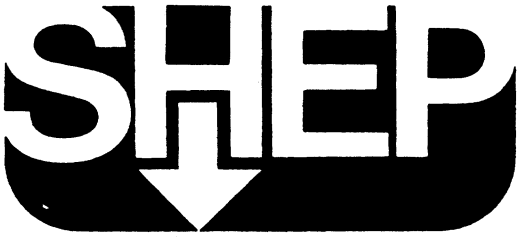


Systolic Hypertension in the Elderly Program

MANUAL OF OPERATIONS

July 1985

SHEP MANUAL OF OPERATIONS

TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

TABLE OF CONTENTS
(Continued)

Revised 8-88

TABLE OF CONTENTS
(Continued)

Revised 8-88

TABLE OF CONTENTS
(Continued)

TABLE OF CONTENTS
(Continued)

TABLE OF CONTENTS
(Continued)

Revised 8-88

TABLE OF CONTENTS
(Continued)

Revised 5-89

TABLE OF CONTENTS
(Continued)

Revised 8-88

PROTOCOL

SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

Revised April 17, 1985

PROTOCOL

SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

TABLE OF CONTENTS

PROTOCOL

SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

TABLE OF CONTENTS
(Continued)

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

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

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

III. Other events

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

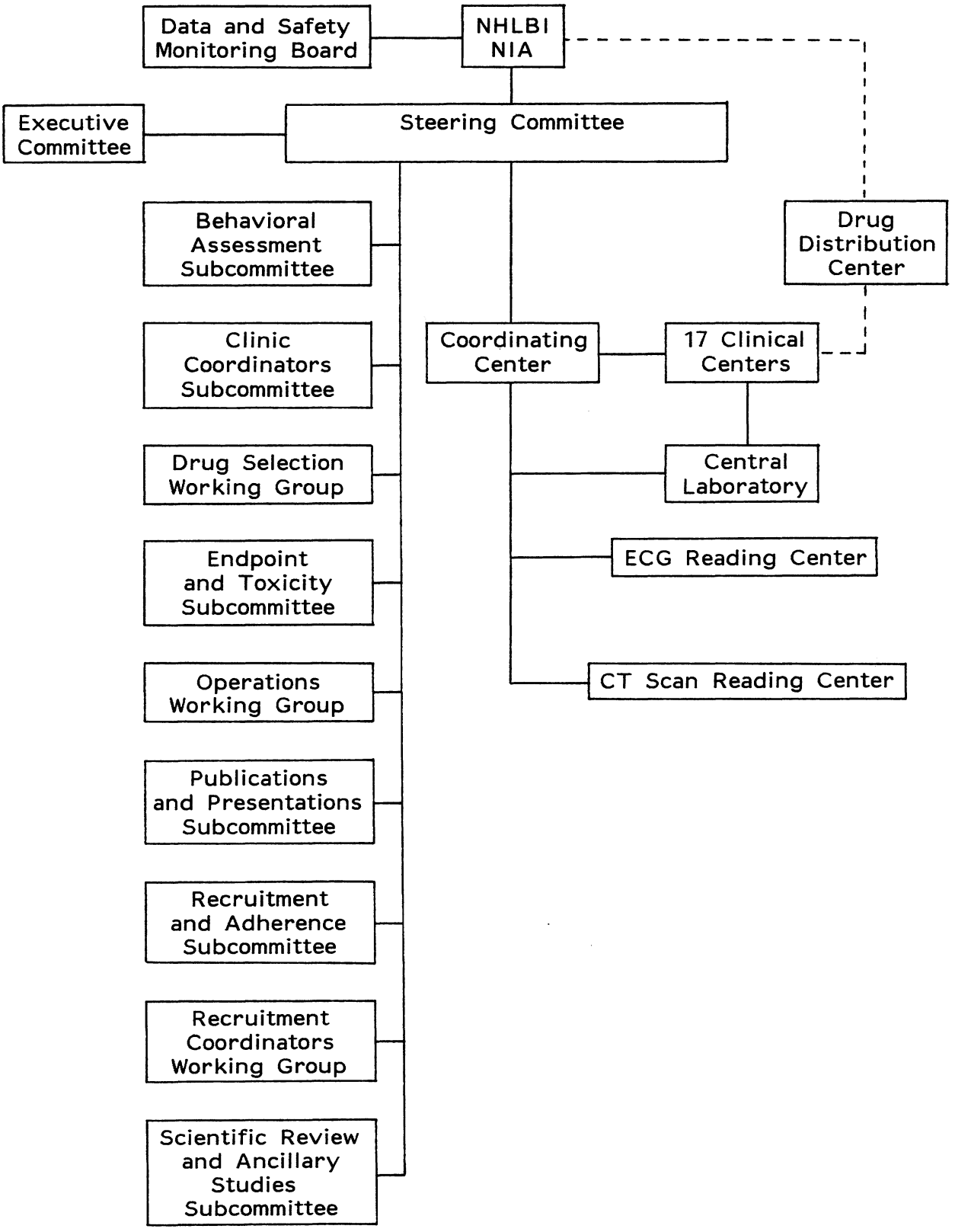
The Steering Committee is composed of a Chairman, the SHEP Principal Investigators and NHLBI and NIA staff. It is the decision-making body for the scientific and technical conduct of the study. During Phase I, the Steering (Planning) Committee is responsible for formulating and developing the research 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 $<\frac{1}{2}$ 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

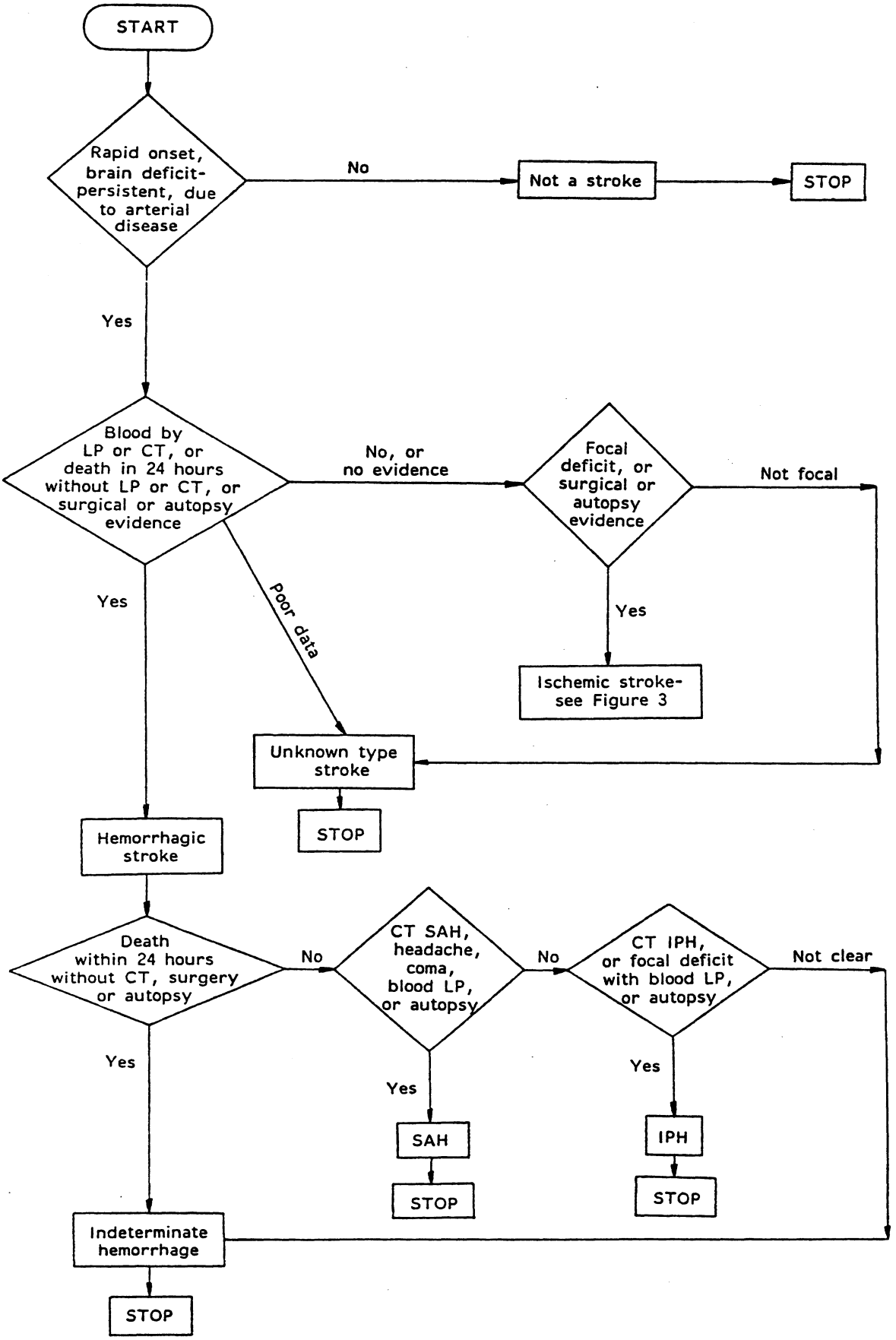
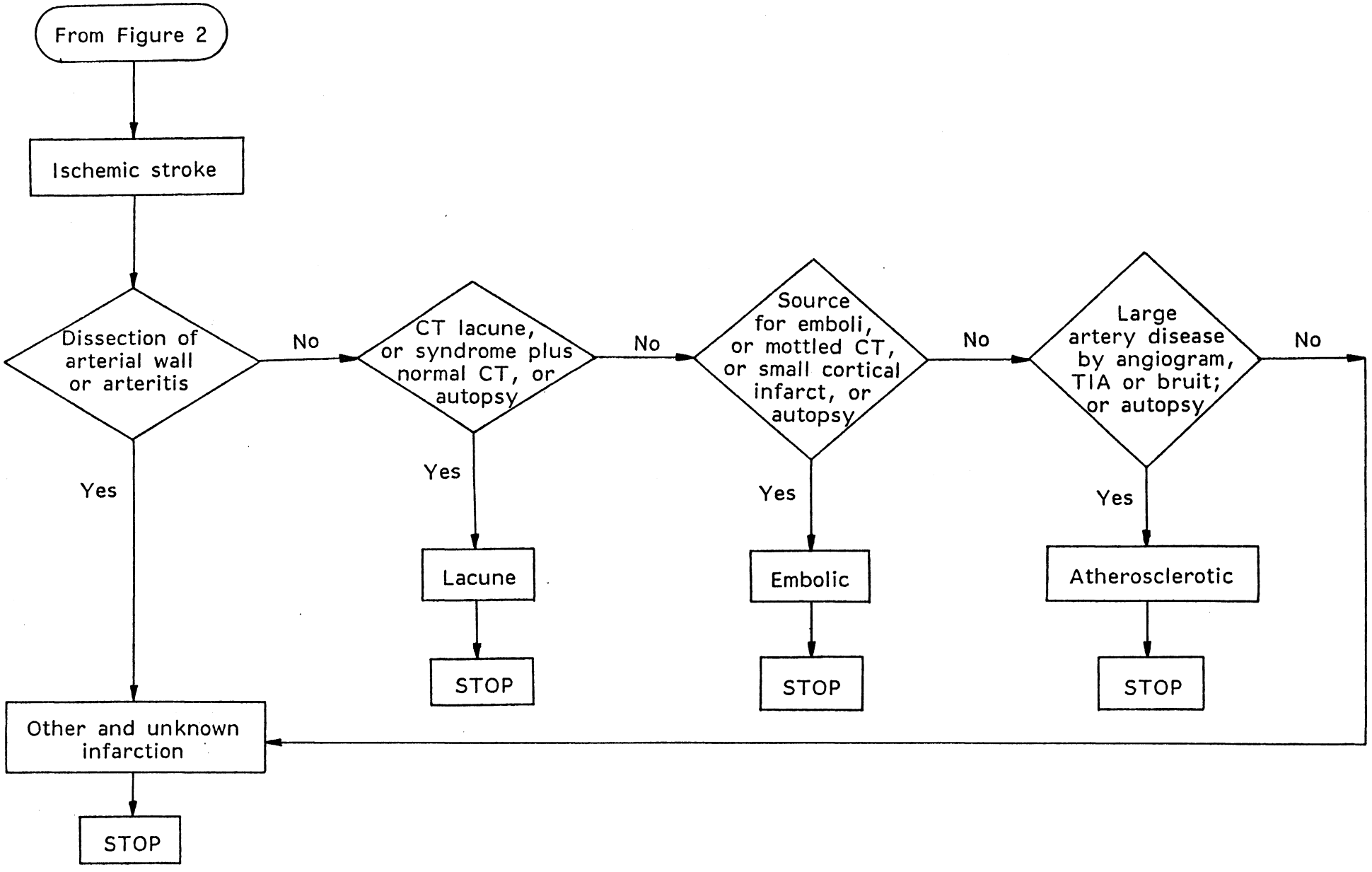


FIGURE 3


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

CHAPTER 2

SCHEDULE AND DESCRIPTION OF VISITS

2.1 Initial Contact

2.1.1 General Description

All participants will have an Initial Contact which may take place at a location in the community convenient to the population being recruited or in a SHEP clinic. 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.

A brochure will be provided locally for use in screening. Screenees may review these while waiting to have their blood pressure taken. These brochures provide a brief description of the SHEP--a short background, the purpose of the study, a brief description of the study design, what will be expected of a participant, and what the participant may expect from the clinic. Interviewers should be ready to answer questions that screenees may have about the study.

For everyone who participates at this visit, the following information will be obtained: date of birth, race, sex, and whether medication for high blood pressure is currently being taken. A single blood pressure reading is taken in the sitting position with a standard sphygmomanometer, by a trained observer, using SHEP blood pressure procedures. Participants must be 60 years of age or older for further consideration.

2.1.2 Blood Pressure Eligibility Criteria

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 of these second and third SBP 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).

2.1.3 Other Exclusion Criteria

Other causes for exclusion may 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.

2.1.4 Form SH01

Two forms (SH01B and SH01C) are available, depending on local Clinical Center recruitment plans. Each form contains exactly the same information in a different order.

TABLE 2-1

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.

2.1.4.1 SH01B

If using the SH01B, the interviewer should fill in Item 1 (Today's Date), and ask for the screenee's date of birth (Item 2a). Race (white, black, Asian, Hispanic or other) and sex (male or female) should be ascertained by asking the participant, not by observation. The interviewer then asks if the participant is currently taking medications for high blood pressure; if the participant is not sure, the interviewer should assume that the participant is not on antihypertensive medications, for the purposes of eligibility determination. A single blood pressure is then taken with a standard sphygmomanometer. If the screenee is not on medications and his or her SBP is less than 150 mm Hg, the screenee may be provided with a written record of their blood pressure and excused. All other screenees will receive two additional blood pressure measurements, and the average of these two measurements determines further eligibility. Persons not on medications will remain eligible if their average SBP is at least 160 and below 220 mm Hg, with average DBP below 100 mm Hg. Those who are currently on medications will remain eligible if their average SBP is at least 130 and less than 220 mm Hg with DBP below 85 mm Hg. Persons not eligible for further evaluation should be provided with a written record of their blood pressure, thanked and excused. For those remaining eligible, several exclusion criteria will be queried. (Using the SH01B, it is probably most convenient for the interviewer to ask these questions of the participant, rather than having the participant answer these items himself or herself, but this is not required.) Again, participants not remaining eligible should be provided with a written record of their blood pressure, thanked, and excused.

The screenee's name, address, home and work (if employed) telephone numbers and a preferred time for contacting the screenee should then be collected. Eligible screenees on antihypertensive medications will then be asked if their physician may be contacted to discuss possible medication changes. The purpose of this question is to initiate the process of getting permission from the participant's physician to discontinue current antihypertensive medication so that he or she may be re-evaluated for SHEP eligibility. Screenees agreeing to this contact will provide the name, address and telephone number of their health care provider or they may have no regular source of care. Some may not wish for their physician to be contacted, and may be excluded at this point. The screenee should be offered either the Baseline Visit 1 or Drug Evaluation Visit 1, as appropriate.

At this point in the Initial Contact, the participant will have been determined to be in one of the following categories:

1) Ineligible: due to blood pressure, other exclusion as queried, or excluded due to refusal to allow their physician to be contacted

2) Eligible for Baseline Visit 1: not on antihypertensive medications, with average SBP at least 160 and less than 220 mm Hg, and DBP less than 100 mm Hg, with no other exclusions

3) Eligible for Drug Evaluation Visit 1: on antihypertensive medications, with average SBP at least 130 and less than 220 mm Hg and DBP less than 85 mm Hg, with no other exclusions, and with no regular source of care or in cases where private physician permission may be obtained during the Initial Contact

4) Private physician permission pending: same medication and blood pressure criteria as above (#3), but for cases where the private physician will be contacted after the conclusion of this visit by either the SHEP clinic or by the screenee

5) Refusal: eligible for either Baseline Visit 1 or Drug Evaluation Visit 1, but refuses to schedule a visit

6) Will call for appointment: some participants will be reluctant, or may not be sure if they want to participate in the next visit, and may want to call the clinic for an appointment. Try to avoid this if possible. These people require immediate follow-up by clinic staff if they are ever to be scheduled for a visit. These persons should not be given the take-home forms (see Section 2.1.5).

The Informed Consent for the first Drug Evaluation Visit may be administered prior to the participant being scheduled for that visit and leaving the Initial Contact. If private physician permission can be obtained on the same day as the Initial Contact, the Drug Evaluation Visits may begin on the same day as the Initial Contact.

The clinic appointment, if made, should be scheduled in 7-10 days, allowing enough time for the screenee to complete the take-home forms as described below. (If the clinic appointment cannot be scheduled within 30 days, the participant must be re-screened.) The Baseline Visit 1 may not be on the same day as the Initial Contact Visit.

2.1.4.2 SH01C

The SH01C contains the same information as the SH01B, in a different order to allow the person being screened to fill in name, address, telephone numbers, preferred time for contact, birthdate, age, race, sex and the several questions on antihypertensive medications and exclusions. Participants remaining eligible will then have their blood pressure taken as described above, and evaluated for further eligibility. In this situation, since participants may be doing some work by filling in some of the information, it may be desirable to do one blood pressure reading even on those who would be excluded due to a "yes" answer on any of Questions 4 through 8, or 9b.

2.1.5 Take-Home Forms

If a screenee is eligible for the Baseline Visit 1 or Drug Evaluation Visit 1, they should to be given the following items to take home:

1) An appointment card that includes their name, the appointment time, type of visit (BL1 or DEV1), and Initial Contact blood pressures. Cards should also contain the clinic address and telephone number, and instructions to bring all of their prescription medication bottles with them to the clinic.
2) SH02--Participant Information Sheet
3) SH03--SHEP Baseline Demographic and Medication History
4) SH04--SHEP Baseline Medical History
5) If desired and allowed locally, a copy of the Informed Consent for the next applicable visit to review, but not to sign, at home. (Informed Consent for DEV1 may be administered at the Initial Contact.)

The SH02, SH03, and SH04 may intimidate some screenees due to their length and/or the fact that the screenee may not be able to read very well. It should be emphasized to the screenee that:

1) these forms do not need to be completed all at one time,
2) they may get help from a family member, friend, or their own physician, and
3) all of these forms will be reviewed with them when they come to the clinic. If there is anything that they do not understand, it will be completed at the next clinic visit.

