subcommittee, but optional suggestions of a scientific nature may result from the review.

APPENDIX I

SAMPLE SIZE CALCULATIONS

The assumptions used for the sample size calculations are summarized here. Participants are 60 years of age or older with isolated systolic hypertension. Half of the participants will be randomized to an active treatment program and the other half to placebo. The average follow-up period will be 5 years (6 years for the first randomized participant). The primary endpoint is fatal plus nonfatal stroke (one-third fatal and two-thirds nonfatal).

It is assumed that the annual event rate among subjects on placebo is 1.6 percent; this estimate was derived from the SHEP pilot study. Based on this estimate the 5-year rate in the placebo group is assumed to be about 7.75 percent. If all subjects were to remain on their assigned treatment, the treatment is assumed to reduce the 5-year rate by 40 percent (i.e., a 5-year rate in the treatment group of 4.65 percent). In order to account for the effects of subjects who do not adhere to their assigned regimen, the 5-year event rates for both groups must be adjusted. The proportion of participants on active medication who terminate or substantially reduce their study medication (drop-out rate) is estimated to be 7 percent in the first year and 3.5 percent in each of the second through fifth years. These proportions were higher in the SHEP pilot study active treatment group, but many of the participants who "dropped out" during the pilot study went on to individual therapy and are not included here as dropouts. It is also estimated that the proportion of participants on placebo who are placed on antihypertensive treatment during the trial (drop-in rate) is 9 percent in the first year and 4.5 percent, 5.0 percent, 5.5 percent, and 6.0 percent in each of the remaining 4 years, respectively. A proportion of participants will die during the trial from causes other than stroke and thus not be at risk of subsequent stroke. This so-called competing risk over the 5 years has been estimated at 15.4 percent. The drop-out rate adjusts the 5-year treatment event rate upward and the drop-in rate adjusts the placebo event rate downward. This modification yields adjusted observed 5-year rates of 4.7 percent for the treatment group and 6.9 percent for the placebo group. Based on these rates the observed treatment effect would be a 32 percent reduction.

The significance level is set to .05 with the hypothesis being two-sided. The null hypothesis is that the 5-year incidence of stroke is the same in the active and placebo treatment groups. The power, the probability of finding a specified difference given that it actually exists, has been set at .90.

In order to detect a 32 percent reduction with a power of .90, a total sample size of approximately 4800 is required. For administrative purposes, the enrollment objective will be 5000.

APPENDIX II

ORGANIZATION AND MANAGEMENT OF THE TRIAL

The participating units of the trial--seventeen Clinical Centers, a Coordinating Center, ECG Laboratory, Central Laboratory, CT Scan Center, Drug Distribution Center and Project Office--are administratively tied through a structure designed to enhance effective communication and collaboration, as well as to monitor and maintain operations of the trial (see Figure 1). Each of the participating units has been involved in the planning and development phase of the trial and will contribute to the writing of the Manual of Operations; all are committed to conducting the study in a consistent and uniform manner in adherence to a common protocol.

The roster of participating institutions and investigators is contained in Appendix III.

Data and Safety Monitoring Board (DSMB)

The DSMB is composed of scientists who are experts in fields relevant to the trial but are not investigators in the trial. This group will periodically review and evaluate study progress, including data on recruitment, quality control, compliance, adverse effects, and fatal and nonfatal events. During Phase II, unblinded data will be available to this group only.

Executive Committee

The Executive Committee includes the Chairman of the Steering Committee, representation from the Coordinating Center, and the NIH Program Office. This committee will develop Steering Committee agendas and recommendations for consideration by the Steering Committee, and will provide study direction between Steering Committee meetings.