The appointment date and time should be written on the front page of the SH03 and SH04 as additional reminders. (The SH02, SH03, and SH04 are described in Section 2.3.4 of this manual.)

2.1.6 Informed Consent for the Initial Contact

Some clinics will require an informed consent for this contact, particularly if name and address information is collected. The informed consent form may be reviewed by the screenee along with the brochure, but must be signed in the presence of the interviewer. If using form SH01B, informed consent may not be required until eligibility has been determined, and may be reviewed and signed at that time.

Each clinic should refer to the requirements imposed by their own Institutional Review Board in planning their Informed Consent activities for this visit. Informed Consent guidelines and samples have been provided for each visit (see Appendix A).

SHEP INITIAL CONTACT FORM

1. Today's Date: ☐☐ Month ☐☐ Day ☐☐ Year

2. a. Date of Birth: ☐☐ Month ☐☐ Day ☐☐☐☐ Year b. Age: ☐☐ years

   c. Race: ☐ White ☐ Black ☐ Asian ☐ Hispanic ☐ Other

   d. Sex: ☐ Male ☐ Female

3. Are you now taking medicine for high blood pressure? ☐ Yes ☐ No ☐ Don't know

4. Blood pressure (standard):

	Systolic	Diastolic
Reading 1	☐☐☐	☐☐☐
Reading 2	☐☐☐	☐☐☐
Reading 3	☐☐☐	☐☐☐
Sum of 2 + 3	☐☐☐	☐☐☐
Average of 2 + 3	☐☐☐	☐☐☐

→ Ineligible for further evaluation: Not on meds and SBP <150 mm Hg

Thank participant and excuse.

5. Review of participant status: (Use average of readings 2 and 3 for determining eligibility.

   ☐ Not on meds and 160 ≦ SBP <220, DBP <100

   ☐ On meds and 130 ≦ SBP <220, DBP <85

   ☐ Other (not eligible for further screening) → Thank participant and excuse.

6. Do you plan to move your residence more than 50 miles in the next year? ☐ Yes ☐ No ☐ Don't know

7. Do you have a pacemaker for your heart? ☐ Yes ☐ No ☐ Don't know

8. Have you had a heart attack or coronary bypass surgery in the past six months? ☐ Yes ☐ No ☐ Don't know

9. Are you taking anticoagulants (blood thinners)? ☐ Yes ☐ No ☐ Don't know

10. Are you taking insulin for diabetes? ☐ Yes ☐ No ☐ Don't know

11. a. Have you ever had a stroke? ☐ Yes ☐ No ☐ Don't know

    ↓ ↓

    Do not answer 11b.

    b. Do you still have problems from it? ☐ Yes ☐ No ☐ Don't know

To the interviewer: If any of Questions 6 through 10, or Question 11b are answered "Yes," thank participant and excuse.

12. Name: _____ Telephone at home: _____

Address: _____ Telephone at work: _____

_____

Preferred Time for Contacting: _____

13. (For persons on antihypertensive medications only):

May we, if necessary, contact your physician to discuss possible changes in the blood pressure medication that you are now taking?

☐ Yes ☐ No → Thank participant and excuse. ☐ No physician

↓

Identification of health care provider:

Name: _____

Address: _____

_____

Telephone Number: _____

14. Disposition: Review before participant is excused.

☐ Ineligible, no appointment made

☐ Appointment for Baseline Visit 1

☐ Appointment for Drug Evaluation Visit 1

☐ Will call for an appointment

☐ Refused

☐ Private MD permission pending → ☐ Approval obtained
☐ Refused

Appointment made on:

☐☐ Month ☐☐ Day ☐☐ Year

☐☐ : ☐☐ ☐ a.m. ☐ p.m

Hour Minute

15. Interviewer signature: _____ ☐☐ Code

Eligible participants should take home Baseline Medical History, Demographic Information and Medication History, and Participant Information Sheet, and the proper consent form (if allowed).

End of initial contact. Thank participant and excuse.

SHEP INITIAL CONTACT FORM

1. Today's Date: ☐☐ Month ☐☐ Day ☐☐ Year

2. Name: _____ Telephone at home: _____

   Address: _____ Telephone at work: _____

   _____ Preferred time for contacting: _____

3. a. Date of Birth: ☐☐ Month ☐☐ Day ☐☐☐☐ Year b. Age in Years: ☐☐

   c. Race: ☐ White ☐ Black ☐ Asian ☐ Hispanic ☐ Other d. Sex: ☐ Male ☐ Female

4. Do you plan to move your residence more than 50 miles in the next year? ☐ Yes ☐ No ☐ Don't know

5. Do you have a pacemaker for your heart? ☐ Yes ☐ No ☐ Don't know

6. Have you had a heart attack or coronary bypass surgery in the past six months? ☐ Yes ☐ No ☐ Don't know

7. Are you taking anticoagulants (blood thinners)? ☐ Yes ☐ No ☐ Don't know

8. Are you taking insulin for diabetes? ☐ Yes ☐ No ☐ Don't know

9. a. Have you ever had a stroke? ☐ Yes ☐ No ☐ Don't know

   ↓ ↓

   Skip to 10.

   b. Do you still have problems from it? ☐ Yes ☐ No ☐ Don't know

10. Are you now taking medicine for high blood pressure? ☐ Yes ☐ No ☐ Don't know

    STOP

To the interviewer: If any of Questions 4 through 8, or Question 9b are answered "Yes," thank participant and excuse.

11. Blood pressure (standard):

	Systolic	Diastolic
Reading 1	☐☐☐	☐☐☐
Reading 2	☐☐☐	☐☐☐
Reading 3	☐☐☐	☐☐☐
Sum of 2 + 3	☐☐☐	☐☐☐
Average of 2 + 3	☐☐☐	☐☐☐

→ Ineligible for further evaluation:
Not on meds and SBP <150 mm Hg

Thank participant and excuse.

12. Review of participant status: (Use average of readings 2 and 3 for determining eligibility.

☐ Not on meds and 160 ≦ SBP <220, DBP <100 → Eligible for Baseline Visit 1; skip to 14.

☐ On meds and 130 ≦ SBP <220, DBP <85

☐ Other (not eligible for further screening) → Not eligible; skip to 14.

13. (For persons on antihypertensive medications only):

Would you be willing to have us contact your physician to discuss possible changes in the blood pressure medication that you are now taking?

☐ Yes ☐ No → Thank participant and excuse. ☐ No physician

↓

Identification of health care provider:

Name: _____

Address: _____

_____

Telephone Number: _____

14. Disposition: Review before participant is excused.

☐ Ineligible, no appointment made

☐ Appointment for Baseline Visit 1

☐ Appointment for Drug Evaluation Visit 1

☐ Will call for an appointment

☐ Refused

☐ Private MD permission pending → ☐ Approval obtained ☐ Refused

Appointment made on:

☐☐ Month ☐☐ Day ☐☐ Year

☐☐ : ☐☐ Hour Minute ☐ a.m. ☐ p.m

Eligible participants should take home Baseline Medical History, Demographic Information and Medication History, and Participant Information Sheet, and the proper consent form (if allowed).

15. Interviewer signature: _____ ☐☐ Code

2.2 Drug Evaluation Visits

2.2.1 General Description

A participant on antihypertensive medications will be a candidate for drug 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 Drug Evaluation Visit 1 (DEV1) is to evaluate whether the participant can be safely taken off medication, considering both the number of antihypertensive drugs and pre-withdrawal level of blood pressure. The take-home forms (SH03 and SH04) may be completed and reviewed for this purpose. Any participant will be excluded from further study if withdrawal from medications is medically contraindicated, including any case in which it is known that medication has been prescribed for diastolic hypertension. Informed consent is required specifically for withdrawal from medications.

Three blood pressure determinations will be taken with a standard sphygmomanometer at each evaluation visit, by a certified observer using SHEP blood pressure procedures. 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 judgment, 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 visit in the next 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. The SHEP clinic may elect to follow such participants longer than eight weeks. However, whether or not they are followed in the SHEP clinic, if they remain off of medication and subsequently reach blood pressure levels eligible for SHEP, they may be re-screened, starting over with the Initial Contact and should be counted as not on medication at Initial Contact.

2.2.2 Getting the Permission of the Participant's Private Physician or Usual Source of Care

Before drug withdrawal begins, permission should be obtained from the participant's private physician. This permission may be sought in a number of ways--by letter or telephone, by either the participant or a SHEP clinician. Although this can be very time-consuming, it is imperative from the standpoint of public relations for the SHEP that every effort be made to obtain this permission.

A sample letter and permission slip are attached to this section.

Sample letter to participant's physician
Page 1

Dear Dr. _____,

As you are probably aware there recently has been increased interest in the problem of isolated systolic hypertension in people who are at least 60 years of age. Many ongoing studies have now shown that systolic hypertension is associated with an increased risk of cardiovascular problems, especially stroke and heart attack. It is not clear however whether treatment of so called isolated systolic hypertension changes the risk of disease or whether therapy for systolic hypertension is associated with an increased frequency of side effects and symptomatology.

We, as one of seventeen Clinical Centers in the United States, have recently begun a clinical trial to determine the efficacy of lowering systolic blood pressure in the older population and the effects on the risk of cerebrovascular and cardiovascular disease. We are attempting to recruit approximately 300 individuals who have isolated systolic hypertension, defined as systolic blood pressure at least 160 mm Hg and diastolic blood pressure less than 90 mm Hg, who are at least 60 years of age and are free of overt cardiovascular disease and disabling stroke. The goals of the study are to determine the efficacy of diuretics and beta blockers as compared to a placebo in lowering systolic blood pressure and preventing cerebrovascular and cardiovascular disease.

We have recently begun to screen individuals in this region to determine who would be eligible for the study. Individuals who have systolic blood pressure of at least 130 mm Hg and diastolic blood pressure less than 85 mm Hg and who are currently on drug therapy could be eligible for the study if their systolic blood pressure rose to at least 160 mm Hg and their diastolic blood pressure remained below 100 mm Hg when they were off drug therapy for at least two weeks. During our initial screening examination we have identified (name) _____ who is currently being treated by you and would be potentially eligible for the study. The patient (name) _____ has agreed to participate in the study with your permission. We would like to discontinue antihypertensive therapy for at least two but no longer than eight weeks and monitor the blood pressure during this time. If the systolic pressure increases to 160 mm Hg or more and the diastolic blood pressure remains below 100 mm Hg then the individual would be potentially eligible for the study. If the systolic remains less than

160 mm Hg, rises to at least 220 mm Hg, or the diastolic blood pressure rises above 100 mm Hg then the individual will be referred back to your office. Please return the enclosed consent form in the self addressed envelope as soon as possible to determine if (name)_____ can participate in this study.

As you know, systolic hypertension is an extremely important problem in the older population since it is very frequent and apparently related to cardiovascular disease. A better understandng of the efficacy of therapy will have important implications in the future. We believe that our study is important and needs your support in making it a success.

We are very interested in identifying any other patients that you think would be a candidate for this study. The criteria would be an individual who is at least 60 years of age with isolated systolic hypertension, defined as a systolic blood pressure of at least 160 mm Hg and a diastolic blood pressure less than 100 mm Hg, not currently on drug therapy, or who is not an insulin dependent diabetic, has not had a recent myocardial infarction, congestive heart failure or disabling stroke, and is ambulatory in the community. Persons currently on antihypertensive medications will be eligible with a systolic blood pressure of 130 mm Hg or above, and a DBP below 85 mm Hg, if they are willing to be monitored for eight weeks off of antihypertensive drug therapy, and meet the remaining criteria as described above.

Thank you very much.

Sincerely yours,

S H E P

Systolic Hypertension in the Elderly Program
(Clinic Address)

(Doctor's Name and Address)

(Participant's Name and Address)

☐ can ☐ cannot participate in the Systolic Hypertension in the Elderly Program.

Date _____ Physician Signature _____

S H E P

Systolic Hypertension in the Elderly Program
(Clinic Address)

(Doctor's Name and Address)

(Participant's Name and Address)

☐ can ☐ cannot participate in the Systolic Hypertension in the Elderly Program.

Date _____ Physician Signature _____

2.2.3 Informed Consent for Drug Withdrawal

Regardless of whether permission needs to be obtained from the participant's usual source of care, informed consent is required from each participant prior to the initiation of any drug withdrawal, at the beginning of Drug Evaluation Visit 1 or the end of the Initial Contact. The participant must understand that all antihypertensive medications currently being prescribed will be completely discontinued unless medically contraindicated or unless their blood pressure increases to levels that would make them ineligible for the study.

A sample Informed Consent form for this purpose has been provided and is attached in Appendix A. If allowed locally, it may have been taken home from the Initial Contact and reviewed, but not signed. (If it is returned to the clinic already signed by the participant, explain that the signature must be witnessed, use a new form, and discard the previously signed form.)

2.2.4 Form SH05

This form has been provided for clinic use and will not be subject to local data entry. (The use of this form is, however, encouraged, as they may be collected in the future and entered at the Coordinating Center.) Before DEV1, the participant's name (Item 3) should be entered onto the form, the date informed consent was obtained from the participant should be entered into 5b, and Item 5a (date private physician permission obtained) should be completed if applicable. Information on specific antihypertensive medications should be obtained from the SH03, Item 9 and entered onto Item 4 on this form. The Baseline Medical History, SH04, along with the SH03, should be

reviewed prior to initiation of drug withdrawal to make sure that withdrawal is not medically contraindicated (Item 6). Starting with DEV1, the date, medication status, three blood pressures and the average of the second and third readings, and an eligibility determination should be recorded at each visit. Other notes may be kept elsewhere in the participant's clinic record (i.e., log of efforts to contact participant's private physician, or details of medication dosage changes), but do not need to be entered here.

At the end of each drug evaluation visit, a participant may be:

1) Eligibile for Baseline Visit 1: off all antihypertensive medications for at least two weeks, SBP at least 160 and less than 220, DBP less than 100 (schedule BL1 in Item 7);

2) Not eligible for SHEP:

   a) SBP <130 or ≧220 mm Hg, or DBP ≧85 mm Hg at DEVI (prior to discontinuation of medications)

   b) SBP at least 220 or DBP at least 100 mm Hg at any visit, regardless of medication status

   c) off medications eight weeks, SBP never 160 mm Hg or above

3) Continue evaluation: all others

Blood pressure eligibility at the Drug Evaluation Visits is always determined by using the average of the second and third blood pressure reading.

These definitions are repeated at the end of the SH05 for ease of reference. It is not anticipated that more than ten drug evaluation visits will be required, but additional SH05s may be used if such a situation occurs.

SHEP DRUG EVALUATION VISIT SUMMARY

To be used for evaluating the potentially eligible participants who are discontinuing all their antihypertensive medications with the consent of their physician. Note: Evaluation must be completed no later than 8 weeks after going off the medications; the participant may be seen clinically as often as needed. Use this form for all of the participant's evaluation sessions.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Name: ____________________

4. Names of antihypertensive medications: ____________________

5. a. Date physican permission obtained: ___/___/___
(A log of efforts to obtain permission may be kept elsewhere.)

b. Informed consent for withdrawal obtained from participant: ___/___/___

c. Date drug withdrawal started: ___/___/___

d. If applicable, date all meds discontinued: ___/___/___

6. Participant is ☐ eligible ☐ not eligible for drug withdrawal

7. If eligible for BL1: Appointment for BL1 made for ___/___/___ (date) at ___:___ (time) ☐ a.m. ☐ p.m.

Date	Is participant off all BP meds at beginning of visit?		Blood Pressure 1	2	3	Ave. 2 + 3	Result*
___/___/___	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
___/___/___	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
___/___/___	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
___/___/___	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
___/___/___	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP

Date	Is participant off all BP meds at beginning of visit?		Blood Pressure 1	2	3	Ave. 2 + 3	Result*
/ /	☐ Yes ☐ Yes	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
/ /	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
/ /	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
/ /	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP
/ /	☐ Yes ☐ No	SBP: DBP:					☐ Eligible for BL1 ☐ Continue evaluation ☐ Not eligible for SHEP

*Eligible for BL1: Off meds at least two weeks, 160 ≦ SBP <220, DBP <100; copy BP to BL1 form, SH06.

Not eligible for SHEP:
(1) SBP <130 or ≧220 mm Hg, or DBP ≧85 mm Hg at DEV1
(2) SBP ≧220 or DBP ≧100 at any visit, regardless of medication status
(3) Off meds eight weeks, SBP never ≧160

Continue evaluation: all others

2.3 Baseline Visit 1

2.3.1 General Description

This visit, which must take place in the SHEP clinic, serves to establish further blood pressure eligibility, and to establish most of the medical eligibility criteria and a baseline medical "status" for each participant.

Blood pressure will be measured by a trained observer using a Random-Zero device, as described in the SHEP Blood Pressure Manual, and blood pressure eligibility will be determined (see below).

Eligible participants will be sent for an ECG and two-minute rhythm strip, and a dipstick urinalysis. The medication history is reviewed, and a complete physical examination is accomplished. The medical history, physical examination results, and ECG are reviewed for medical exclusions and other important baseline items, and an eligibility decision is made by the clinician. Participants with proteinuria (at least trace) or hematuria (at least non-hemolyzed trace) on dipstick urinalysis may, at local option, have a blood sample drawn for local analysis of serum creatinine.

2.3.2 Blood Pressure Eligibility Criteria

Participants will remain eligible if the average of the two seated systolic blood pressures is at least 150 and less than 220 mm Hg, and the average diastolic is less than 95 mm Hg.

2.3.3 Other Exclusion Criteria

Most of the medical exclusion information is determined at this visit. Exclusion criteria to be applied at this visit include the following:

(a) ECG evidence of:

1) atrial fibrillation or flutter,

2) second or third degree A-V block,

3) multifocal VPBs, VPBs in pairs or runs, or VPBs more frequent than 10 percent of beats,

4) bradycardia (<50 beats/minute).

(b) Permanent pacemaker, judging by history and/or ECG.

(c) History of stroke with residual paresis or other major neurological disability.

(d) Alcohol abuse (alcoholism a problem in the past year; currently drinks six or more drinks per day; or curent alcoholic liver disease, including current varices or ascites).

(e) History of coronary bypass surgery or myocardial infarction within the past six months.

(f) Active treatment with insulin, anticoagulants, or drugs having antihypertensive activity (e.g.: beta-blockers, calcium channel blockers, diuretics, sympatholytics, etc.). Examples of allowed and disallowed drugs are:

Allowed	Disallowed
Persantin	Any experimental drug
Timoptic	Peripheral vasodilators
Coronary vasodilators	Diamox
Long-acting nitrates	Neptazene
Nitroglycerine patches	

(g) Congestive heart failure that is not adequately controlled.

(h) Malignant neoplasm (other than non-melanomatous skin cancers) or other life-threatening disease.

(i) Contraindications to chlorthalidone (including a history of allergy or reaction to any sulfa drug).

(j) Contraindications to both atenolol and reserpine.

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

(l) Dementia, judged clinically.

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

(n) History of two TIAs in the same location.

(o) Malignant hypertension, past or present.

(p) Suspect or established significant renal dysfunction (serum creatinine above 2.0 mg/dl).

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

2.3.4 Reviewing the Take-home Forms

The SH03 (SHEP Baseline Demographic Information and Medication History) must be completed for all participants who attend Baseline Visit 1. The SH02 (Participant Information Sheet) and SH04 (SHEP Baseline Medical History) must be completed for all participants who are blood pressure-eligible at this visit.