Steering Committee

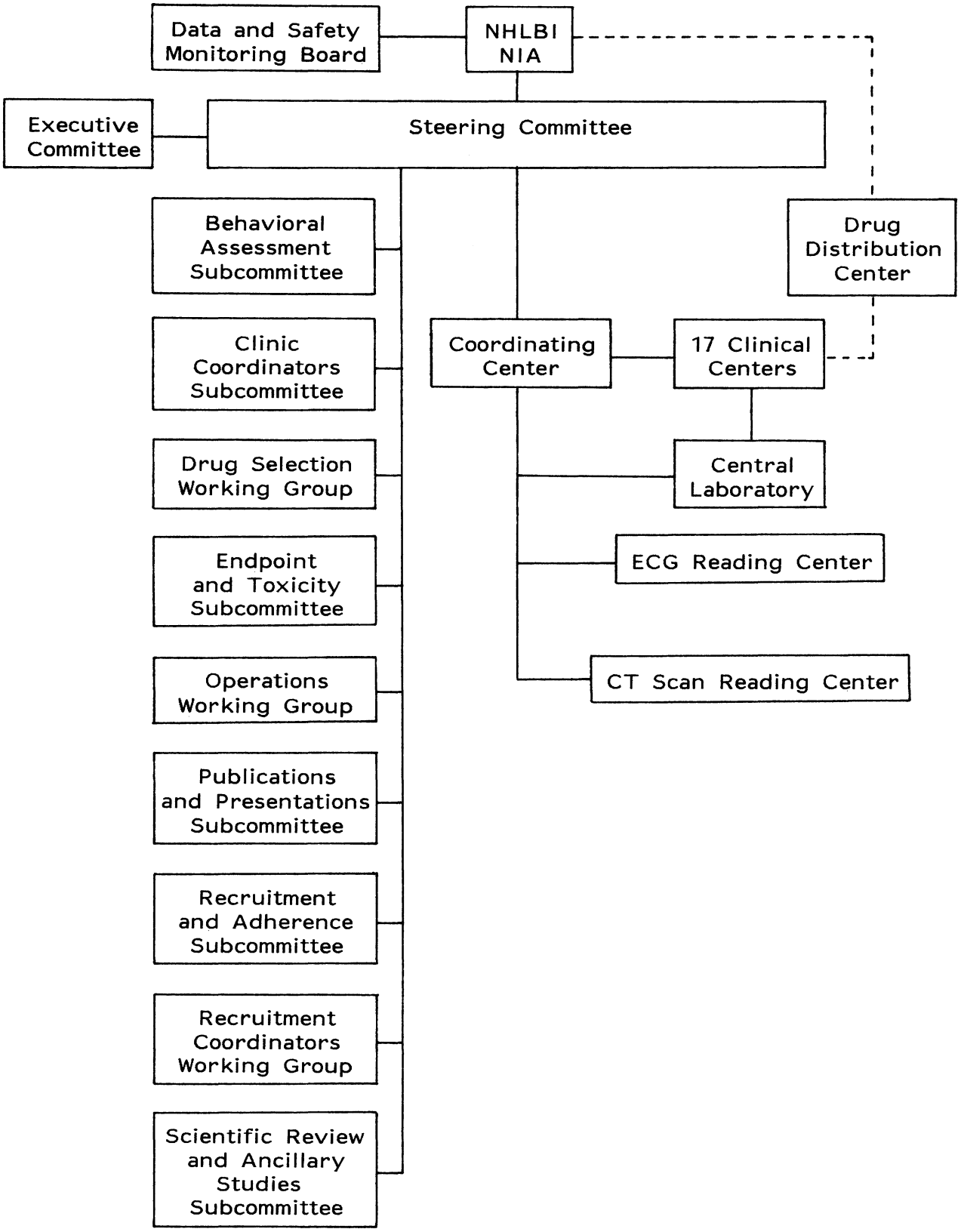
The Steering Committee is composed of a Chairman, the SHEP Principal Investigators and NHLBI and NIA staff. It is the decision-making body for the scientific and technical conduct of the study. During Phase I, the Steering (Planning) Committee is responsible for formulating and developing the research design and Protocol of the study. During Phase II, the Steering Committee will monitor the progress of the trial and consider special issues that may arise. The Steering Committee will not have access to blinded study data before the end of Phase II.