2.3.4.1 SH02--Participant Information Sheet

This sheet is for clinic use, and aids in identifying the participant, and locating the participant in case of eventual loss to follow-up. Make sure that each item is complete, if applicable, and legible. Write the participant's SHEP ID (SH06, #1) and acrostic (SH06, #2, defined below) onto the top of this form. Items of particular importance to the Coordinating Center are the birthdate (#3),

Social Security number (#4), Medicare number (#5), father's last name (#9) and participant's state of birth (#10). Other items will be important in communicating with the participant by mail or telephone, or for local efforts in locating a participant who has been lost to follow-up. The information on this form should be checked by the participant at least semi-annually at SHEP clinic visits.

2.3.4.2 SH03--SHEP Baseline Demographic Information and Medication History

This form provides important baseline personal and habits information (sex, race, education, employment status, marital status, smoking, and alcohol consumption) as well as information on current medication use (prescription and over-the-counter). Permission is also asked to send blood pressure results to the participant's physician.

If some of these items are not completed at the time of the clinic visit, they should be completed prior to the beginning of the visit, by a clinic staff person using inquiries appropriate to the specific questions that were left blank. In some cases, the problem may be one of an inability to read, and the staff person will need to ask the questions as written on the form. Regardless, the participant should have brought their medications to the clinic visit, and these should be checked against Items 9 and 11.

Some of the items on all of these forms require that a two or three-digit number be entered into boxes. For example:

6b. How many cigarettes do you now smoke per day? [ ]

The clinic staff person reviewing the form should make sure that these types of boxes are filled in as per instructions in Appendix F.

2.3.4.3 SH04--SHEP Baseline Medical History

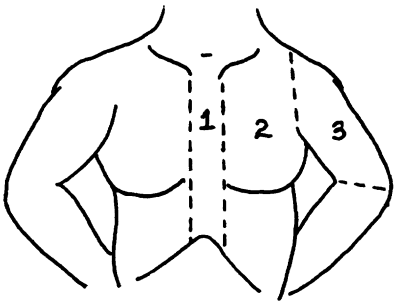
This form, as well as providing important information needed to establish eligibility, provides a medical history necessary for good general medical care. This form should be collected from the participant, completed by the participant with the help of a clinic staff person, and the positive responses should be highlighted for quick reference by the SHEP clinician. In addition, on page 4, Item 42h, several judgments must be made regarding the location of chest pain or discomfort (if any). If both 42a and 42b are answered "No," then no judgment needs to be made. If either is "Yes," then the location of the pain or discomfort should be indicated on the drawing, and documented in the box marked "Do not use--clinic use only" in the following manner:

42h(1) -- This is "yes" if there is an X in the sternum (upper, middle or lower). Otherwise, mark "no."

42h(2) -- This is "yes" if there is an X in the left anterior chest. Otherwise, mark "no."

42h(3) -- This is "yes" is there is an X in the left arm. Otherwise, mark "no."

The areas described above are as per the following drawing:



RIGHT LEFT

2.3.5 Form SH06

SHEP ID, acrostic and date of visit (Items 1-3):

SHEP ID numbers are assigned in Item 1 of this form. The first two digits are the clinic number (01 through 17, per attached list). The middle four digits identify the participant and are pre-printed in the upper right corner. Copy these pre-printed digits into the middle four digits of the SHEP ID, using leading zeros as necessary. The last two digits are also the clinic number. While it seems that the first two digits and last two digits serve the same purpose, the first two may change if the participant transfers to a different Clinical Center during the trial--these two digits indicate the Clinical Center where the participant is being treated. The last two digits, which always remain the same, indicate the participant's original Clinical Center (where he or she was randomized). For most SHEP participants, the first two and last two digits will always be the same. This SHEP ID should be transferred to the participant's Initial Contact Form, Drug Evaluation Visit Summary, and take-home forms.

The acrostic, Item #2, serves for further identification, and consists of the first three letters of the participant's last name, the first two letters of the first name, and the middle initial (if any). For example, the acrostic for Jane A. Doe would be DOEJAA. If either the first or last name are only two letters, blanks should be left for the missing letters. As with the ID, the acrostic should be transferred to the participant's Initial Contact Form, Drug Evaluation Visit Summary, and take-home forms. The participant's acrostic will remain exactly the same throughout the study.

Item 3 (Today's date) is the date of the visit, and not the date the form was prepared, if prepared ahead of time.

Initial Contact and DEV information (Item 5):

After entering the date of the Baseline Visit 1, several items of information need to be copied from the Initial Contact Form, the Participant Information Sheet, and, if applicable, the Drug Evaluation Visit Summary. On page 2 of the SH06, Item 5a, the participant's date of birth, should be copied from Item 2a (Initial Contact). Items 5b and 5c should be filled in with the participant's Social Security and Medicare Numbers, respectively. If either of these are not available, DO NOT fill the items with all 9s -- rather, leave them blank as indicated on the form. Item 5e, blood pressure at Initial Contact, should be taken from the participant's Initial Contact Form (SH01). Item 5f, regarding antihypertensive medications, should be answered using the most up-to-date information available to the Clinic staff (e.g., if the participant does not know about his or her antihypertensive medication status at Initial Contact, but subsequently was withdrawn from drugs in order to participate in the trial). If the participant was not on antihypertensive medications at the Initial Contact, the rest of page 2 should be left blank. Items 5g through 5j are for participants who were withdrawn from antihypertensive medications and should be copied from the SH05 (Drug Evaluation Visit Summary). Specifically, information is requested about when medications were completely withdrawn, and when the participant qualified for Baseline Visit 1, and the blood pressure readings on those days. If the participant was told over the telephone to discontinue medications (e.g., upon receipt of private MD permission), fill Item 5h with 9s.

Prior to actually initiating any of the clinic procedures for the Baseline Visit 1, including a review of the take-home forms, informed consent should be obtained for this visit. If allowed, consent for both

baseline visits may be obtained at this time. A model has been provided for this consent. (See Appendix A.) It should be reviewed in detail with the participant, and prior to signing and witnessing, the participant should understand every item and have the opportunity to ask questions. If the participant has taken this consent home from a previous visit to review, and signed the form before returning it, a new consent form should be used, and the participant's signature should be witnessed.

The remaining items on page 1 are to be completed at the end of the visit.

Pulse and blood pressure (Item 6):

Pulse and blood pressure are the first clinic procedures required at this visit, and should be carried out by a trained observer according to the SHEP Blood Pressure Manual. Participants will remain eligible if the average SBP is at least 150 and less than 220 mm Hg, and DBP less than 95 mm Hg. The two standing pulse and blood pressure measurements do not need to be completed for participants who do not remain eligible (these items should be filled in with 9s); in this case, Item 6c may be left blank. The observer should perform the blood pressure eligibility check in Item 6d, and sign the form and enter his or her ID code in 6e. Ineligible persons should be provided with a written record of their blood pressure, thanked, and excused. Participants who are blood pressure eligible but who are obviously ineligible for other reasons from the medical history, may also be excused at this time. However a reason must be given for their exclusion elsewhere in the appropriate section of the SH06 (e.g., excluding drugs in Item 8, medical and other exclusions in Items 24-44). An SH04 must be completed for these participants if they were blood pressure eligible.

ECG and dipstick urinalysis:

Participants remaining eligible should then be directed to the proper area of the clinic, should be instructed on how to obtain a urine sample, should provide the sample for dipstick analysis, and then receive the 12-lead ECG and two-minute rhythm strip evaluation. These should be accomplished according to the appropriate sections of this Manual of Operations (Appendix D for urinalysis and Appendix C for ECG recording). Item 7 refers to the medical history and results of the dipstick urinalysis. Participants who have a history of kidney disease or protein (at least trace) or blood (at least non-hemolyzed trace) in the urine may, at local option, have a blood sample drawn, according to Appendix D, for analysis of serum creatinine. The blood draw, if done, and the result should be documented as directed on the form. Participants having a blood sample drawn for this reason should continue with the remaining procedures for this visit.

Clinician review of medication history (Item 8):

During these procedures, the clinician should be reviewing the medication history and completing Item 8, which is a medication checklist. Antihypertensive medications discontinued during the Drug Evaluation Visits should not be included as current (last two weeks), although they may have been listed by the participant on the SH03. If the participant is on any drug with antihypertensive action, or beta-blockers (other than Timoptic eye drops), or insulin or anticoagulants or any experimental drug, they are not eligible for participation in the SHEP. Ineligible presons should be provided with a written record of their blood pressure, thanked and excused.

Physical examination (Items 9-22):

A SHEP clinician should then perform a general physical examination, paying particular attention to the specific items listed. Height and weight should be measured first, as described in Appendix E. The physical examination has two purposes: (1) to provide good general medical care, and (2) to provide information on possible study endpoints and exclusions. The physical examination is described in Appendix E of this manual. The clinician should then sign the form and enter his or her ID code in Item 22.

Clinician judgment and exclusion criteria review (Items 23-46):

After the physical examination is completed, and while the participant is getting dressed, the clinician should review the medical history, physical exam and ECG, and complete Items 23-46 of this visit form. For each disease or organ system, reference questions are listed to direct the clinician to items that are applicable from the medical history form (SH04). For example, Question 2 on the SH04 asks if the participant has ever had high blood pressure severe enough to lead to hospitalization. This indicates a possible history of malignant hypertension, and so is listed with "Hypertension." All items marked with  are exclusion criteria. Prior to answering Item 45 (judgment on eligibility), these items should be very carefully reviewed. The clinician reviewing this section should sign the form and enter his or her ID code in Item 46.

If participants do not remain eligible, they should receive an explanation of why they are not eligible, should be provided with a written record of their blood pressure, thanked and excused.

Review of visit (Items 4a-4e):

When all of the procedures have been completed, but before the participant leaves the clinic, the front page of the SH06 should be reviewed and completed. The SHEP ID and acrostic should be checked, and the forms filled out at this visit should be checked for completeness and legibility.

If the paricipant is not blood pressure eligible, Item 4a (Procedures completed) should be checked "None, participant not BP eligible" and then skip to 4b. For all BP eligible participants, Items 4a(1)-4a(5) should be indicated as done ("Yes") or not done ("No"). Any procedures required but not done should be explained in comments (Item 4d).

"Result of visit" (Item 4b) refers to the participant's eligibility and participation status at the end of this visit. The participant will fall into one of three categories:

- Not eligible for BV2
- Eligible but currently refuses BV2
- Eligible and BV2 scheduled

(The fourth choice is explained in Section 2.3.7.) The participant's status should be indicated by an "X" in the appropriate box. Please check the entire form carefully for eligibility.

If the participant has had a blood sample drawn for local analysis of serum creatinine, a final judgement on eligibility (Item 7c) cannot be made until the result is obtained. If the participant is otherwise eligible, the Baseline Visit 2 may be tentatively scheduled and, if the creatinine level is above 2.0 mg/dl, then later cancelled. When the result is obtained, document the result in Item 7c and on the SH11.

Baseline Visit 2 should then be scheduled for eligible participants in 10 to 28 days from the Baseline Visit 1. (If the Baseline Visit 2 cannot be accomplished within 60 days of Baseline Visit 1, the participant must be re-started from Initial Contact.)

The participant should be instructed not to eat for 12 hours prior to the Baseline Visit 2, so that a fasting blood sample may be drawn at that time.

Space is allowed in Item 4d for any comments on this visit.

The person reviewing and completing Items 4a-4d should then sign the form and enter their two-digit ID code in Item 4e.

2.3.6 Auxiliary Forms for Baseline Visit 1

SH11 - Local Laboratory Results - use for dipstick urinalysis results and, if done, serum creatinine result (see Section 9.2); the same SH11 should be used for both results

2.3.7 Item 4b, Response #4

The "Result of visit" option #4 is given to allow for participants who are eligible and scheduled for BV2, but become ineligible or die or refuse prior to the BV2. In these cases, option #3 ("Participant is eligible and Baseline Visit 2 scheduled") would have originally been marked, the scheduled date and time for the BV2 completed, and the form electronically transmitted. Suppose, then, that the participant becomes ineligible (e.g., has an MI), dies or subsequently refuses prior to the BV2. In this case, simply submit a change to the SH06, #4b, to change from "3" to "4"; the date and time will then not have to be blanked out. Changes to electronically transmitted forms are described in Appendix F.

SHEP CLINICAL CENTER NUMBERS

01	Albert Einstein College of Medicine New York, New York
02	Emory University Atlanta, Georgia
03	Kaiser Foundation Research Institute Portland, Oregon
04	Miami Heart Institute Miami, Florida
05	Northwestern University Chicago, Illinois
06	Medical Research Institute of San Francisco San Francisco, California
07	UMDNJ-Rutgers Medical School New Brunswick, New Jersey
08	University of Alabama at Birmingham Birmingham, Alabama
09	University of California at Davis Davis, California
10	University of Hawaii Honolulu, Hawaii
11	University of Kentucky Lexington, Kentucky
12	University of Maryland Baltimore, Maryland
13	University of Minnesota Minneapolis, Minnesota
14	University of Pittsburgh Pittsburgh, Pennsylvania
15	University of Tennessee Memphis, Tennessee
16	Washington University St. Louis, Missouri
17	Yale University New Haven, Connecticut

This Box For Clinic Staff Use Only

SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ ACROSTIC: ☐☐☐☐☐☐

DEAR PARTICIPANT:

PLEASE FILL OUT THIS FORM AS COMPLETELY AS YOU ARE ABLE. BRING IT WITH YOU WHEN YOU NEXT COME TO OUR CLINIC. IF THERE ARE PARTS THAT YOU CANNOT FILL OUT, WE WILL GO OVER IT AT THAT TIME.

PARTICIPANT INFORMATION SHEET

PLEASE PRINT IN BLOCK CAPITALS:

1. Name: _____ (First) _____ (Middle) _____ (Last)

   Address: _____ (#) _____ (Street) _____ (Apt. #)

   _____ (City) _____ (State) _____ (Zip)

   Telephone: (_____) (Area) _____ - _____

2. When is the best time to contact you (days and times)? _____

3. Birthdate: _____

4. Social Security #: _____ - _____ - _____

5. Medicare Number: _____

6. (If Employed):
   Name of Employer: _____

   Title: _____

   Address: _____ (#) _____ (Street)

   _____ (City) _____ (State) _____ (Zip)

   Telephone: (_____) (Area) _____ - _____ May we call you at work? _____

   Days worked: _____ Which hours worked: _____

(PLEASE TURN OVER)

7. Name and address of two relatives or friends who do not live with you, and who would know where you might be contacted:

a. Name: _____

Address: _____
(#) (Street)

_____ _____ _____
(City) (State) (Zip)

Telephone: (_____) _____ - _____
(Area)

Relationship: _____

b. Name: _____

Address: _____
(#) (Street)

_____ _____ _____
(City) (State) (Zip)

Telephone: (_____) _____ - _____
(Area)

Relationship: _____

8. Name and address of health care provider:

Name: _____

Address: _____
(#) (Street)

_____ _____ _____
(City) (State) (Zip)

Telephone: (_____) _____ - _____
(Area)

9. Father's Last Name: _____

10. State of birth: _____

11. Names of senior citizen organizations that you belong to, if any:

_____

_____

_____

SHEP BASELINE DEMOGRAPHIC INFORMATION AND MEDICATION HISTORY

This Space for Clinic Use Only

NAME: _____

SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ ACROSTIC: ☐☐☐☐☐☐

DATE OF CLINIC VISIT: ☐☐ Month ☐☐ Day ☐☐ Year AT ☐☐ Hour : ☐☐ Minute ☐ a.m. ☐ p.m.

DEAR PARTICIPANT:

PLEASE FILL OUT THIS FORM AS COMPLETELY AS POSSIBLE AND BRING IT WITH YOU TO THE CLINIC VISIT SCHEDULED ABOVE. IF YOU DO NOT UNDERSTAND SOME OF THE QUESTIONS, LEAVE THEM BLANK UNTIL YOUR CLINIC VISIT. WE WILL REVIEW THE WHOLE FORM WITH YOU AT THAT TIME.

PERSONAL INFORMATION:

1. SEX:

MALE ☐ 1
FEMALE ☐ 2

2. RACE:

WHITE ☐ 1
BLACK ☐ 2
ASIAN ☐ 3
HISPANIC ☐ 4
OTHER (SPECIFY): ☐ 5
_____

3. WHAT IS THE HIGHEST GRADE OR YEAR OF SCHOOL THAT YOU COMPLETED? ☐☐

4. WHICH OF THE FOLLOWING MOST CLOSELY DESCRIBES YOUR EMPLOYMENT STATUS?

EMPLOYED FULL TIME ☐ 1
EMPLOYED PART TIME ☐ 2
RETIRED OR NOT EMPLOYED ☐ 3

5. WHAT IS YOUR CURRENT MARITAL STATUS?

- MARRIED ☐ 1
- WIDOWED ☐ 2
- SEPARATED ☐ 3
- DIVORCED ☐ 4
- NEVER MARRIED ☐ 5

6. a. DO YOU CURRENTLY SMOKE CIGARETTES? YES ☐ 1
(IF NO, SKIP TO QUESTION 7.) NO ☐ 2

b. HOW MANY CIGARETTES DO YOU NOW SMOKE PER DAY? ☐☐☐

c. HOW OLD WERE YOU WHEN YOU STARTED SMOKING? ☐☐
(SKIP TO QUESTION 8.)

7. a. DID YOU EVER SMOKE CIGARETTES? YES ☐ 1
(IF NO, SKIP TO QUESTION 8.) NO ☐ 2

b. HOW MANY CIGARETTES A DAY DID YOU USUALLY SMOKE BEFORE YOU QUIT SMOKING? ☐☐☐

c. HOW OLD WERE YOU WHEN YOU STARTED SMOKING CIGARETTES? ☐☐

d. HOW OLD WERE YOU WHEN YOU FINALLY STOPPED SMOKING CIGARETTES? ☐☐

8. a. WHICH ANSWER BEST DESCRIBES HOW OFTEN YOU DRINK WINE, BEER, WHISKEY OR LIQUOR? (CHECK ONE.)

- NEVER DRANK ☐ 1
- I USED TO DRINK, BUT DON'T DRINK NOW ☐ 2
- 1 OR 2 TIMES A YEAR OR VERY OCCASIONALLY ☐ 3
- LESS THAN ONE PER WEEK OR ONLY AT PARTIES ☐ 4
- 1 TO 2 TIMES A WEEK ☐ 5
- 3 TO 4 TIMES A WEEK ☐ 6
- NEARLY EVERY DAY ☐ 7
- EVERY DAY ☐ 8

b. WHEN YOU DRINK ALCOHOLIC BEVERAGES, HOW MANY DO YOU USUALLY DRINK IN A DAY? ☐☐
(ONE DRINK = 1 CAN OF BEER, OR 1 GLASS OF WINE OR 1 SHOT OF WHISKEY OR LIQUOR)

9. a. ARE YOU TAKING ANY MEDICINES THAT REQUIRE A PRESCRIPTION FROM A DOCTOR?

YES ☐ 1
NO ☐ 2
↓
(CONTINUE TO QUESTION 10)

NAME ALL OF THE MEDICINES THAT ARE BEING PRESCRIBED FOR YOU BY A DOCTOR OR CLINIC.

	MEDICINE NAME	WHAT ILLNESS IS MEDICINE FOR?
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

b. TOTAL NO. OF PRESCRIPTION MEDICINES BEING TAKEN ☐☐

Clinic Use Only

SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ ACROSTIC: ☐☐☐☐☐☐

10. HAVE YOU STOPPED TAKING ANY PRESCRIPTION MEDICATIONS IN THE PAST TWO WEEKS?

YES ☐ 1
NO ☐ 2
↓
(CONTINUE TO QUESTION 11)

PLEASE LIST THEM BELOW

	MEDICINE NAME	WHAT ILLNESS IS MEDICINE FOR?
1.	_____	
2.	_____	
3.	_____	

WHY DID YOU STOP TAKING THE MEDICINE(S)?

MEDICINE NO. 1	CHECK IF YES
1. THE DOCTOR ADVISED ME TO STOP	☐ 1
2. THE PRESCRIPTION RAN OUT	☐ 1
3. I FELT BETTER	☐ 1
4. I COULDN'T REMEMBER TO TAKE THEM	☐ 1
5. I COULDN'T BE BOTHERED	☐ 1
6. THEY MADE ME FEEL SICK	☐ 1
7. I DIDN'T THINK THEY WERE WORKING	☐ 1
8. A FRIEND TOLD ME TO STOP	☐ 1
9. DON'T KNOW	☐ 1
10. OTHER:	☐ 1

_____

_____

MEDICINE NO. 2	CHECK IF YES
1. THE DOCTOR ADVISED ME TO STOP	☐ 1
2. THE PRESCRIPTION RAN OUT	☐ 1
3. I FELT BETTER	☐ 1
4. I COULDN'T REMEMBER TO TAKE THEM	☐ 1
5. I COULDN'T BE BOTHERED	☐ 1
6. THEY MADE ME FEEL SICK	☐ 1
7. I DIDN'T THINK THEY WERE WORKING	☐ 1
8. A FRIEND TOLD ME TO STOP	☐ 1
9. DON'T KNOW	☐ 1
10. OTHER:	☐ 1

_____

_____

MEDICINE NO. 3	CHECK IF YES
1. THE DOCTOR ADVISED ME TO STOP	☐ 1
2. THE PRESCRIPTION RAN OUT	☐ 1
3. I FELT BETTER	☐ 1
4. I COULDN'T REMEMBER TO TAKE THEM	☐ 1
5. I COULDN'T BE BOTHERED	☐ 1
6. THEY MADE ME FEEL SICK	☐ 1
7. I DIDN'T THINK THEY WERE WORKING	☐ 1
8. A FRIEND TOLD ME TO STOP	☐ 1
9. DON'T KNOW	☐ 1
10. OTHER:	☐ 1

_____

_____

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11. a. ARE YOU PRESENTLY TAKING ANY MEDICINES OR DIET SUPPLEMENTS THAT YOU BUY IN A DRUGSTORE, SUPERMARKET OR HEALTH FOOD STORE WITHOUT A PRESCRIPTION? FOR EXAMPLE, ASPIRIN, LAXATIVES, VITAMINS, ANTACIDS.

YES ☐ 1
NO ☐ 2
↓
(CONTINUE TO QUESTION 12)

WHAT KIND?

	BRAND NAME	WHAT ILLNESS DO YOU TAKE IT FOR?
1.		
2.		
3.		
4.		
5.		

(IF MORE THAN 5, LIST ON A BLANK SHEET OF PAPER.)

b. TOTAL NO. OF NON-PRESCRIPTION MEDICINES BEING TAKEN ☐☐

12. a. WOULD YOU OBJECT TO US SENDING YOUR BLOOD PRESSURE RESULTS TO THE PERSON OR CLINIC THAT USUALLY SUPPLIES YOUR HEALTH CARE?

- YES ☐ 1
- NO ☐ 2
- DON'T KNOW ☐ 3
- I DO NOT HAVE A PERSONAL PHYSICIAN OR CLINIC THAT SUPPLIES HEALTH CARE ☐ 4

b.

CLINIC NAME OR DOCTOR: _____

ADDRESS: _____

_____

TELEPHONE: _____

THANK YOU FOR COMPLETING THIS FORM. PLEASE REMEMBER TO BRING THIS FORM AND ANY PRESCRIPTION MEDICATIONS THAT YOU ARE NOW TAKING WITH YOU FOR YOUR CLINIC VISIT WHICH IS SCHEDULED ON THE DATE SHOWN ON THE FRONT PAGE.

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SHEP BASELINE MEDICAL HISTORY

This Space for Clinic Use Only

Name: _____

SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ Acrostic: ☐☐☐☐☐☐

Date of Clinic Visit: ☐☐ Month ☐☐ Day ☐☐ Year at ☐☐ Hour : ☐☐ Minute ☐ a.m. ☐ p.m.

DEAR PARTICIPANT:

PLEASE FILL OUT THIS FORM AS COMPLETELY AS POSSIBLE AND BRING IT WITH YOU TO THE CLINIC VISIT SCHEDULED ABOVE. IF YOU DO NOT UNDERSTAND SOME OF THE QUESTIONS, LEAVE THEM BLANK UNTIL YOUR CLINIC VISIT. WE WILL REVIEW THE WHOLE FORM WITH YOU AT THAT TIME.

HAS A DOCTOR EVER TOLD YOU THAT YOU HAD ANY OF THE FOLLOWING?

1.	High blood pressure	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
2.	High blood pressure severe enough to lead to hospitalization?	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
3.	Heart attack (myocardial infarction, coronary occlusion or coronary thrombosis)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
4.	Angina (chest pain)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
5.	Congenital heart problems (born with a heart defect)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
6.	Rheumatic heart problems	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
7.	Other heart problems	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
8.	Stroke (cerebrovascular accident, CVA)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
9.	Epilepsy (spells, fits or seizures)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
10.	Memory problems or other problems of the brain	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
11.	Diabetes (high blood or urine sugar)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
12.	Gout	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

(PLEASE TURN OVER)

13.	Kidney problems (nephritis, kidney infection, kidney stones)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
14.	(Men only) Problems of the prostate (infection, enlargement)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
15.	(Women only) Problems of the female organs	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
16.	Urinary tract infection or bladder problem	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
17.	Pneumonia	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
18.	Lung problems (TB, emphysema pleurisy, bronchitis, or other problems)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
19.	Thyroid problem	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
20.	Ulcer of the stomach or duodenum	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
21.	Colitis or intestinal problems	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
22.	Liver problems (hepatitis, cirrhosis or other problems)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
23.	Gallstones or gall bladder disease	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
24.	Anemia	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
25.	Cancer	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
26.	Nervous or emotional disorder	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
27.	Arthritis	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
28.	Hives or hay fever, or other allergies	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
29.	Other major diseases (specify): _____	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

DURING THE PAST YEAR, HAVE YOU EXPERIENCED ANY OF THE FOLLOWING?

30.	Skin rash or unusual bruises	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
31.	Headaches that were so bad you had to stop what you were doing	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
32.	Headache attack, racing heart and sweating all at the same time	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
33.	Faintness or light-headedness when you stood up quickly	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
34.	Your heart beating unusually fast or skipping beats	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
35.	Blacking out or losing consciousness	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
36.	Frequent stomach pains	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
37.	Waking up early, having trouble getting back to sleep	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
38.	Black or tarry stools	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
39.	Bright red blood in your stools	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
40.	Weight loss without dieting	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

41. a. How many days in the past two weeks have you had to substantially reduce your social activities outside the home (meetings, shopping) because you did not feel well? ☐☐

b. How many days in the past two weeks have you had to substantially reduce your major work activities at home (house cleaning, laundry) because you did not feel well? ☐☐

c. How many days in the past two weeks have you had to substantially reduce your ordinary activities at home (cooking, dressing) because you did not feel well? ☐☐

d. How many days in the past two weeks did you spend most of the day in bed because you did not feel well? ☐☐

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(PLEASE TURN OVER)

42. a. Have you ever had any pain or discomfort in your chest?

Yes □ 1 No □ 2

↓

Skip to 42c

b. Have you ever had any pressure or heaviness in your chest?

Yes □ 1 No □ 2

↓

Skip to 43

c. Do you get this pain, discomfort, pressure or heaviness when you walk uphill or hurry?

Yes □ 1 No □ 2

↓

Skip to 43

d. Do you get it when you walk at an ordinary pace on the level ground?

Yes □ 1 No □ 2

e. What do you do when you get this pain while you are walking?

Stop or slow down □ 1
Continue at same pace □ 2

f. Does it go away when you stand still?

Yes □ 1 No □ 2

↓

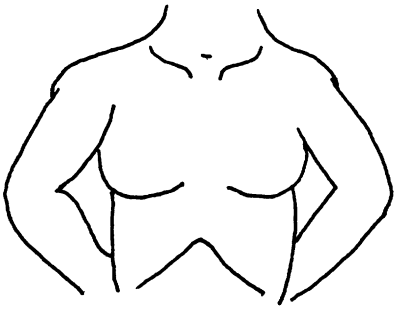
Skip to 42h

g. How soon?

10 minutes or less □ 1
More than 10 minutes □ 2

h. Where do you get this pain or discomfort? (Mark the places with an "X" on the diagram.)

RIGHT SIDE



LEFT SIDE

Do not use--clinic use only.

(1) Yes □ 1 No □ 2
(2) Yes □ 1 No □ 2
(3) Yes □ 1 No □ 2

---

43. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

Yes □ 1 No □ 2

---

44. a. Have you ever had a heart attack (myocardial infarction, coronary thrombosis)? Yes ☐ 1 No ☐ 2 ↓ Don't know ☐ 3 ↓

Skip to 45

b. Were you ever hospitalized for any heart attacks? Yes ☐ 1 No ☐ 2

c. How many such attacks have you had? ☐☐

d. What were the dates of these heart attacks? (month/year) _____

---

45. a. Do you get a pain in either leg on walking? Yes ☐ 1 No ☐ 2 ↓

Skip to 46

b. Does this pain ever begin when you are standing still or sitting? Yes ☐ 1 No ☐ 2

c. Do you get this pain in your calf? (or calves?) Yes ☐ 1 No ☐ 2

d. Do you get it when you walk uphill or hurry? Yes ☐ 1 No ☐ 2 ↓

Skip to 46

e. Do you get it when you walk at an ordinary pace on the level ground? Yes ☐ 1 No ☐ 2

f. Does this pain ever disappear while you are still walking? Yes ☐ 1 No ☐ 2

g. What do you do if you get it when you are walking? Stop or slow down ☐ 1 Continue at same pace ☐ 2

h. Does it go away when you stand still? Yes ☐ 1 No ☐ 2 ↓

Skip to 46

i. How soon? 10 minutes or less ☐ 1 More than 10 minutes ☐ 2

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(PLEASE TURN OVER)

46. a. Do you usually cough first thing in the morning in the winter? (If you cough with your first smoke or when first going outside, you should mark "yes." Do not respond "yes" for clearing of throat or a single cough.)

Yes ☐ 1 No ☐ 2

↓

Skip to 46c

b. Do you usually cough during the day or at night in the winter? (Do not respond "yes" for a single cough.)

Yes ☐ 1 No ☐ 2

↓

Skip to 47

c. Do you cough like this on most days for as much as 3 months each Year?

Yes ☐ 1 No ☐ 2

d. Do you usually bring up any phlegm (mucus) from your chest first thing in the morning in the winter?

Yes ☐ 1 No ☐ 2

e. Do you usually bring up any phlegm from your chest during the day or at night in the winter?

Yes ☐ 1 No ☐ 2

↓

Skip to 47

f. Do you bring up phlegm like this on most days for as much as 3 months each year?

Yes ☐ 1 No ☐ 2

g. In the past 3 years, have you had a period of increased cough and phlegm lasting for 3 weeks or more?

Yes, once ☐ 1
Yes, more than once ☐ 2
No ☐ 3

---

47. a. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

Yes ☐ 1 No ☐ 2

b. Do you get short of breath walking with other people of your own age on level ground?

Yes ☐ 1 No ☐ 2

c. Do you ever wake up at night gasping for breath?

Yes ☐ 1 No ☐ 2

d. Do you get short of breath at night unless you sleep on two or more pillows?

Yes ☐ 1 No ☐ 2

e. Have you ever had asthma?

Yes ☐ 1 No ☐ 2

↓

Skip to 48

f. Have you had any asthma attacks in the past three years?

Yes ☐ 1 No ☐ 2

g. Do you take medication to control or treat asthma?

Yes ☐ 1 No ☐ 2

---

48. a. Have you ever had any sudden feeling of numbness, tingling or loss of feeling in either arm, hand, leg, foot or face?

Yes ☐ 1 No ☐ 2

↓

Skip to 49

b. How many attacks of such numbness or tingling have you had? (Check one.)

Only one ☐ 1
Two ☐ 2
Three to five ☐ 3
More than five ☐ 4

c. How long did each of the attack(s) usually last?

Less than 5 minutes ☐ 1
From 5 minutes to one hour ☐ 2
From 1-6 hours ☐ 3
From 6-24 hours ☐ 4
More than 24 hours ☐ 5

d. Did you see a doctor for the numbness, tingling, or loss of feeling?

Yes ☐ 1 No ☐ 2

---

49. a. Have you ever had any sudden attacks of paralysis or loss of use of either arm, hand, leg or foot?

Yes ☐ 1 No ☐ 2

↓

Skip to 50

b. How many attacks of such paralysis have you had? (Check one.)

Only one ☐ 1
Two ☐ 2
Three to five ☐ 3
More than five ☐ 4

c. How long did the attack(s) usually last?

Less than 5 minutes ☐ 1
From 5 minutes to one hour ☐ 2
From 1-6 hours ☐ 3
From 6-24 hours ☐ 4
More than 24 hours ☐ 5

d. Did you see a doctor for this paralysis?

Yes ☐ 1 No ☐ 2

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(PLEASE TURN OVER)

50. a. Have you ever had any sudden loss of eyesight or blurring of vision for a short period of time? Yes ☐ 1 No ☐ 2

↓

Skip to 51

b. What part of your vision was affected?

- Right eye only ☐ 1
- Left eye only ☐ 2
- Both eyes ☐ 3
- Vision to the right side ☐ 4
- Vision to the left side ☐ 5

c. How many attacks of loss of eyesight or blurring of vision have you had?

- Only one ☐ 1
- Two ☐ 2
- Three-five ☐ 3
- More than five ☐ 4

d. How long did the attack(s) usually last?

- Less than 5 minutes ☐ 1
- From 5 minutes to one hour ☐ 2
- From 1-6 hours ☐ 3
- From 6-24 hours ☐ 4
- More than 24 hours ☐ 5

e. Did you see a doctor for this vision problem? Yes ☐ 1 No ☐ 2

---

51. a. Have you ever had any sudden attacks of changes in speech, loss of speech or inability to say words? Yes ☐ 1 No ☐ 2

↓

Skip to 52

b. How many attacks of loss of speech have you had?

- Only one ☐ 1
- Two ☐ 2
- Three-five ☐ 3
- More than five ☐ 4

c. How long did the attack(s) usually last?

- Usually less than 5 minutes ☐ 1
- From 5 minutes to one hour ☐ 2
- From 1-6 hours ☐ 3
- From 6-24 hours ☐ 4
- More than 24 hours ☐ 5

d. Did you see a doctor for your speech problem? Yes ☐ 1 No ☐ 2

---

52. Have you ever had any of the following:

a.	Dizziness	Yes ☐ 1	No ☐ 2
b.	Spinning sensation (vertigo)	Yes ☐ 1	No ☐ 2
c.	Loss of balance	Yes ☐ 1	No ☐ 2
d.	Difficulty walking	Yes ☐ 1	No ☐ 2
e.	Blackouts or fainting	Yes ☐ 1	No ☐ 2
f.	Frequent falls	Yes ☐ 1	No ☐ 2

---

53. a. Did you answer "yes" to any of the problems in Question 52? Yes ☐ 1 No ☐ 2

↓

Skip to 54

b. About how many total attacks of all conditions checked do you think you ever had?

- Only one ☐ 1
- Two ☐ 2
- Three-five ☐ 3
- More than five ☐ 4

c. How long did the attack(s) usually last?

- Usually less than 5 minutes ☐ 1
- From 5 minutes to one hour ☐ 2
- From 1-6 hours ☐ 3
- From 6-24 hours ☐ 4
- More than 24 hours ☐ 5

d. Did you see a doctor for any of these spells? Yes ☐ 1 No ☐ 2

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(PLEASE TURN OVER)

54. a. Have you ever had surgery to improve the blood flow in your arteries or vessels (endarterectomy, by-pass surgery)? (Do not include surgery for varicose veins.) Yes ☐ 1 No ☐ 2

↓

Skip to 55

b. Did you have surgery on your neck vessels (carotid artery)? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

c. Did you have surgery on your heart (coronary by-pass)? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

d. Did you have surgery on the aorta or leg arteries? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

---

55. a. Have you been hospitalized for any reason within the past 5 years? Yes ☐ 1 No ☐ 2

↓

Skip to 56

b. List the reason, the name and address of the hospital, and the year of the hospitalization.

	Reason	Year	Name of Hospital, City and State
(1)			
(2)			
(3)			
(4)			
(5)			

(If more than 5 hospitalizations, list rest on a blank sheet of paper.)

56. Have you ever had a fracture of the:

a. Hip? Yes ☐ 1 No ☐ 2
When? _____

b. Spine? Yes ☐ 1 No ☐ 2
When? _____

c. Forearm? Yes ☐ 1 No ☐ 2
When? _____

---

57. a. About how many times would you say that you have fallen to the floor or ground for no obvious reason in the past three months?

None ☐ 1
Once ☐ 2
Twice ☐ 3
Three times ☐ 4
Four or five times ☐ 5
More than five times ☐ 6
Don't know ☐ 7

If "None," skip to 58

b. Did you have any injury from those falls that required a doctor's attention? Yes ☐ 1 No ☐ 2 Don't know ☐ 3

Describe injury: _____

---

58. Has any medicine you may be taking, or have taken in the past, ever caused you to have a skin rash or other kind of allergic reaction? Yes ☐ 1 No ☐ 2

Describe medicine, reaction and circumstances:

_____

_____

_____

THANK YOU FOR COMPLETING THIS FORM. PLEASE REMEMBER TO BRING THIS FORM AND ANY PRESCRIPTION MEDICINES THAT YOU ARE NOW TAKING WITH YOU FOR YOUR CLINIC VISIT WHICH IS SCHEDULED ON THE DATE SHOWN ON THE FRONT PAGE.

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BASELINE VISIT 1

Name: _____

1. SHEP ID: [ ] - [ ] - [ ] 2. Acrostic: [ ]

3. Today's Date: [ ] Month [ ] Day [ ] Year

PRIOR TO INITIATING PROCEDURES FOR THIS VISIT, COLLECT, REVIEW AND COMPLETE THE FOLLOWING ITEMS.

- ☐ Consent for Baseline Visit 1 (and Baseline Visit 2, if allowed)
- ☐ SH02, Participant Information Sheet
- ☐ SH03, Demographic Information and Medication History
- ☐ Item 5 (page 2 of this form), Summary of Initial Contact and Drug Evaluation Visits

---

COMPLETE SECTION BELOW AT TERMINATION OF VISIT BEFORE PARTICIPANT LEAVES. CHECK TO BE SURE THAT THE ACROSTIC (ITEM 2) IS CORRECT. BE SURE THAT EVERY ITEM ON EACH PAGE IS COMPLETE (IF REQUIRED) AND LEGIBLE. CHECK YELLOW COPY FOR LEGIBILITY, ALSO. ANY ITEMS OR PROCEDURES REQUIRED BUT NOT COMPLETED SHOULD BE EXPLAINED IN COMMENTS, ITEM 4d.