The following are standing subcommittees and temporary working groups of the Steering Committee:

Behavioral Assessment Subcommittee
Clinic Coordinators Subcommittee
Drug Selection Working Group
Endpoint and Toxicity Subcommittee
Operations Working Group
Publications and Presentations Subcommittee
Recruitment and Adherence Subcommittee
Recruitment Coordinators Working Group
Scientific Review and Ancillary Studies Subcommittee

FIGURE 1

MANAGEMENT OF THE SHEP



APPENDIX III

PARTICIPATING INSTITUTIONS AND INVESTIGATORS

A. Steering Committee Chairman

Kenneth G. Berge, M.D.
Mayo Clinic
Rochester, Minnesota

B. Clinical Centers and Principal Investigators

Albert Einstein College of Medicine	M. Donald Blaufox, M.D., Ph.D.
Emory University	W. Dallas Hall, M.D.
Kaiser Foundation Hospitals	Thomas M. Vogt, M.D.
Miami Heart Institute	Jeff Raines, Ph.D.
Northwestern University	David M. Berkson, M.D.
Medical Research Institute of San Francisco	W. McFate Smith, M.D.
UMDNJ-Rutgers Medical School	John B. Kostis, M.D.
University of Alabama	Harold Schnaper, M.D.
University of California at Davis	Nemat O. Borhani, M.D.
Pacific Health Research Institute	J. David Curb, M.D.
University of Kentucky	Theodore A. Kotchen, M.D.
University of Maryland	Roger Sherwin, M.D.
University of Minnesota	Richard H. Grimm, M.D., Ph.D.
University of Pittsburgh	Lewis H. Kuller, M.D.
University of Tennessee	William B. Applegate, M.D.
Washington University	H. Mitchell Perry, Jr., M.D.
Yale University	Henry R. Black, M.D.

C. Coordinating Center

University of Texas Health Science Center at Houston	C. Morton Hawkins, Sc.D., Director

D. Laboratories

ECG Reading Center University of Minnesota	Ronald Prineas, M.B., M.S., Ph.D.
MetPath, Inc. Teterboro, New Jersey	Michael W. Fordice, Ph.D. (Director, Quality) Melissa Rybb (Marketing)
CT Scan Reading Center University of Maryland	C.V.G. Krishna Rao, M.D.

E. Drug Distribution Center

U.S. Public Health Service Supply Center Perry Point, Maryland	Tom Miller Officer in Charge

F. NIH Agencies

National Heart, Lung and Blood Institute	Curt Furberg, M.D., Program Director Jeffrey Cutler, M.D., Project Officer Jeffrey L. Probstfield, M.D., Deputy Project Officer C. Eugene Harris, Contracting Officer
National Institute on Aging	Teresa S. Radebaugh, Sc.D. Evan Hadley, M.D. Richard Suzman, Ph.D.

G. Subcommittee and Working Group Chairpersons

Philip Weiler, M.D.	Behavioral Assessment Subcommittee
(Rotating Chairperson)	Clinic Coordinators Subcommittee
Robert McDonald, M.D.	Drug Selection Working Group
H. Mitchell Perry, Jr., M.D.	Endpoint and Toxicity Subcommittee
Harold Schnaper, M.D.	Operations Working Group
Jeremiah Stamler, M.D.	Publications and Presentations Subcommittee
Nemat O. Borhani, M.D.	Recruitment and Adherence Subcommittee
Shirley Arch	Recruitment Coordinators Subcommittee
W. McFate Smith, M.D.	Scientific Review and Ancillary Studies Subcommittee

APPENDIX IV

STROKE DEFINITIONS AND ALGORITHM FOR STROKE SUBTYPES

Stroke is the rapid onset of a persistent brain deficit thought to be due to obstruction or rupture in the arterial system and not secondary to brain trauma, tumor or infection. The deficit must last more than 24 hours unless death intervenes or there is a persistently demonstrable lesion which is consistent with deficit (by CT scan). The diagnosis of stroke will be made by the toxicity and endpoint committee based on the suspicion of the consulting neurologist that a stroke has occurred and the satisfaction of the appropriate algorithms. It will include strokes occurring during surgery.