---

4. a. Procedures completed: ☐ 1 None, participant not BP eligible (skip to 4b).

	Yes	No	
(1)	☐ 1	☐ 2	Baseline Medical History (SH04)
(2)	☐ 1	☐ 2	ECG and two-minute rhythm strip
(3)	☐ 1	☐ 2	Dipstick urinalysis (SH11)
(4)	☐ 1	☐ 2	Physical examination
(5)	☐ 1	☐ 2	Local determination of serum creatinine (SH11) --not required

b. Result of this visit--please check entire form carefully for eligibility:

- ☐ 1 Participant is not eligible for Baseline Visit 2 (skip to 4d).
- ☐ 2 Participant is eligible but currently refuses Baseline Visit 2 (skip to 4d).
- ☐ 3 Participant is eligible and Baseline Visit 2 scheduled.
- ☐ 4 Participant was eligible and scheduled for BV2 but became ineligible or died or refused prior to BV2 (explain in Comments, Item 4d).

c. Baseline Visit 2 scheduled:

[ ] Month [ ] Day [ ] Year at [ ] Hour : [ ] Minute a.m. ☐ 1 p.m. ☐ 2

d. Comments: _____

_____

_____

e. Signature of person completing this section:

_____ [ ] Code

SUMMARY OF INITIAL CONTACT AND DRUG EVALUATION VISITS--
Copy from Initial Contact Form SH01, Participant Information Sheet SH02 and, if applicable, Drug Evaluation Visit Summary SH05:

5. a. Date of birth: ____ (Month) ____ (Day) ____ (Year)

b. Social Security Number (leave blank if no number): ____ - ____ - ____

c. Medicare Number (leave blank if no number): ____ - ____ - ____ - ____

d. Initial Contact Visit date: ____ (Month) - ____ (Day) - ____ (Year)

e. Initial Contact Visit blood pressure readings:

	Systolic	Diastolic
Reading 1:		
Reading 2:		
Reading 3:		

f. Using most up-to-date information available, was participant on antihypertensive medications at the Initial Contact Visit?

Yes ☐ 1 No ☐ 2 → (Skip to Item 6.)

g. Date antihypertensive medications completely withdrawn: ____ (Month) - ____ (Day) - ____ (Year)

h. Blood pressure readings on day medications completely withdrawn:

	Systolic	Diastolic
Reading 1:		
Reading 2:		
Reading 3:		

i. Date of most recent Drug Evaluation Visit: ____ (Month) - ____ (Day) - ____ (Year)

j. Blood pressure readings at most recent Drug Evaluation Visit:

	Systolic	Diastolic
Reading 1:		
Reading 2:		
Reading 3:		

PULSE AND BLOOD PRESSURE--If any pulse or blood pressure is not obtained, enter all 9s in the appropriate spaces.

6. a. Pulse: Beats in 30 seconds _____ x 2 = ☐☐☐ beats per minute.

b. Cuff Size:

1 ☐ Regular
2 ☐ Large arm
3 ☐ Thigh
4 ☐ Pediatric

Pulse Obliteration Pressure:

Observed Value: ☐☐☐
Subtract Zero Level: - ☐☐
Corrected Value: ☐☐☐
Add Maximum Zero Level Plus 20: + ☐☐
Peak Inflation Level: ☐☐☐

Seated Readings:

	Systolic	Diastolic
First	☐☐☐	☐☐☐
Zero level	☐☐	☐☐
Corrected	☐☐☐	☐☐☐
+ Second	☐☐☐	☐☐☐
+ Zero level	☐☐	☐☐
+ Corrected	☐☐☐	☐☐☐
Sum of two corrected readings	☐☐☐	☐☐☐
Average of two corrected readings	☐☐☐	☐☐☐

Standing Readings:

One minute

Pulse: Beats in 15 seconds _____
x 4 = ☐☐☐ beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	☐☐☐	☐☐☐
Zero	☐☐	☐☐
Corrected	☐☐☐	☐☐☐

Three minutes

Pulse: Beats in 15 seconds _____
x 4 = ☐☐☐ beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	☐☐☐	☐☐☐
Zero	☐☐	☐☐
Corrected	☐☐☐	☐☐☐

(If standing blood pressure not done, skip to 6d.)

c. Did the participant volunteer any symptoms on standing? Yes ☐ 1 No ☐ 2 → SKIP to 6d.

(1) Dizziness? Yes ☐ 1 No ☐ 2
(2) Other (specify)? Yes ☐ 1 No ☐ 2

d. Eligibility check (use average of two corrected seated readings):

□ 1 SBP 150-219 and DBP <95 mm Hg → Eligible

□ 2 SBP < 150 or SBP ≧ 220 or DBP ≧ 95 mm Hg → Not blood pressure eligible

e. Observer: _____ Code

Ineligible persons should proceed to scheduling area for termination of their participation in the SHEP screening process.

Only blood pressure eligible participants should proceed with the remaining items in Baseline Visit 1. If the Baseline Medical History (SH04) has not been completed, it must be completed at this time.

PARTICIPANT SHOULD NOW BE SENT FOR ECG, TWO-MINUTE RHYTHM STRIP AND DIPSTICK URINALYSIS.

---

7. a. Does the participant have a history of kidney disease, or protein (at least trace) or blood (at least non-hemolyzed trace) in urine?

Yes □ 1 No □ 2

A blood sample may be drawn at local option for local determination of serum creatinine. Document result on Local Laboratory Results, SH11, with dipstick urinalysis results. If a blood sample is drawn, hold this form and final determination of eligibility until local creatinine result is obtained.

b. Was a blood sample drawn for local determination of serum creatinine?

Yes □ 1 No □ 2 → SKIP to 8.

c. Local creatinine result:

1 □ Creatinine >2.0 mg/dl → Ineligible

2 □ Creatinine ≦ 2.0 mg/dl → Eligible

CLINICIAN REVIEW OF MEDICATION HISTORY--To be completed by clinician using information from the Baseline Demographic Information and Medication History Form, SH03. Do not count drugs that the participant discontinued in order to participate in the SHEP.

---

8. Is the participant taking any of the drugs listed below? Drugs marked with an * are exclusions if checked "Current."

		Current (last 2 weeks)	Not Current or Not Sure
* a.	Any medication for blood pressure, or any drugs with antihypertensive action (including Neptazene and Diamox)	□ 1	□ 2
b.	Digitalis	□ 1	□ 2
c.	Nitrates, including nitroglycerine, or other coronary vasodilator	□ 1	□ 2

(Continued on next page)

CLINICIAN REVIEW OF MEDICATION HISTORY (Continued)

		Current (last 2 weeks)	Not Current or Not Sure
* d.	Propranolol or other beta blockers for other than treatment of blood pressure (excluding Timoptic eye drops)	□ 1	□ 2
e.	Timoptic eye drops	□ 1	□ 2
f.	Anti-arrhythmic drugs	□ 1	□ 2
g.	Lipid-lowering drugs, including clofibrate, cholestryramine, colestipol, nicotinic acid, etc.	□ 1	□ 2
h.	Agents for gout, including probenecid, allopurinol or colchicine	□ 1	□ 2
* i.	Insulin	□ 1	□ 2
j.	Oral hypoglycemic agents	□ 1	□ 2
* k.	Anticoagulants	□ 1	□ 2
l.	Antibiotics or anti-infection agents	□ 1	□ 2
m.	Cortisone or other gluco corticoids	□ 1	□ 2
n.	Amphetamines or other stimulant	□ 1	□ 2
o.	Flurazepam or other sedative	□ 1	□ 2
p.	Anti-depressants	□ 1	□ 2
q.	Librium, valium or other antianxiety agents	□ 1	□ 2
r.	Other psychotropic agents	□ 1	□ 2
s.	Potassium supplementation other than dietary recommendations	□ 1	□ 2
t.	Estrogen	□ 1	□ 2
u.	Anturane® (Sulfinpyrazone) at least 4 weeks	□ 1	□ 2
v.	Persantine® (Dipyridamole) at least 4 weeks	□ 1	□ 2
w.	Aspirin at least 4 weeks	□ 1	□ 2
x.	Non-steroidal anti-inflammatory drugs	□ 1	□ 2
* y.	Any experimental drug	□ 1	□ 2

If any of 8a, 8d, 8i, 8k, or 8y are marked "Current," the participant is not eligible for participation in the SHEP. Ineligible persons should proceed to the scheduling area for termination of their participation in the SHEP screening process. Only eligible participants should proceed with the physical examination.

PHYSICAL EXAMINATION--The clinician should perform a general physical examination, paying particular attention to the specific items listed below, entering comments for each indicated abnormality.

9. a. Weight in pounds: [ ] b. Height in inches: [ ]

	Area Examined		Comments
10.	SKIN	Abnormal □ 1 Normal □ 2	
11.	HEAD, EARS, NOSE, THROAT	Abnormal □ 1 Normal □ 2	
12.	EYES		
	Fundi:	a. Abnormal □ 1 Normal □ 2 Not Visualized □ 3	
	Other (Specify)?	b. Yes □ 1 No □ 2	

(Physical examination continued on the next page)

PHYSICAL EXAMINATION (Continued)

	Area Examined			Comments
13.	NECK			
	Raised jugular venous pressure?	a.	Yes ☐ 1 No ☐ 2	
	Carotid bruits?	b.	Yes ☐ 1 No ☐ 2	
			↓	
		c.	Right only ☐ 1 Left only ☐ 2 Bilateral ☐ 3	
	Carotid pulses absent or markedly diminished?	d.	Yes ☐ 1 No ☐ 2	
			↓	
		e.	Right only ☐ 1 Left only ☐ 2 Bilateral ☐ 3	
	Thyroid abnormality?	f.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	g.	Yes ☐ 1 No ☐ 2	
14.	LYMPH NODES		Abnormal ☐ 1 Normal ☐ 2	
15.	CHEST, LUNGS			
	Bilateral rales that do not clear with coughing?	a.	Yes ☐ 1 No ☐ 2	
	Respiratory rate 20+?	b.	Yes ☐ 1 No ☐ 2	
	Wheezing?	c.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	d.	Yes ☐ 1 No ☐ 2	
16.	HEART			
	PMI more than 2 centimeters lateral to midclavicular line?	a.	Yes ☐ 1 No ☐ 2	
	Any murmur?	b.	Yes ☐ 1 No ☐ 2	
	Third heart sound?	c.	Yes ☐ 1 No ☐ 2	
	Fourth heart sound?	d.	Yes ☐ 1 No ☐ 2	
	Pulse irregular?	e.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	f.	Yes ☐ 1 No ☐ 2	
17.	BREASTS		Abnormal ☐ 1 Normal ☐ 2	
18.	ABDOMEN			
	Liver span 10 cm or more?	a.	Yes ☐ 1 No ☐ 2	
	Abnormal abdominal pulse?	b.	Yes ☐ 1 No ☐ 2	
	Any masses?	c.	Yes ☐ 1 No ☐ 2	
	Bruit?	d.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	e.	Yes ☐ 1 No ☐ 2	

Area Examined			Comments
19. EXTREMITIES			
Pitting ankle edema?	a.	Yes □ 1 No □ 2	
Femoral bruit?	b.	Yes □ 1 No □ 2	
Any peripheral pulses absent or markedly dimished? (specify location)	c.	Yes □ 1 No □ 2	
Other (Specify)?	d.	Yes □ 1 No □ 2	
20. NEUROLOGICAL (UA = unable to assess)			
Gait			
Left hemiparetic?	a.	Yes □ 1 No □ 2 UA □ 3	
Right hemiparetic?	b.	Yes □ 1 No □ 2 UA □ 3	
Walking on toes			
Left weakness?	c.	Yes □ 1 No □ 2 UA □ 3	
Right weakness?	d.	Yes □ 1 No □ 2 UA □ 3	
Walking on heels			
Left weakness?	e.	Yes □ 1 No □ 2 UA □ 3	
Right weakness?	f.	Yes □ 1 No □ 2 UA □ 3	
Stationary 30 seconds			
Eyes closed?	g.	Can do □ 1 Cannot do □ 2 UA □ 3	
Eyes open (only if unable to do with eyes closed)	h.	Can do □ 1 Cannot do □ 2 UA □ 3	
Cranial nerves			
Facial weakness left?	i.	Yes □ 1 No □ 2 UA □ 3	
Facial weakness right?	j.	Yes □ 1 No □ 2 UA □ 3	
Visual field deficit			
Left side?	k.	Yes □ 1 No □ 2 UA □ 3	
Right side?	l.	Yes □ 1 No □ 2 UA □ 3	
Motor wrist extensors			
Weakness left?	m.	Yes □ 1 No □ 2 UA □ 3	
Weakness right?	n.	Yes □ 1 No □ 2 UA □ 3	
Coordination			
Left hand patting?	o.	Slowed □ 1 Normal □ 2 UA □ 3	
Right hand patting?	p.	Slowed □ 1 Normal □ 2 UA □ 3	

PHYSICAL EXAMINATION (Continued)

Area Examined					Comments
Neurological (UA = unable to assess)					
Reflexes					
Assymetry of Patellar tendon	q.	L>R □ 1 R>L □ 2	Equal □ 3 UA □ 4		
Babinski sign left?	r.	Yes □ 1	No □ 2	UA □ 3	
Babinski sign right?	s.	Yes □ 1	No □ 2	UA □ 3	
Other					
Any speech or language problems (specify)?	t.	Yes □ 1	No □ 2		

21. OTHER PHYSICAL FINDINGS (SPECIFY):

22. Clinician's signature: _____ Code

CLINICIAN'S JUDGMENT AND EXCLUSION CRITERIA REVIEW--To be completed by the clinician using information from the participant's history and from the physical examination. These are clinical data for study eligibility determination as well as analysis at the Coordinating Center and they should reflect the clinician's interpretation of the findings. The study eligibility questions are identified with ⊛. These questions must all be covered prior to scheduling the participant to return for Baseline Visit 2. Pertinent items on the Baseline Medical History (SH04) are listed with the section headings.

Hypertension - SH04 Items 2, 55

23. On the basis of your history and physical exam, do you believe that the participant has ever had malignant hypertension? Yes □ 1 No □ 2 ⊛

Angina Pectoris - SH04 Items 4, 42

24. On the basis of your history and physical exam, do you believe that the participant has angina pectoris? Yes □ 1 No □ 2

Note: The Rose Questionnaire for angina (from SH04) is positive if:

Either 42a or 42b is "Yes,"
and either 42c or 42d is "Yes,"
and 42e is "Stop or slow down,"
and 42f is "Yes,"
and 42g is "10 minutes or less,"
and either 42h(1) is "Yes," (X placed in sternum upper, middle or lower) or both 42h(2) and 42h(3) are "Yes"
(X in both left anterior chest and in left arm).

CLINICIAN'S JUDGMENT (Continued)

Myocardial Infarction (MI) - SH04 Items 3, 43, 44, 54

25. a. On the basis of the ECG and your history and physical examination, do you believe the participant has ever had a myocardial infarction? Yes ☐ 1 No ☐ 2 → SKIP to 26.

b. Was it in the past 6 months? Yes ☐ 1 No ☐ 2

26. a. Is there a history of coronary bypass? Yes ☐ 1 No ☐ 2 → SKIP to 27.

b. Was it in the past six months? Yes ☐ 1 No ☐ 2

Congestive Heart Failure - SH04 Item 47

27. On the basis of your history and physical examination, do you believe that the participant has had congestive heart failure during the past year?
☐ 1 Yes, controlled
☐ 2 Yes, not controlled →
☐ 3 No

ECG

28. Are any of the following present?

a. Atrial fibrillation or flutter? Yes ☐ 1 No ☐ 2
b. Second or third degree A-V block? Yes ☐ 1 No ☐ 2
c. VPBs--multifocal, pairs or runs, or more than 10% of beats? Yes ☐ 1 No ☐ 2
d. Bradycardia (<50 beats/min.)? Yes ☐ 1 No ☐ 2

29. Does the participant currently have a pacemaker? Yes ☐ 1 No ☐ 2

Vascular System - SH04 Items 45, 48, 54

30. a. Is there a history of vascular surgery? Yes ☐ 1 No ☐ 2 → SKIP to 31.

b. Aortic, iliac, popliteal or femoral bypass or graft? Yes ☐ 1 No ☐ 2

c. Angioplasty? Yes ☐ 1 No ☐ 2
Which vessel(s)? _____

d. Other (Specify) _____ Yes ☐ 1 No ☐ 2

CLINICIAN'S JUDGMENT (Continued)

31. On the basis of your history and physical examination, does the participant have arterial disease with tissue necrosis or related loss of an extremity? Yes ☐ 1 No ☐ 2

Note: The Rose Questionnaire for intermittent claudication (from SH04) is positive if:

Item 45a is "Yes"
and 45b is "No"
and 45c is "Yes"
and 45d or 45e is "Yes"
and 45f is "No"
and 45g is "Stop or slow down"
and 45h is "Yes"
and 45i is "10 minutes or less."

Pulmonary - SH04 Items 18, 46, 47

32. On the basis of the history and physical examination, does the participant have:

a. Chronic bronchitis? Yes ☐ 1 No ☐ 2
b. Emphysema? Yes ☐ 1 No ☐ 2

Stroke/TIA - SH04 Items 8, 48-55

33. a. On the basis of your history and physical examination, and keeping the SHEP criteria in mind, do you believe the participant has ever had a stroke? Yes ☐ 1 No ☐ 2 ↓ SKIP to 34.

b. When was the most recent episode of probable stroke (not TIA)?

Month ____ Year ____

c. Are any residual effects still present? Yes ☐ 1 No ☐ 2

34. On the basis of your history and physical examination, do you believe that the participant has had transient cerebral ischemic attacks within the past 12 months?

☐ 1 Yes, based on history and presence of carotid bruit
☐ 2 Yes, based on history of two or more TIA in same location
☐ 3 Yes, based on other combinations of evidence
☐ 4 No

35. Is there a history of carotid endarterectomy? Yes ☐ 1 No ☐ 2

Contraindications and Allergies to Study Drugs

36. On the basis of your history and physical examination, does this participant have any contraindication or allergy to chlorthalidone? Yes ☐ 1 No ☐ 2 

37. On the basis of your history and physical examination, does this participant have any contraindication or allergy to atenolol? Yes ☐ 1 No ☐ 2

38. On the basis of your history and physical examination, does this participant have any contraindication or allergy to reserpine? Yes ☐ 1 No ☐ 2

39. Are both Question 37 and Question 38 answered "Yes?" Yes ☐ 1 No ☐ 2 

Other Exclusion Criteria

40. Alcohol--on the basis of your history and physical examination, do you believe the participant currently drinks 6 or more drinks/day, or that alcoholism has been a problem in the past year, or alcoholic liver disease is currently present? Yes ☐ 1 No ☐ 2 

41. Dementia--on the basis of your history and physical examination, do you believe the participant definitely has any form of dementia? Yes ☐ 1 No ☐ 2 

42. On the basis of your history and physical examination is there any life-threatening disease, or any other reason which might seriously impair the individual's participation in the SHEP over the next five years? Yes ☐ 1 No ☐ 2 

    Specify: _____

Falls and Fractures

43. Do you believe that the participant has ever had a fracture of:

    a. Hip? Yes ☐ 1 No ☐ 2

    b. Spine? Yes ☐ 1 No ☐ 2

    c. Forearm? Yes ☐ 1 No ☐ 2

44. Do you believe that the participant has had a problem with frequent falls? Yes ☐ 1 No ☐ 2

Result

Items 23 through 44 that are marked with ⊛ are exclusions if answer is "Yes," or, in the case of CHF (Question 27), answered "Yes, not controlled," or, in the case of TIA (Question 34), answered "Yes, based on history and presence of carotid bruit" or "Yes, based on history of two or more TIAs in same location." Please review these criteria very carefully before answering Item 45.

45. Based on the information contained in this review:

- ☐ 1 The participant remains eligible for the SHEP.
- ☐ 2 The participant is not eligible for the SHEP.

46. Clinician's signature: _____ ☐ Code

Ineligible persons should proceed to scheduling area for termination of their participation in the SHEP screening process. Baseline Visit 2 may then be scheduled for eligible persons.

PLEASE REVIEW PAGE 1

2.4 Baseline Visit 2

2.4.1 General Description

At this visit, the eligibility determination is completed, including blood pressure, administration of the SHORTCARE, and a detailed side effects history. Participants who are eligible and agree to participate in the study will receive a complete orientation using the booklet provided for that purpose (see Appendix B), sign the Informed Consent, and will be randomized by telephone contact with the Coordinating Center. Randomized participants will then receive the remainder of the behavioral evaluation, have a fasting blood specimen drawn, and will be given their SHEP medications.

2.4.2 Blood Pressure Eligibility Criteria

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. For participants who are eligible, the average of the blood pressures at the first and second Baseline Visits is designated the "baseline blood pressure." Those participants with SBP of 220 mm Hg or greater and DBP less than 95 mm Hg will be allowed one more clinic visit within one week to qualify. (This is not mandatory.) In this case, a new Baseline Visit 2 form (SH07) is used for the repeat visit, although the first three pages of the original SH07 should be kept in the participant's file. (The original SH07 should not be sent to the Coordinating Center.)

2.4.3 Other Exclusion Criteria

Other than by blood pressure, a person may be excluded from the SHEP at this visit based on any one of the following:

a) a dementia score of 4 or more on the SHORTCARE and the SHEP clinician's judgment that the person is not able to participate in the study

b) other condition that the clinician feels would interfere with participation in the SHEP.

2.4.4 Participant Orientation

Before an eligible participant may sign the informed consent for study participation and be randomized, he or she must understand the purpose of the SHEP, have some concept of the study design, be aware of what is expected of a study participant, and what may be expected of the SHEP clinic. A booklet has been provided for this purpose, and includes information on the above, space for the participant's name and address, the SHEP clinic address, and some general information on diet, smoking, exercise and weight loss. (See Appendix B.) The informed consent form should be read, but not signed, prior to this orientation.

The following specific points should be included in the orientation to the SHEP:

a) A reminder that the participant has ISH and a simple definition of what it is.

b) A statement that the purpose of the SHEP is to determine whether control of ISH will reduce the incidence of stroke.

c) A statement that the participant will be part of a cooperative study, funded by the NIH, that will involve many participants throughout the country; that the participant can make a valuable contribution to the study through his/her cooperation.

d) A statement that the participant will receive a continuous review of his/her medication condition while in the study that includes medical examinations, ECGs and laboratory tests, all at the expense of the study. However, comprehensive medical care is not provided and is the responsibility of the private health care provider.

e) A brief outline of what is required for participation, that is, the visits for monitoring the treatment plan (initially at monthly intervals), etc. The fact that this study may last until 1991 should be emphasized and the participant psychologically prepared.

f) A statement to the effect that the study drugs were chosen for their ability to lower blood pressure safely and that several fully established antihypertensive drugs will be used. The participant should also be told that he/she may be on placebo therapy. The possibility of placebo therapy should be explicitly noted, with a clear statement that it is not known whether drugs or placebo will have a better effect on health.

g) A statement that the participant will not be told which of the drugs is to be received, but that should the information be needed in an emergency it will be immediately available through the SHEP clinical center.

h) A statement that it is possible the drugs included in the study do have certain side effects. It should be stressed that these side effects are thought to be relatively minor, especially if it can be shown that one or more of the drugs is effective in increasing the health of a person who has ISH. The participant should be encouraged to report <u>any</u> unusual side effect experienced to the clinic. The particular problem can then be discussed individually in detail. If specific questions are asked in the orientation, replies should be frank. The extent of this discussion will probably vary in each orientation.

i) A statement that a behavioral evaluation component is included in the study. A thorough explanation of this procedure, and the reason for including it, must be given. Explain in simple terms, not in psychological jargon.

j) A statement that the full cooperation of the participant is essential. If the participant agrees to take part and then drops out at a later date, the study suffers and the efforts of the other participants may be wasted. Information should be given that every effort will be made to find the participant if he/she drops out without notification. The issue of motivation based on an understanding of what the study can do for the participant and the contribution to society through the study should be discussed. Additionally, the participant should be reassšured that dropping out of the study will not jeopardize his/her care.

k) A statement that an Identification Card will be furnished to each member of the study.

l) It is essential that the participant be given every opportunity to ask questions throughout the orientation. After the orientation session is completed and the investigator is certain that the participant has a thorough understanding of what is involved in being a participant, the investigator should ask the person if he/she is interested in being a participant. If the person agrees to participate in the study a consent form must then be signed.

After the orientation is completed, and the participant has had all questions answered to his or her satisfaction, the informed consent may be signed and witnessed.

2.4.5 Randomization

Randomization will be carried out by telephone contact with the Coordinating Center. Several items of information will be required prior to contacting the Coordinating Center; some may be copied from the SH06 prior to the visit. These include:

a) SHEP ID and acrostic

b) Birthdate

c) Blood pressure from Initial Contact (averages of second and third SBP and DBP readings)

d) Antihypertensive medication status at Initial Contact

e) If applicable, blood pressure from the last DEV (averages of second and third SBP and DBP readings)

f) Baseline Visit 1 SBP and DBP (average of two corrected seated readings)

g) Clinician's eligibility judgment (SH06, Item 45)

h) Serum creatinine, if available

i) Baseline Visit 2 SBP and DBP (average of two corrected seated readings)

j) Baseline SBP and DBP (average of Baseline Visit 1 and Baseline Visit 2 pressures)

k) Any other exclusions (yes/no)

l) Has the informed consent for randomization been signed (yes/no)

m) The two-digit ID code of the clinical center staff person calling for randomization

The Coordinating Center person responsible for the randomization will review these items, verify the baseline SBP and DBP, verify goal SBP, and give the Step 1, Dose 1 bottle number over the telephone. A randomization report will be generated at the Coordinating Center, which verifies the baseline and goal blood pressures, contains all five bottle numbers for the participant, and includes a target visit schedule for the two-month and all quarterly visits.

2.4.6 Form SH07

SHEP ID, acrostic, and date (Items 1-3):

The SHEP ID number and acrostic (assigned at the Baseline Visit 1) should be copied onto Items 1 and 2 of the SH07, checking carefully to make sure that they are copied correctly from the SH06. This is very important, as these two identifiers are used to locate and match records belonging to a given participant. The participant's name may be entered at the top of the form for ease of reference by interviewers and clinicians, but this is not required. Item 3 is today's date, the date of the clinic visit.

Repeat BV2s:

It should be noted in Item 4 whether or not this is a repeat Baseline Visit 2. A repeat BV2 is allowed if, and only if at the first BV2, the average of the two corrected seated SBPs is 220 or more mm Hg, with DBP <95 mm Hg. If this visit is a repeat BV2, the average of the two corrected readings for SBP and DBP at the original BV2

should be filled in, in Items 4b and 4c. For participants who have been rescreened and assigned a new SHEP ID, their original BV2 (under the old ID) does not count when answering Item 4a.

Informed consent:

Prior to initiating any procedures at this visit, the informed consent for this visit must be obtained, if not already collected.

The remainder of page 1 (Items 5a-5l) should be reviewed at the completion of this visit, before the participant leaves the clinic.

Pulse and blood pressure (Item 6):

The pulse and blood pressure (Items 6a and 6b) should be taken by a trained observer using procedures as per the SHEP Blood Pressure Manual. Participants will remain eligible if the average SBP is at least 150 and less than 220 mm Hg, and DBP less than 95 mm Hg (see below). The two standing pulse and blood pressure measurements do not need to be completed for participants who do not remain eligible (these items should be filled in with 9s); in this case, 6c may be skipped (left blank). If the participant volunteers any symptoms on standing (for the measurement of standing blood pressure), up to the time the standing pressures are completed, this should be recorded in Item 6c.

At this point, several eligibility criteria are applied (Item 6d(1) and 6d(2)):

The blood pressure observer should determine into which category the average of the second and third blood pressure readings at this visit falls:

SBP <150 or ≧220 mm Hg, or DBP ≧95 mm Hg	→	Ineligible
150 ≦SBP <220 mm Hg, and DBP <95 mm Hg	→	Eligible.

This result should be indicated in 6d(1).

A repeat BV2 is allowed (not mandatory) if, and only if at the first BV2, the average of the two corrected seated SBPs is 220 or more mm Hg, with DBP <95 mm Hg. A repeat BV2 should be scheduled within one week. Those with SBP 220 or more mm Hg, but DBP 95 or more mm Hg may not be rescheduled for a second BV2.

Participants who are not eligible should receive an explanation of why they are not eligible, should be provided with a written record of their blood pressure, thanked and excused.

For those remaining eligible, the Baseline blood pressure (BL SBP, BL DBP) will then be calculated as instructed on the form. (The Baseline Visit 1 blood pressure should be carefully copied from the SH06 prior to this visit.) If the result is not a whole number (e.g., 159.5), it should be rounded down to the next lower mm Hg (e.g., 159 mm Hg). The result will fall into one of the following categories and should be indicated in Item 6d(2):

SBP <160 or ≧220 mm Hg, or DBP ≧90 mm Hg	→	Ineligible
150 ≦SBP <220 mm Hg, and DBP <90 mm Hg	→	Eligible.

As described above, participants who are not blood pressure eligible should receive an explanation of why they are not eligible, should be provided with a written record of their blood pressure, thanked and excused.

Upon completion of this blood pressure eligibility determination, the observer should sign the form and enter their two-digit personnel code in Item 6e.

Participants who remain eligible should have blood samples drawn at this time for central and local baseline analyses, according to Appendix D of this manual. If the participant has not fasted for 12 hours, the drawing of blood may be rescheduled for the following one to two days, or, if the fast is close to 12 hours, the participant may continue with BV2 procesures. If a fasting sample is impossible, a non-fasting sample may be drawn. It should be indicated on the form whether the sample was drawn fasting or non-fasting, and the date drawn. If the participant refuses the blood sample, "Blood sample refused" should be checked. Several local analyses are required (hemoglobin, hematocrit and white blood cell count); blood should be drawn for this at the same time as blood is drawn for central analysis, even though these are not required to be fasting determinations.

SHORT/CES-D (Item 8):

The SHORTCARE and CES-D (SH30) should then be administered by a trained interviewer, as described in the SHEP Behavioral Evaluation Manual. If the Total Score #1 (the criterion score for dementia) is 4 or more, the participant should be referred back to the SHEP clinician for further judgment regarding the dementia exclusion criterion. The result should be recorded in Item 8 (only one box should be checked):

Participant did not reach criterion score for dementia	→	Eligible
Participant reached criterion score for dementia, but remains eligible in the judgment of the SHEP clinician	→	Eligible
Participant reached criterion score for dementia, and should be excluded in the judgment of the SHEP clinician	→	Ineligible

Participants who are not eligible should receive an explanation of why they are not eligible, should be provided with a written record of their blood pressure, thanked and excused.

Interval History (Items 9-11):

An interval history is then taken. All questions refer to the time since Baseline Visit 1. Items 9, 10 and 11 do not have to asked using the exact wording as specified, but the interviewer should use comfortable phraseology, using words that the participant is able to understand. Any "Yes" answer requires further probing. If the participant does not understand the question as phrased, it should be explained and/or re-phrased.

If the participant responds "No" to Item 9a ("Have you felt unwell . . . ,") then Item 9b should be skipped, as directed on the form. If the response is "Yes," then the interviewer should probe for details with a statement like, "Can you tell me about how you felt?" or, "Can you tell me what was wrong?" The interviewer should not suggest details in any way to the participant. Also, on a "Yes" response to Item 9a, the interviewer should continue to Item 9b, which asks if the problem is different from the way things were at the previous clinic visit.

Item 10 asks about visits that the participant has had with his/her own physician or usual source of care. If the participant has seen a doctor for any reason, the interviewer should probe for details as described for Item 9a.

Item 11 asks about hospitalizations since the last clinic visit. If the participant responds "No," the interviewer should skip to the next section. A "Yes" response to Item 11 requires further probing; for each hospitalization, the following information should be obtained:

- Hospital name
- Date of admission
- Number of days
- Reason--a diagnosis is requested, but if the participant does not know the actual diagnosis, the symptom(s) that led to the hospitalization are acceptable.

Emergency room visits and outpatient surgeries should not be counted or listed. If more than three hospitalizations are mentioned, list the rest on a blank sheet of paper. (This extra sheet must be copied to send to the Coordinating Center with the hardcopy form.

Specific queries (Items 12-43):

Items 12-43 ask about specific problems that the participant may be having. These must be asked using the specified phraseology. Characteristics of positive responses should be recorded. These include whether or not the problem is new since the last visit, the frequency of the problem, and the severity, all of which should be in the judgment of the participant. Selected problems require a short, directed physical examination as specified in the right-hand column.

If there are no positive responses in Items 9-43, the participant remains eligible. This should be indicated in Item 44. If there are any positive responses, the SHEP clinician may judge the condition or problem to be severe enough to exclude the participant (Item 45a); comments may be added in Item 45b and are required if the participant is excluded at this point. Participants to be excluded should receive an explanation of why they are not eligible, should be provided with a written record of their blood pressure, thanked and excused.

Orientation and randomization:

Participant orientation and informed consent and randomization should then be accomplished as previously described. The result (complete or incomplete) should be indicated in Item 46; if completed, be sure to write in the Step 1, Dose 1 bottle number, verify the participant's baseline blood pressure and goal blood pressure. The person completing the randomization should sign and enter their two-digit ID code in Item 47, and a clinic physician should review the randomization, sign and enter their ID code in Item 48.

Baseline Compliance (Items 49-55):

After randomization has been completed, pill-taking instructions should be reinforced using Items 49-55 (Baseline Compliance), with an appropriate introduction to assure the participant that this is not a "quiz," but we want to make sure that he or she understands how to take the medicines (Step 1, Dose 1) that will be given. If the participant is not sure how and when to take the medication, reinforce the instructions.

Blood Samples, if not already done:

If not already done, the blood samples should then be drawn as specified in Appendix D of this manual, and documented in Item 7. If the blood draw is rescheduled for another day, the SHEP medications should be temporarily withheld and the SH07 should be held (i.e., not entered into the data system and not sent to the Coordinating Center) until the blood is drawn and Item 7 completed.

Behavioral Evaluation:

The remainder of the behavioral evaluation should then be completed as described in the SHEP Behavioral Manual. As for the blood sample, if the behavioral evaluation must be rescheduled for another day, the SHEP medications should be temporarily withheld and the SH07 should be held until these procedures are either complete or refused.

Review of visit (Items 5a-5l):

When all of the procedures have been completed, but before the participant leaves the clinic, the front page of the SH07 should be reviewed and completed. The SHEP ID and acrostic should be checked, and the forms filled out at this visit should be checked for completeness, and legibility. The participant's eligibility status (Item 5a) should be checked. For participants who are not blood pressure eligible, skip to Item 5k (Comments). For blood-pressure eligible participants only, indicate in Item 5b whether the SHORTCARE was completed; if not, an explanation is required in 5k. If the participant was subsequently not randomized, skip to 5k. For randomized participants only, indicate whether Items 5c-5f were completed. Any item required but not completed requires a comment in 5k. The goal SBP must be entered in 5q and the Step 1, Dose 1 bottle number in 5h. If the blood sample was rescheduled for another day, this visit is not considered to be complete. The SHEP medications and the SH07 form should be held (i.e., not entered and not sent to the Coordinating Center) until the blood sample is either drawn or refused, and the front of the form should be marked "Fasting blood sample drawn" or "Non-fasting blood sample drawn" or

"Blood sample refused." Similarly, if the behavioral evaluation must be rescheduled, the form and SHEP medications should be held temporarily. Item 5i requests the minimum name information that is necessary for using the HCFA (Medicare) system to track SHEP events. This includes the first six letters of the last name and the first and middle initials.

The randomized participant should then be given the SHEP Step 1, Dose 1 medication; verify that the drug bottle label has the same number on it that is listed in Item 5h. The one-month visit should then be scheduled for three to five weeks from the date of Baseline Visit 2. Provide the participant with an appointment card listing the date and time of this appointment, and a reminder to bring all of his or her SHEP medicines and other medicines to the clinic at the next visit.

2.4.7 Auxiliary Forms for Baseline Visit 2

Blood-pressure eligible participants:

SH30 - SHEP SHORTCARE Form

SH36 - SHORTCARE Scoring Sheet

Randomized participants only:

SH10 - SHEP ECG Coding Form - submit ECGS and two-minute rhythm strips (from Baseline Visit 1)

SH11 - Local Laboratory Results (use for hematology results; do not use for Central Laboratory analyses)

SH33 - Activities of Daily Life

SH35 - Behavioral Evaluation--Part II (six centers)

MetPath Request Slip

Name: _____

1. SHEP ID: [ ] - [ ] - [ ] 2. Acrostic: [ ]

3. Today's Date: [ ] Month [ ] Day [ ] Year

4. a. Is this a repeat Baseline Visit 2? Yes ☐ 1 No ☐ 2 → SKIP to 5.

Previous BV2 blood pressures (average of two corrected seated readings):

b. SBP: [ ] mm Hg c. DBP: [ ] mm Hg

PRIOR TO INITIATING PROCEDURES FOR THIS VISIT, COMPLETE THE FOLLOWING ITEMS.

☐ Consent obtained for Baseline Visit 2, if not previously collected.

COMPLETE THIS SECTION AT TERMINATION OF VISIT BEFORE PARTICIPANT LEAVES. CHECK TO BE SURE THAT THE PARTICIPANT'S ID AND ACROSTIC (ITEMS 1 AND 2) ARE CORRECT--THE ACROSTIC SHOULD BE THE SAME AS THE ACROSTIC ON THE SH06. BE SURE THAT EVERY ITEM ON EACH PAGE IS COMPLETE (IF REQUIRED) AND LEGIBLE. CHECK YELLOW COPY FOR LEGIBILITY, ALSO. ANY ITEMS OR PROCEDURES REQUIRED BUT NOT COMPLETED SHOULD BE EXPLAINED IN COMMENTS, ITEM 5k.