The algorithm is by branching logic.

For patients that satisfy the above criteria for stroke the choices are:

(A) Hemorrhagic
(B) Ischemic
(C) Unknown type stroke

A. <u>Hemorrhagic Stroke</u>

1. Blood in subarachnoid space or intraparenchymal hemmorrhage by CT scan. (Intraparenchymal blood must be dense and not mottled--mixed hyperdensity and hypodensity.)

OR

2. Bloody spinal fluid by lumbar puncture

OR

3. Death from stroke within 24 hours of onset and no LP or CT or autopsy

OR

4. Surgical or autopsy evidence of hemorrhage as cause of clinical syndrome.

B. Ischemic Infarction

1. Focal brain deficit without CT or LP evidence of blood--except mottled cerebral pattern. Either decreased density by CT in a compatible location or a negative CT or none done.

OR

2. Surgical or autopsy evidence of ischemic infarction.

C. Unknown Type Stroke

1. Inadequate information to categorize as A or B. Satisfies criteria for stroke.

Hemorrhagic Stroke (A) is further divided into Subarachnoid Hemorrhage (SAH); Intraparehchymal Hemorrhage (IPH) and Indeterminate Hemorrhagic stroke (UH).

A. Subarachnoid Hemorrhage (SAH)

1. Headache or coma or combination with possibly some focal deficit and CT shows subarachnoid blood in basal cistern, tissues or convexity or blood clots in these locations. May also see aneurysm or arteriovenous malformation with enhancement.

OR

2. Similar clinical picture with bloody CSF. Headaches, stiffness and coma outweights focal deficit. May have subhyloid hemorrhage, 3rd nerve palsy.

OR

3. Autopsy evidence of SAH

B. Intraparenchymal Hemorrhage (IPH)

1. CT shows intraparenchymal increased density (not mottled). Location is compatible with deficit.

OR

2. Bloody CSF with a progressive focal deficit.

OR

3. Autopsy evidence for IPH.

C. Indeterminate Type Hemorrhagic Stroke

1. Death within 24 hours of onset without evidence by CT, surgery or autopsy of location of blood.

OR

2. Bloody LP but no definite clinical picture compatible with either SAH or IPH.

Ischemic Strokes

Further divided into Lacunes (L), Embolic (Emb), Atherosclerotic (ATL) and Other-Unknown Type Ischemic Inf. (O-U).

A. Lacune (L) 1 + 2, or 1 + 3, or 4

1. Angiogram if done shows no evidence of adjacent major artery occlusion or severe stenoisis.

AND EITHER 2 OR 3

2. By CT a deep area of decreased density less than 2 cm. in maximum length in a location compatible with the clinical picture (see 2+ sensory motor stroke and hemichorea).

3. Clinical syndrome of pure motor hemiparesis, pure sensory stroke, ataxia hemiparesis, dysarthria clumsy hand syndrome and a normal CT.

OR

4. Autopsy evidence of lacunar stroke due to small vessel disease.

B. Embolic Stroke (Emb)

1. Cerebral hemisphere infarction with a recognized source for emboli or systemic emboli--and no lacune by CT compatible with the clinical picture. Sources for emboli include atrial fibrillation, endocarditis, mitral valve disease, clot in the heart by echocardiogram or CT, recent cardiac surgery or trauma or myocardial infarction.

OR

2. Hemorrhagic infarction (mottled) by CT.

OR

3. CT shows small <½ lobe cortical infarction compatible with clinical findings with no prior TIAs in the same territory.