---

5. a. Result of this visit:

☐ 1 Participant is eligible and has been randomized.
☐ 2 Participant is eligible, but refuses to continue at any time during the visit, or refuses to be randomized (explain in Comments, Item 5k).
☐ 3 Participant is not eligible for randomization

Blood pressure-eligible participants only:	Done	Not Done
b. SHORTCARE Evaluation (SH30)	☐ 1	☐ 2
Randomized participants only:		
c. Blood sample drawn (refer to page 4)	☐ 1	☐ 2
d. Local hematology results entered on SH11, Local Laboratory Results	☐ 1	☐ 2
e. Activities of Daily Life (SH33)	☐ 1	☐ 2
f. Behavioral Evaluation--Part II (SH35) (participating centers only)	☐ 1	☐ 2

g. Goal SBP [ ] mm Hg

h. Step 1, Dose 1 bottle number [ ]

i. Other participant identification: [ ] Last Name (First six letters) [ ] FI [ ] MI

Give the participant Step 1, Dose 1 medication and SHEP identification card. Make sure that the participant understands when and how to take the medications. Make a clinic appointment for the one-month visit (three to five weeks from today's visit).

j. Appointment for one-month visit:

1 ☐ Appointment made on: [ ] Month [ ] Day [ ] Year at [ ]:[ ] Hour Min. a.m. ☐ 1 p.m. ☐ 2

2 ☐ Appointment not made; reason: _____

k. Comments: _____

_____

l. Signature of person reviewing this page: _____ [ ] Code

PULSE AND BLOOD PRESSURE--If any pulse or blood pressure is not obtained, enter all 9s in the appropriate spaces.

6. a. Pulse: Beats in 30 seconds _____ x 2 = ☐☐☐ beats per minute.

b. Cuff Size:

1 ☐ Regular
2 ☐ Large arm
3 ☐ Thigh
4 ☐ Pediatric

Pulse Obliteration Pressure:

Observed Value: ☐☐☐
Subtract Zero Level: - ☐☐☐
Corrected Value: ☐☐☐
Add Maximum Zero Level Plus 20: + ☐☐☐
Peak Inflation Level: ☐☐☐

Seated Readings:

	Systolic	Diastolic
First	☐☐☐	☐☐☐
Zero level	☐☐☐	☐☐☐
Corrected	☐☐☐	☐☐☐
+ Second	☐☐☐	☐☐☐
+ Zero level	☐☐☐	☐☐☐
+ Corrected	☐☐☐	☐☐☐
Sum of two corrected readings	☐☐☐	☐☐☐
Average of two corrected readings	☐☐☐	☐☐☐

Standing Readings:

One minute

Pulse: Beats in 15 seconds _____
x 4 = ☐☐☐ beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	☐☐☐	☐☐☐
Zero	☐☐☐	☐☐☐
Corrected	☐☐☐	☐☐☐

Three minutes

Pulse: Beats in 15 seconds _____
x 4 = ☐☐☐ beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	☐☐☐	☐☐☐
Zero	☐☐☐	☐☐☐
Corrected	☐☐☐	☐☐☐

(If standing blood pressure not done, skip to 6d.)

c. Did the participant volunteer any symptoms on standing? Yes ☐ 1 No ☐ 2 ↓

(1) Dizziness Yes ☐ 1 No ☐ 2
(2) Other (specify)? Yes ☐ 1 No ☐ 2

_____

SKIP to 6d.

d. Eligibility check (use average of two corrected seated readings):

(1) Blood Pressure at this visit:

☐ 1 SBP <150 or ≧220 mm Hg, or DBP ≧95 mm Hg → Ineligible

Note: Participants with SBP ≧220 mm Hg and DBP < 95 mm Hg may return in one week for a repeat blood pressure measurement

☐ 2 SBP 150-219 mm Hg, and DBP <95 mm Hg → Continue

	Systolic	Diastolic
Baseline Visit 1 Average R-Ż Blood Pressure	☐☐☐	☐☐☐
Average R-Ż Blood Pressure from Section 6b:	+ ☐☐☐	+ ☐☐☐
Sum	☐☐☐	☐☐☐
Baseline = Sum ÷ 2	☐☐☐	☐☐☐

(2) Baseline Blood Pressure (Average of BL1 and BL2):

☐ 1 BL SBP <160 or ≧220 mm Hg, or BL DBP ≧90 mm Hg → Ineligible

☐ 2 BL SBP 160-219 mm Hg, and BL DBP <90 mm Hg → Continue

Ineligible participants should proceed to scheduling area for termination of their participation in the SHEP screening process. Only eligible participants should proceed with the remaining items in Baseline Visit 2.

e. Observer's signature: _____ ☐ Code

BLOOD SAMPLE

7. Type of sample:

1 ☐ Fasting blood sample drawn

2 ☐ Non-fasting blood sample drawn → Date drawn: ☐☐ Month ☐☐ Day ☐☐ Year

3 ☐ Blood sample not drawn

SHORTCARE/CES-D (SH30, SH36)

8. Result of SHORTCARE evaluation, dementia component:

☐ 1 Participant did not reach criterion score for dementia → Eligible

Participant reached criterion score for dementia, and:

☐ 2 Remains eligible, in the judgment of the SHEP clinician → Eligible

☐ 3 Should be excluded, in the judgment of the SHEP clinician → Ineligible

Ineligible participants should proceed to scheduling area for termination of their participation in the SHEP screening process. Only eligible participants should proceed with the remaining items in Baseline Visit 2.

INTERVAL HISTORY--Items in this section may be rephrased. Use phraseology that you are comfortable with.

9. a. Have you felt unwell in any way since your last clinic visit; has anything been bothering you? 1 ☐ Yes 2 ☐ No → Go to 10.

(Specify): _____

b. Are any of these problems different from the way things were at your last clinic visit? 1 ☐ Yes 2 ☐ No

10. Since your last visit, have you seen a doctor for any reason? 1 ☐ Yes 2 ☐ No

(Specify): _____

11. Since your last visit, have you been in the hospital for any reason? 1 ☐ Yes 2 ☐ No → Go to 12.

How many times? ☐

When? (Start with the first one after your last visit.)

(If more than 3 hospitalizations, list rest on blank sheet of paper.)

	Hospitalization #1	Hospitalization #2	Hospitalization #3
Hospital name	_____	_____	_____
Date of admission	☐☐ Month ☐☐ Day ☐☐ Year	☐☐ Month ☐☐ Day ☐☐ Year	☐☐ Month ☐☐ Day ☐☐ Year
Number of days	☐	☐	☐
Reason	_____	_____	_____

SPECIFIC QUERIES--Elicit symptoms by asking about each of the items listed on the next pages using the specified phraseology. Record characteristics of positive responses.

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	
12. Unusual coldness or numbness of the hands or feet?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
13. Unusual skin rash or bruising?	Yes ☐ 1 → No ☐ 2	☐	☐	☐ → (e)	Is an acute skin rash present on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
14. Any feelings of unsteadiness or imbalance?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
15. Faintness or light headedness when you stand up quickly?	Yes ☐ 1 → No ☐ 2	☐	☐	☐ → (e)	Is there an observable postural drop in blood pressure? Yes ☐ 1 No ☐ 2
16. Loss of consciousness or passing out	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
17. Falls?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
18. Fractures?	Yes ☐ 1 → No ☐ 2	☐	☐	☐ → (e)	Hip? Yes ☐ 1 No ☐ 2
				(f)	Spine? Yes ☐ 1 No ☐ 2
				(g)	Forearm? Yes ☐ 1 No ☐ 2
19. Unusual pain in any joint?	Yes ☐ 1 → No ☐ 2	☐	☐	☐ → (e)	Are there physical signs of acute arthritis? Yes ☐ 1 Possibly ☐ 2 No ☐ 3

Since your last visit, have you had:	(a)	(b) New since last visit? 1=Yes 2=No	(c) Frequency: 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	(d) Severity: 1=Not troublesome 2=Troublesome 3=Intolerable
20. Muscle weakness or cramping?	Yes □ 1 → No □ 2			
21. Excessive thirst?	Yes □ 1 → No □ 2			
22. Loss of appetite?	Yes □ 1 → No □ 2			
23. Nausea or vomiting?	Yes □ 1 → No □ 2			
24. Unusual indigestion?	Yes □ 1 → No □ 2			
25. Change in bowel habits?	Yes □ 1 → No □ 2			
26. Tarry black stools or red blood in the stools?	Yes □ 1 → No □ 2			
27. Heart beating unusually fast or skipping beats?	Yes □ 1 → No □ 2			
28. Heart beating unusually slow?	Yes □ 1 → No □ 2			
29. Episodes of chest pain or heaviness in the chest?	Yes □ 1 → No □ 2			
30. Headaches so bad you had to stop what you were doing?	Yes □ 1 → No □ 2			
31. Stuffy nose?	Yes □ 1 → No □ 2			

→ (e) Is an arrhythmia present on physical exam?
Yes □ 1
Possibly □ 2
No □ 3

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	
32. Unusual shortness of breath or wheezing?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	(e) Is there evidence for bronchospasm on auscultation of the chest? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
33. Unusual tiredness or loss of pep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	(e) Is there evidence of CHF on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
34. Swelling of the ankles?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
35. Feeling so depressed (sad sad or blue) that it interfered with your work, recreation or sleep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
36. Any trouble with your memory or concentration?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
37. Nightmares?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	
38. Any changes in your sexual activity?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	(e) Loss of interest? Yes ☐ 1 No ☐ 2 (f) Decline in frequency? Yes ☐ 1 No ☐ 2 (g) Loss of enjoyment? Yes ☐ 1 No ☐ 2 (h) Functional impairment? Yes ☐ 1 No ☐ 2

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	
39. Trouble going to sleep, or waking early and having trouble getting back to sleep?	Yes □ 1 → No □ 2	☐	☐	☐	
40. Waking up in the night more frequently to urinate?	Yes □ 1 → No □ 2	☐	☐	☐	
41. More worry or anxiety than usual?	Yes □ 1 → No □ 2	☐	☐	☐	
42. Weakness or numbness on one side, or unexpected difficulties talking or thinking?	Yes □ 1 → No □ 2	☐	☐	☐ → (e)	Is there evidence of a stroke on physical exam? Yes □ 1 Possibly □ 2 No □ 3
43. Other relevant symptoms: Specify: _____ _____ _____	Yes □ 1 → No □ 2	☐	☐	☐ → (e)	Are there other relevant signs on physical exam? Yes □ 1 Possibly □ 2 No □ 3 Specify: _____ _____

44. Are there any positive responses in Items 9 through 43?

□ 1 Yes □ 2 No → GO TO NEXT SECTION - ORIENTATION AND INFORMED CONSENT.

45. a. In the clinician's judgment, should the participant be excluded from the SHEP due to any of these conditions? Yes □ 1 No □ 2

b. Comments: _____

_____

_____

Participants to be excluded should proceed to the scheduling area for termination of their participation in the SHEP. Only eligible participants should proceed with the remaining items in Baseline Visit 2.

ORIENTATION AND INFORMED CONSENT CHECKLIST--Do not proceed with randomization until all of these have been completed.

□ Participant orientation completed.
□ Consent form signed for randomization and participation in the trial.

RANDOMIZATION

• The following items of data should be available prior to calling the Coordinating Center:

SHEP ID _____ and Acrostic _____

Birthdate: _____

On BP meds at Initial Contact? □ Yes □ No

Initial Contact Visit average of BP readings 2 and 3: SBP _____ DBP _____

If applicable, average of BP readings 2 and 3 at last DEV: SBP _____ DBP _____

Baseline Visit 1 BP readings (average of two seated corrected readings): SBP _____ DBP _____

Judged to be eligible by SHEP clinician at Baseline Visit 1 review, according to SHEP criteria (SH06, Item 45)? □ Yes □ No

Is a serum creatinine measurement available? □ Yes □ No

↓

_____ mg/dl

Baseline Visit 2 BP (average of two corrected readings): SBP _____ DBP _____

Baseline BP (average of BV1 and BV2): SBP _____ DBP _____

Other exclusions (Items 7 and 45 this form)? □ Yes □ No

Has the informed consent for randomization been signed? □ Yes □ No

Your Clinical Center personnel code: _____

- Use the above information to verify eligibility and baseline blood pressure, as queried by Coordinating Center personnel.

- Verify Baseline SBP _____ DBP _____

- Goal SBP: _____ mm Hg
(For participants with baseline SBP 160-179 mm Hg, goal SBP is a 21 mm Hg drop; participants with a baseline SBP of 180 mm Hg or more will have a goal SBP of 159.)

46. Result:

□ 1 Randomization complete: Step 1, Dose 1 drug bottle number _____

□ 2 Randomization incomplete: (describe)

_____

_____

47. Signature of person completing this section: _____ [ ] Code

48. Signature of clinic physician: _____ [ ] Code

BASELINE COMPLIANCE--Tell the participant, "We would like to make sure that you understand how to take your medicine that we will give you."

---

49. What have you been told you should do when you miss taking your SHEP medicine? (Don't provide the specific categories: if only one response given, ask, "anything else?")

		Mentioned	Not Mentioned
a.	Wait and double up the next dose	□ 1	□ 2
b.	Do nothing and take usual dose next time	□ 1	□ 2
c.	Report missed dose(s) at next clinic visit	□ 1	□ 2
d.	Call SHEP clinic	□ 1	□ 2
e.	Record missed dose(s)	□ 1	□ 2
f.	Take it later	□ 1	□ 2
g.	Nothing	□ 1	□ 2
h.	Other (Specify _____)	□ 1	□ 2

50. How many times per day should you take your pills that you were given today?

One time per day □ 1
Other (specify): □ 2

_____

51. How many pills should you take each time?

One □ 1
Two □ 2
Other (specify): □ 3

_____

52. When should you take these pills?

Morning when getting up □ 1
Other (specify): □ 2

_____

53. a. Will you need to do anything to help you to remember to take the SHEP medicine(s)? Yes □ 1 No □ 2 Maybe □ 3

↓

Skip to 54.

b. What will you do? _____

_____

54. a. Will there be anyone who helps you to remember to take your SHEP medicine(s)? Yes □ 1 No □ 2 Maybe □ 3

↓

Skip to 55.

b. Who is that person?

Friend □ 1
Relative □ 2
Neighbor □ 3
Other (Specify): □ 4

_____

c. Does this person live with you? Yes □ 1 No □ 2

55. People have different reasons for taking part in a study like this. We'd like to find out why you joined the SHEP and how important these reasons are to you.

		Not Important	Important	Very Important
a.	Improve my health	□ 1	□ 2	□ 3
b.	Free medical care	□ 1	□ 2	□ 3
c.	Contribute to science	□ 1	□ 2	□ 3
d.	Improve health of others	□ 1	□ 2	□ 3
e.	Some place to go	□ 1	□ 2	□ 3
f.	Someone to talk with	□ 1	□ 2	□ 3
g.	Other Reasons (Please list)	□ 1	□ 2	□ 3

_____

_____

BEHAVIORAL EVALUATIONS

The participant should now be administered the Activities of Daily Life (SH33) and, in participating centers, the Behavioral Evaluation--Part II (SH35).

PLEASE REVIEW PAGE 1

2.5 Post-Randomization Visits (Not Annual)

2.5.1 One-Month, Two-Month, and Quarterly Visits, and Other Visits Required by the SHEP Protocol

All participants are required to be seen at one month, two months, and quarterly after the date of randomization. (Annual visits are described in Section 2.6.) Participants may also be scheduled for other required protocol visits based on their blood pressure status. These visits may take place in the participant's home, or on the telephone, if a clinic visit is impossible (specific directions for telephone and home visits are in Section 2.5.3 and Section F.8).

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, transient ischemic attack 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. Following a medication change, and if specific 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 semiannual visits, and at other quarterly visits as required. The Social Network and Behavioral Evaluation--Part II are required at specific visits as described in Section 2.5.3. Additional procedures will include a serum potassium determination (central) at the next visit after starting or increasing a Step 1 drug. Other local lab work is at the discretion of the SHEP clinician.

2.5.2 Interim Visits

Any visit that is not required by the SHEP protocol is an interim visit. These visits may be scheduled at the SHEP clinic for various reasons:

(a) blood pressure check not required by the SHEP protocol

(b) local re-check of serum potassium, if symptomatic of hypokalemia at the prior visit, and central serum potassium is less than 3.2 meq/l

(c) possible side effects

(d) other miscellaneous reasons

Interim visits will usually be requested by the participant but may also be scheduled at the option of the SHEP clinic.

The following procedures are required at every interim visit:

- pulse, blood pressure and weight (except for potassium re-check as described above)
- assessment of general well-being
- protocol review, blood pressure review and medication decision

The detailed side effects questionnaire is required if the interim visit was scheduled due to possible side effects or on specific positive responses in the general well-being section.

The compliance evaluation, SHORTCARE/CES-D, Social Network Questionnaire and the Behavioral Evaluation--Part II are never required at interim visits.

If a serum potassium from the Central Lab is less than 3.2 meq/l, a local serum potassium is required within one week of notification. (If a central potassium is at least 3.2 meq/l but less than 3.5 meq/l, the

potassium is re-checked at the next required visit.) An interim visit is required for local recheck of serum potassium if both of the following conditions are met at the prior visit:

1. central serum potassium less than 3.2 meq/l; and,
2. participant is symptomatic of hypokalemia (i.e., heart beating fast or skipping beats, muscle weakness or cramping, fatigue, constipation, frequent urination).

If the participant is not symptomatic but the central serum potassium is less than 3.2 meq/l, then the participant may be recalled to the Clinic for local blood work, but only the laboratory form (SH11) is required (use the sequence number of the previous SHEP Clinic visit).

Other local lab work is at the SHEP Clinician's discretion.

2.5.3 Form SH08 - SHEP Clinic Visit Documentation

This form is to be used for all SHEP clinic visits except annual visits.

Prior to the visit, several items of information should be entered onto this form:

SHEP ID and Acrostic (Items 1 and 2): Check to make sure that they are legible and correct. The acrostic should always match what is on the participant's SH06 (Baseline Visit 1 form).

Item 3 (Today's date) is the date of the visit, and not the date the form was prepared (if prepared ahead of time).

The sequence number of the contact (Item 4) helps the Coordinating Center and the Clinics to match the main clinic visit form with auxiliary study forms such as the SH11 (Local Laboratory Results). The first

visit after randomization is sequence number 03, with each subsequent clinic visit being assigned a consecutive sequence number, regardless of reason. (Baseline Visit 1 is sequence 01, and Baseline Visit 2 is sequence 02.)

Type and reason for visit (Items 5-7), along with a few other items, dictate the procedures that are necessary at each visit. The lower and upper date windows between which the quarterly visits should be scheduled are generated at randomization by the Coordinating Center. (This list of target windows should be kept in the front of the participant's folder for ease of reference.) Other "required" visits are quarterly visits, plus those usually scheduled on the basis of the participant's blood pressure status as required by the treatment protocol. If the visit is a quarterly or other required visit, the appropriate box should be checked in Item 5; do not fill out Items 6 or 7.

As described above, all other visits are interim visits; in these cases, box 3 should be checked in Item 5, and Items 6 and 7 are required. If the participant initiated the scheduling of the visit, Item 6 box 2 ("participant's request") should be checked; if the visit was scheduled at the SHEP clinic option, "by SHEP Clinic" should be checked. There may be multiple reasons for scheduling a particular interim visit, and all applicable reasons should be checked in Items 7a-7d; if the visit was scheduled for any reason other than a blood pressure check, lab work or side effects, Item 7d must be checked and the reason specified.