OR

4. Autopsy shows area of infarction thought to be due to embolus.

C. Atherosclerotic Infarction (Ath)

1. Focal infarct in the setting of evidence for large vessel disease, consisting of preceeding TIAs in the same vascular territory or carotid artery bruit over the proximate artery or internal carotid occlusion or severe stenosis at the carotid bifurcation if compatible, with no evidence of lacunar, mottled infarction, or small cortical infarct by CT and no sources of emboli.

OR

2. Autopsy evidence of infarction caused by atherosclerosis.

D. Other-Unknown Infarction (O-U)

1. Includes all cases not classified by the above rules for lacunes, emboli or atherosclerotic infarction.

2. All cases that could be classified in more than one of the above categories.

3. All cases attributed to arteritis, dissection of the arterial wall.

NOTES FOR STROKE ALGORITHM

CT--means computed tomography

LP--means Lumbar Puncture

Rapid--means usually minutes to hours and occasionally days. Patients who progress for more than one week are suspect.

This definition will include patients with headache in whom the CT or LP discloses blood and also stroke during endarterectomy.

This definition excludes patients with:

- Headache alone and no demonstrated blood by LP or CT.
- Palsy, labyrinthine disease.
- Metabolic problems as a cause of altered consciousness such as diabetic, uremic or hepatic coma. Brain tumor can be found or ruled out by the course, CT, angiography, biopsy, or autopsy. Trauma is ruled out by the history, CT or angiography; infection (encephalitis, abscess) by CT, LP, absence of fever.
- Old stroke by CT is excluded. This is usually diagnosed if the location of the infarct is in an inappropriate location to explain the findings or when there is nearby focal ventricular enlargement. Recent infarcts often have edema or show distortion of the brain, are enhanceable or show progression between CT scans.
- Seizures with status and post ictal paralysis (Todds) are ruled out by the history, observation and history of past seizures. Sometimes when a stroke causes seizure, CT or angiogram can confirm this.
- Also excluded are venous infarcts and subdural hematomas. Hysteria can usually be differentiated by inconsistences on examination and evidence of secondary gain.

A stroke can be diagnosed if the symptoms last less than 24 hours but a CT shows an infarct or hemorrhage in a location to explain the findings.

"Mottling" is high density (blood) within a low density infarction and is usually found with embolic infarctions.

Bloody CSF means -> 100,cells/cu mm--The LP thought to be non-traumatic and counts in the last tube are similar to those in the first tube (no clearing) or xanthochromia when the specimen is spun down.

Death within 24 hours of onset of stroke is nearly always due to a hemorrhage.

Focal deficit means localizable to one or a few locations. At least the examining physician should be able to state some locations that are not involved.

Deep infarcts < 2 cm in length probably covers all lacunes due to single vessel disease. Larger lesions clearly include middle cerebral artery stenosis or occlusion due to atherosclerosis or emboli.

Compatible with--means can explain the neurological deficit.

Classic lacunar syndromes are: pure motor hemiparesis, pure sensory stroke, ataxia hemiparesis, dysarthria clumsy hand syndrome.

Other symptoms caused by lacunes include sensory--motor stroke and hemichorea.

Other less certain or less common sources of emboli for stroke in this age group are: prolapsed mitral valve, pulmonary embolus with right to left shunt, myocarditis, and atrial myxoma.

Autopsy for embolism--feeding vessel may be patent if autopsy occurs after a few days post stroke.

Large vessel diseases mean--of the carotid vertebral and basilar arteries.

Dissection of the arterial wall can be shown by autopsy or angiography.

Arteritis can be found from evidence of systemic disease or angiography.

FIGURE 2

STROKE ALGORITHM

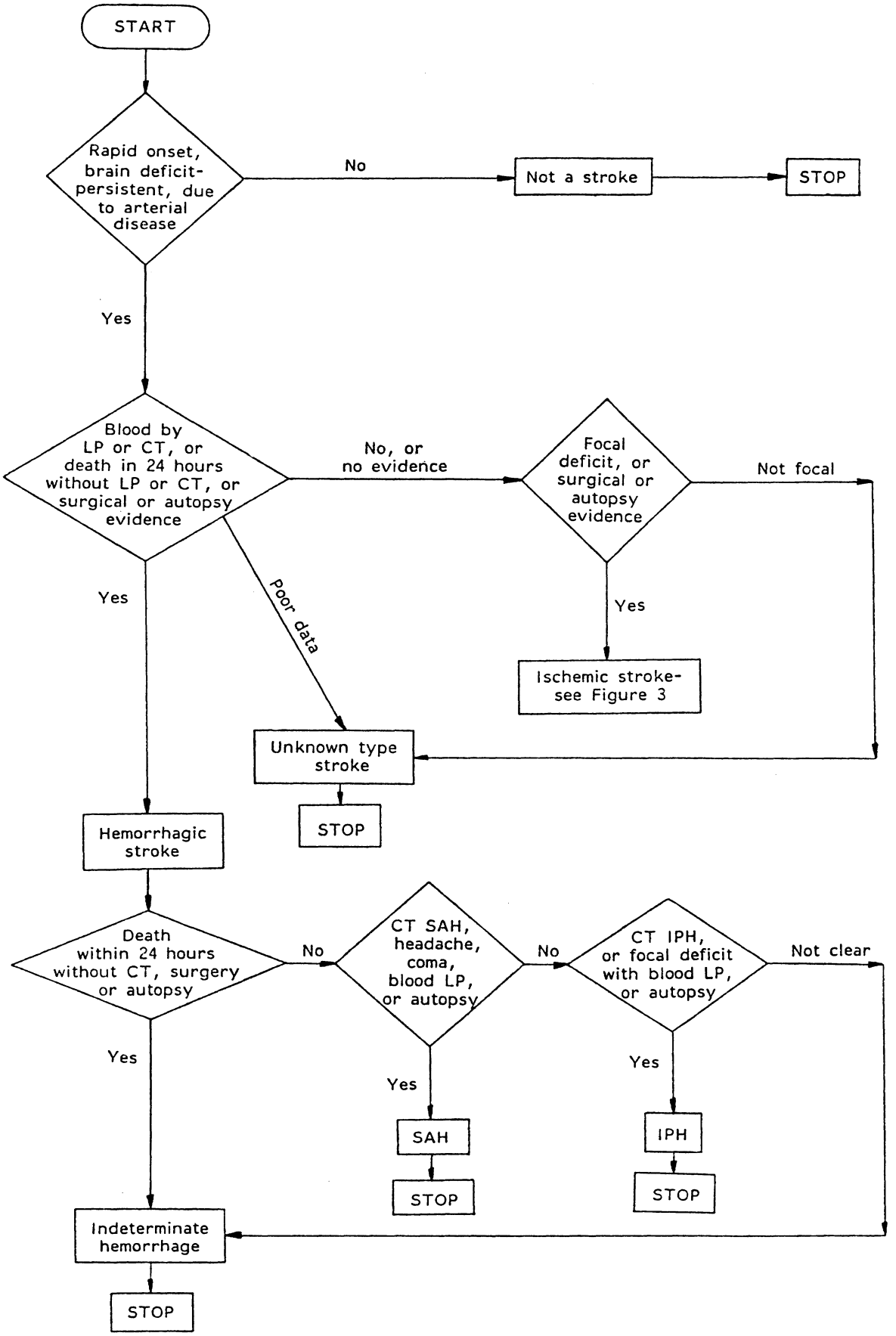
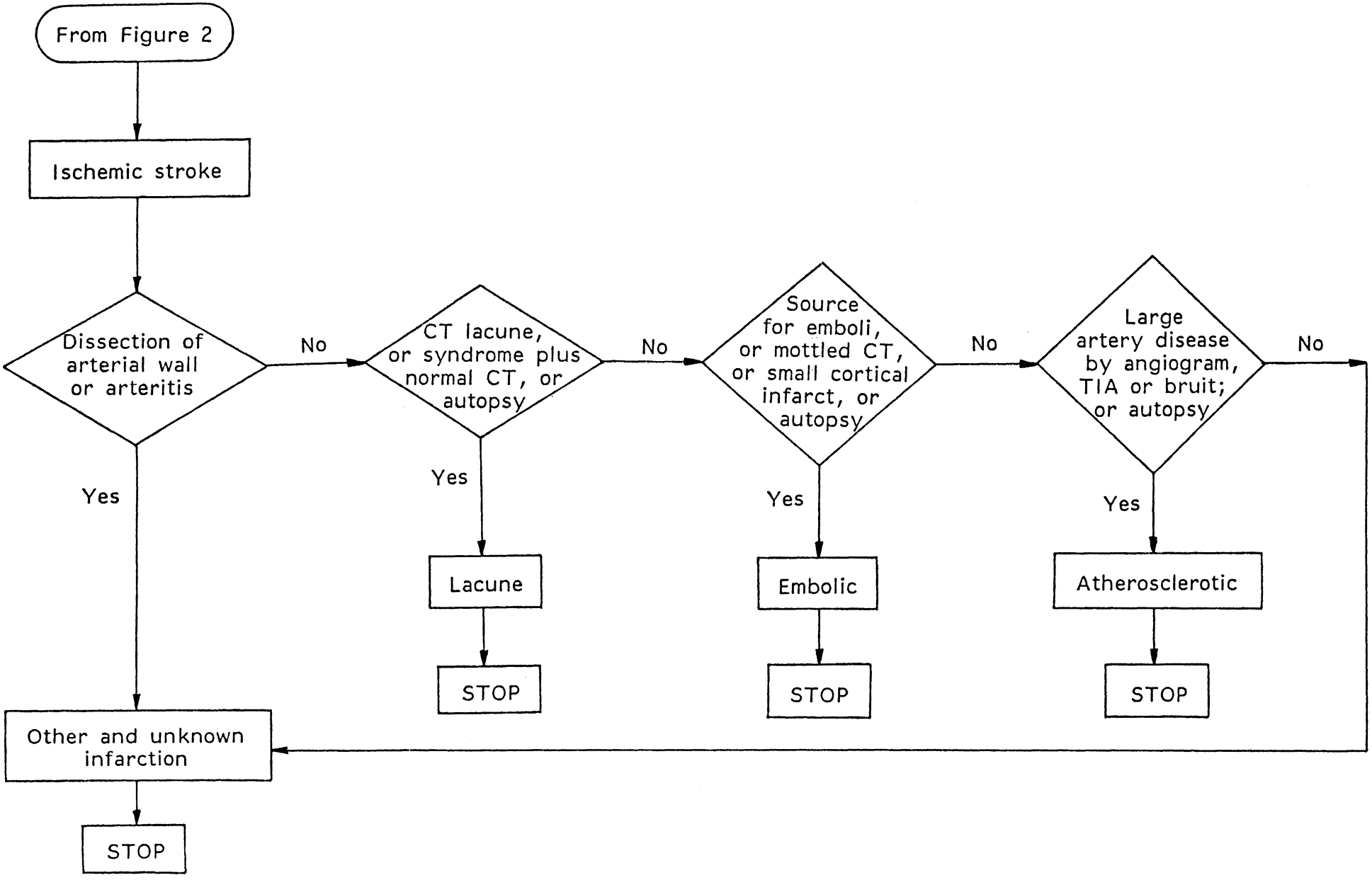


FIGURE 3


From Figure 2
Ischemic stroke
Dissection of arterial wall or arteritis
No
CT lacune, or syndrome plus normal CT, or autopsy
No
Source for emboli, or mottled CT, or small cortical infarct, or autopsy
No
Large artery disease by angiogram, TIA or bruit; or autopsy
No
Yes
Yes
Yes
Yes
Lacune
Embolic
Atherosclerotic
STOP
STOP
STOP
Other and unknown infarction
STOP