Place of visit (Item 8): Ordinarily, visits will take place in the SHEP clinic. If circumstances prohibit a scheduled visit in the clinic, the visit may take place in the hospital or at home (e.g., if the participant becomes disabled) or by telephone (e.g., if the participant refuses to come to the clinic but is willing to be followed by telephone). The place of visit must be indicated by an "X" in the appropriate box; any visit at which the participant is physically seen outside the SHEP Clinic (e.g., at the participant's home, other home or in the hospital or a nursing home) should be counted as a "home" visit.

Medications at last visit (Items 9a and 9b) - These two items allow decisions to be made on which procedures need to be carried out at this visit. Refer to the participant's records in determining whether or not SHEP blinded medications were started or increased at the last visit.

Procedures required at this visit (Items 10a-10k):

The chart on page 1 of the SH08 should be reviewed carefully to determine which procedures should be carried out at this visit. Guidelines as to when each procedure is required are given in the "Comments" column. It will be most convenient to review this prior to the visit and collect, in order, those forms that are required or that may be needed at the clinician's discretion. Items required should be checked in the "Required this visit?" section. These procedures should be carried out in the order specified. Please note that the SH08 (documentation, pulse, BP, weight, the General Well-being, and the Medication and Scheduling Decision sections are always required and are contained on the SH08. Procedures specific to any auxiliary forms (SH11, SH40, SH42, SH30, SH33, SH34, and SH35) are described either in Chapter 9 of this manual (Auxiliary Study Forms) or in the SHEP Behavioral Evaluation Manual.

Pulse, blood pressure and weight (Items 15a-15e):

These items are required, except at telephone visits. For telephone visits the cuff size and Item 15c may be left blank; fill the other items with 9s.

The pulse and blood pressure procedures should be carried out by a certified SHEP blood pressure observer, as described in the SHEP Blood Pressure Manual. If any blood pressure or pulse is not obtained, 9s should be entered onto the form in the appropriate boxes. If the standing blood pressures are not obtained for any reason, then Item 15c (symptoms on standing) may be left blank.

If a visit must be completed in two sessions, the blood pressure and pulse may be done on both days at the Clinic discretion. However, the official blood pressure and pulse for that visit are the data from the first session.

The participant's weight is not required for telephone or home visits, but must be done for visits in the clinic. The weight in pounds should be obtained as described in Appendix E of this manual.

The person completing this section should always sign and enter their two-digit personnel code in Item 15e.

Compliance evaluation (SH40) :

If any SHEP medication was started or increased at the last required visit (or at the last interim visit), or if the visit is a semi-annual visit, the compliance evaluation is required. However, this should not be administered if SHEP medications were not prescribed at the last clinic visit. Specific directions for the compliance evaluation may be found in Section 9.16 and in Chapter 6 of this manual.

General Well-Being (Items 16-28):

Questions in this section are to be asked at every visit, regardless of type and reason and place of visit. These items constitute a general interval history and are for ascertaining both possible side effects and SHEP endpoints.

If the participant responds "No" to Item 16 (Have you felt unwell . . .), then Item 17 should be skipped as directed on the form. If the response is "Yes," then the interviewer should prompt for details with a statement like, "Can you tell me about how you felt?" or, "Can you tell me what was wrong?" The interviewer should not suggest details in any way to the participant. Also, on a "Yes" response to Item 16, the interviewer should continue to Item 17, which asks if the problem is different from the way things were at the previous clinic visit.

Item 18 asks about visits that the participant has had with his/her own physician or usual source of care. This may be confusing for clinics providing primary care to their SHEP participants. A response to this question should not include official SHEP treatment visits (i.e., visits scheduled for a reason provided for in the protocol, such as required visits, or any SHEP interim visits scheduled for any reason). If the participant has seen a doctor for non-SHEP reasons, the interviewer should probe for details as described for Item 16.

Item 19 asks about hospitalizations since the last clinic visit. If the participant responds "No," the interviewer should skip to Item 20. A "Yes" response to Item 19 requires further probing; for each hospitalization, the following information should be obtained:

- Hospital name
- Date of admission
- Number of days
- Reason--a diagnosis is requested, but if the participant does not know the diagnosis, the symptom(s) that led to the hospitalization are acceptable.

Emergency room visits and outpatient surgeries should not be counted or listed. If more than three hospitalizations are mentioned, list the rest on a blank sheet of paper. (This extra sheet must be copied to send to the Coordinating Center with the hardcopy form.)

Item 20-25 are screening questions for possible stroke and/or TIA. Item 20 asks about sudden feelings of numbness, tingling, or loss of feeling in either arm, hand, leg, foot or face. Item 21 asks about attacks of paralysis or loss of use of either arm, hand, leg or foot. Item 22 asks about sudden loss of eyesight or blurring of vision for a short period of time. Item 23 asks about sudden attacks of changes in speech, loss of speech or inability to say words. Item 24 asks about other problems, including dizziness, vertigo, loss of balance, difficulty walking, blackouts or fainting, or frequent falls. For a "Yes" response, the details regarding the number of attacks, how long they lasted, and a few other items are probed. Item 25 inquires whether the participant has been told that he/she had a stroke, since the last clinic visit.

Item 26 inquires about non-SHEP medication changes since the last clinic visit (stop, increase, decrease, start). Both prescription and non-prescription medications should be considered. Medications that are changed in any way should be specified. The participant will have been

instructed to bring all non-SHEP medications to the clinic at every visit. Whether or not this was done should be indicated in Item 27; if the participant reports that he/she is not taking any other medications, then "Not on any non-SHEP medications" should be checked.

Items 28a and 28b are for the interviewer, who should take into account all of Items 16-27 to determine if the participant has volunteered that possible side effects have occurred, or any other problem has occurred which may be related to the use of SHEP medications, not including actual blood pressure status, but including symptoms possibly due to hypokalemia or hypotension. If the participant volunteered any complaints or problems in Items 16-25, including hospitalizations and doctor visits, "Yes" should be checked in Item 28a and then 28b should also be answered. If any of the volunteered problems or complaints may, in the interviewer's judgment, be due to the SHEP medications, then "Yes" should be indicated in 28b; if not, then "No" or "Not on SHEP medications" should be checked as appropriate. If the participant did not volunteer any complaints or problems, "No" should be checked in 28a and Item 28b should be skipped (left blank).

Side Effects (SH42):

An SH42 (specific queries) is required at the first required visit after starting or increasing any SHEP medication, or if a positive response is given to Item 28b, and at interim visits for possible side effects. This form is not required under any conditions for participants who have been off of SHEP medications more than six months. Specific details of the SH42 are given in the Section 9.17 of this manual.

Possible Events:

Items 29-34 are a review of the interval history and, if administered, form SH42, for possible SHEP events. If no positive answers are given to Items 16-25 or on the SH42, this should be indicated by checking "No" in Item 29, and skipping to Item 33 (comments). If "Yes" is checked in Item 29, the interviewer should consider the list of events in Items 30a-30g and check each listed event as "Yes," "Possibly," or "No." It should be stressed that in Items 30a-g we are looking for new events that have not previously been detected (e.g., participant with permanent stroke residual effect.) If a participant has already had a TIA confirmed by the SHEP endpoint coders, new possible TIAs do not need to be submitted on a morbid event form. If "Stroke" is checked as "Yes" or "Possibly," a SHEP Neurological Evaluation for Stroke (SH27) should be carried out as soon as possible. If "Transient ischemic attack" is checked "Yes" or "Possibly," a SHEP Neurological Evaluation for TIA (SH28) should be carried out as soon as possible. The specific events listed in Item 30 are defined in Chapter 5 of this manual.

If the participant was hospitalized or seen by a physician for a stroke, acute myocardial infarction, left ventricular failure, or transient ischemic attack, the pertinent records should be obtained with the participant's permission. For other hospitalizations, or for admission to an intermediate or skilled care nursing home, the discharge summary or admission record should be obtained. Each of these events requires an SH20, Initial Report of Morbid Event.

The participant should then be asked if he/she thinks that any of the conditions (whether considered to be events or not) might be due to the SHEP medications (Item 32).

Space for comments is provided in Item 33.

Upon completion of this section of the visit, the interviewer should sign the form in Item 34, and enter their two-digit ID code.

Medication Review (Items 35-37):

This section is to be filled out by the SHEP clinician at each visit regardless of type, reason, or place of visit.

Items #35a-c and #36a-b review the participant's medication status (SHEP and open-label therapy) at the last visit, and review possible changes since the last visit. Item #37 indicates reasons for not following the recommended SHEP blood pressure treatment regimen. Item #38 reviews the participant's current blood pressure status. Items #39-41 review the medication and scheduling decision.

In Items #35a-c, "SHEP blinded medications" refers to the C, A and R drugs normally used in the SHEP Clinics. If any SHEP medications, regardless of dose, were prescribed at the last visit, then Item #35a should be "Yes." If not, then Item #35a should be "No," and Items #35b-c should be skipped.

If SHEP medications were prescribed at the last visit, then we want to know if those medications were completely discontinued since the last visit--if so, mark Item #35b "Yes," and skip to Item #36a. This does not include simple noncompliers. An example that would fit the "Yes" category would be if a participant definitely is refusing to take SHEP medications since the last visit, or their private MD has discontinued SHEP medications. It should be noted here that we do not want to know about transient changes in SHEP medications (i.e., a temporary discontinuation for assessment of side effects), unless that change in medications lasts more than one month.

If SHEP medications were prescribed at the last visit and have not been completely discontinued, then Item #35c asks about other changes in SHEP medication since the last visit. It should be noted here that we do not want to know about transient changes in SHEP medications (i.e., a temporary reduction for assessment of side effects), unless that change in medications lasts more than one month. Any other changes should prompt a "Yes" response to this item, with an explanation in the space provided.

"Last visit" refers to the visit with the next previous sequence number, regardless of type, reason or place of visit.

Items #36a-b ask about other medications which may affect the participant's blood pressure. Medications considered as "open-label" medications are listed in Table 2-2--if you have medications that you are unsure about, please contact the Coordinating Center as soon as possible. If open-label antihypertensives were prescribed at the last visit (either from SHEP or another source), the Item #36a should be "Yes" and you should skip to Item #37a. If not, or you don't know, then we want to know if open-label drugs have been prescribed since the last visit.

Blood Pressure Review (Items #37a-b):

The blood pressure review section documents protocol requirements for given levels of blood pressure at the last few visits, as well as escape blood pressure levels. Space is provided for the participant's goal blood pressure, today's blood pressure and the blood pressure at the last visit, for ease of reference. Details on the use of the blood pressure chart can be found in Chapter 3 of this manual.

Items #37a-b refer specifically to escape blood pressures (listed on the blood pressure chart). These items should be skipped for participants already on OLT. If the chart does not indicate that the participant is in an escape blood pressure sequence at this visit, then "No" should be checked, and Item #37b should be skipped. If the participant is in escape blood pressure, then the specific escape blood pressure sequence should be listed in Item #37b. "Visit 1," "Visit 2," and "Visit 3" correspond with the same terms in the blood pressure chart, with "Visit 1" being the earliest applicable visit. For all SBP escape sequences, the Visit 3 data should be left blank. If only one blood pressure is involved (e.g., SBP ≧240 mm Hg), the Visit 2 and Visit 3 data should be left blank.

Items #38a-m review (1) why a participant will not be on SHEP blinded medications, or (2) if on SHEP medications, why the prescribed treatment regimen will not be used, and/or (3) why a participant will start or continue on open-label antihypertensive therapy. This would include, for example, a step-down for possible or probable side effects, or a participant being on open-label medications for any reason (escape blood pressure, stroke, etc.), or the participant refusing SHEP medication altogether. If the participant will be prescribed SHEP medications at this visit and that SHEP medication prescription will follow the recommendation on the blood pressure chart (e.g., if a step up is required, that a step up is accomplished, etc.), Item #38a is "Yes." If the participant will not be prescribed SHEP medications or the SHEP medication treatment recommendation is not accomplished, Item #38a is "No." If the participant will remain on SHEP medications, but you don't have a SHEP blood pressure at this visit (e.g., on telephone visits), you have no way of determining the recommended treatment--check "DK" in this case.

If the participant will be prescribed open-label antihypertensives (from any source) at this visit, then Item #38b is "Yes." Check Table 2-2 for the list of medications considered as "open-label antihypertensives." If none of those medications will be prescribed, then Item #38b is "No." If you cannot determine whether or not the participant is being prescribed open-label medications, then check "DK."

If Item #38a is "Yes" and Item #38b is "No," skip to Item #39. Otherwise, check all of the reasons that apply in Item #38c-m. Be sure to differentiate between problems that the SHEP clinician thinks may be side effects to the SHEP medication, and problems which are probably not side effects in the SHEP clinician's judgment but are thought to be side effects by the participant. Also, use the following guidelines in differentiating between "other medical," "participant refusal/ preference," and "PMD request":

Other medical--Any reason such as arrhythmias, diabetes, gout, cancer or any other medical reason that a participant may be on OLT or have some non-routine SHEP medication decision. Does not include stroke, MI, LVF, or angina (noted elsewhere). This would not include side effects to study meds (this is included elsewhere) and would not include high BP in PMD office. It would include conditions that contraindicate study meds.

Participant refusal/preference--Would not include medical reasons; would include cases where the decision or recommendation was made by the participant and not by SHEP or the PMD.

PMD request--Does not include medical reasons as stated above. Does not include stroke, MI, LVF, or angina (noted elsewhere). High BP in PMD office would be included here.

Medication Prescription and Scheduling (Items #39-43):

A medication decision should then be made considering all parts of the Medication and Scheduling section.

The medications prescribed at the last visit should be indicated in Items #39a-e. If the participant is prescribed a Step 1 or Step 2 drug, check those in Items #39a and/or c, and fill in the appropriate bottle

numbers in #39b and/or d. For Item #39e(1), refer to the list of open-label drugs in Table 2-2. Any drug on that list will prompt a "Yes" response to that item, and Item #39e(2) should be answered. It is possible that some open-label drugs may be prescribed by SHEP, and another open-label drug could be prescribed by a private MD; in that case, be sure to check "both" for Item #39e(2). If the participant was prescribed a potassium supplement at the last visit, indicate "Yes" in Item #39f(1), and indicate the dose in meq/day in Item #39f(2) (if unknown, list "99"). Similarly, if the participant was prescribed a uric acid drug at the last visit, indicate "Yes" in Item #39g and indicate the drug and dose in the space underneath the item. If any of Items #39e(1) or #39f(1) or #39g are not known (e.g., on a telephone visit), be sure to check "DK" for those items.

If the medication prescription will not be altered at this visit, check "No change" in Item #40 and skip to Item #41. Otherwise, complete all of Items #40a-g (not just those medications that are changed), as directed above.

Item #41 indicates when the participant should return for their next visit--these are directed in the blood pressure chart. "Other" reflects the clinician's discretion option.

Comments on the medication and scheduling decision should be made as appropriate in Item #42. The person completing this section should sign the form and enter their SHEP ID code in Item #43.

Other Procedures:

Any behavioral evaluations required at this visit should then be carried out as described in the SHEP Behavioral Evaluation Manual. If any lab work is required, they should then be carried out as described in Appendix D.

Review of Visit

When all procedures are completed, Page 1 of the SH08 should be reviewed. In Item 10, in response to "Done This Visit?", each item (10a-10k) should be marked "Yes," or "No," as appropriate. Items that are required but not done should be explained in Comments, Item 12.

Item 11 asks about possible procedures and forms which may be required as a result of this visit. If none are required, check the box labelled "None of 11a-11f required this visit" and skip to Comments, Item 12. Otherwise, check off those that are indicated. All of these should be completed, if possible, or at least scheduled before the participant leaves. If necessary, ask participant to sign an authorization to obtain medical or hospital records.

In Item 12, space is provided for any other comments on this visit.

The next clinic visit should then be scheduled using the guidelines to scheduling provided with the form and also referring to the participant's target windows provided by the Coordinating Center. If the next scheduled visit falls within an annual visit window, the participant may take home the Annual Medical, Medication and Habits History (SH44).

The participant should always be provided with their SHEP medications, an appointment card, including the date, time and place of the next visit, and a reminder to bring their SHEP and other medicines with them to the next clinic visit.

The person reviewing this section should then sign and enter their two-digit code in Item 14.

2.5.4 Auxiliary Forms for Post-randomization Clinic Visits

SH11 - Local Laboratory Results--use one SH11 for all local lab results for a visit

SH30 - SHEP SHORT-CARE

SH33 - Activities of Daily Life

SH34 - Social Network Questionnaire

SH35 - Behavioral Evaluation--Part II

SH36 - SHORT-CARE Scoring Sheet

SH40 - Compliance Evaluation

SH42 - Side Effects Questionnaire

SH62 - Pill Count Worksheet

MetPath Request Slip

SHEP CLINIC VISIT

Name: _____

1. SHEP ID: [ ] - [ ] - [ ]
2. Acrostic: [ ]
3. Today's date: [ ] [ ] [ ] (Month Day Year)
4. Sequence number: [ ]
5. Type of visit:
   1 ☐ Quarterly (Skip to 8)
   2 ☐ Other required (Skip to 8)
   3 ☐ Interim
6. Visit scheduled:
   1 ☐ by SHEP Clinic
   2 ☐ at participant's request
7. Reason for visit (check all that apply):
   a. 1 ☐ BP check
   b. 1 ☐ Potassium re-check (local)
   c. 1 ☐ Possible side effects
   d. 1 ☐ Other (Specify in Comments, Item 12)
8. Place of visit:
   1 ☐ Clinic
   2 ☐ Home
   3 ☐ Telephone
9. a. Were Step 1 medications started or increased at last visit? 1 ☐ Yes 2 ☐ No
   b. Were Step 2 medications started or increased at last visit? 1 ☐ Yes 2 ☐ No

10. Refer to following chart in determining procedures required at this visit.

Procedure	Check if Required This Visit	Comments	Done This Visit? Yes	No
a. Pulse, BP, Weight	☐	Every visit except telephone visits.	☐ 1	☐ 2
b. Blood, central	☐	Serum potassium required at visit after Step 1 start or increase.	☐ 1	☐ 2
c. Local lab work (SH11)	☐	Local re-check of central laboratory results; as required in clinician's judgment.	☐ 1	☐ 2
d. Compliance (SH40)	☐	Required at visit after SHEP medications started or increased, and semi-annually. Do not administer if SHEP medications were not prescribed at the last visit. Circle correct SHEP prescription in Items 9 and 12 on SH40.	☐ 1	☐ 2
e. General well-being	☐	Required every visit.	☐ 1	☐ 2
f. Specific side effects (SH42)	☐	Required at next regularly scheduled visit after SHEP medications started or increased, at interim visits for possible side effects, and in response to a "Yes" to Item 28b in the General Well-Being section. Do not administer if participant has been off of SHEP medications more than six months.	☐ 1	☐ 2
g. Medication and Scheduling Decision	☐	Required every visit. Fill in SHEP medication prescription at last visit (Item 39) prior to visit.	☐ 1	☐ 2
h. SHORTCARE/CES-D (SH30)	☐	Required at the next quarterly visit after SHEP medications are started or increased, and semi-annually. Also required at other quarterly visits if participant reached criterion score at last SHORTCARE but did not qualify for referral at that time. Also required if the Behavioral Evaluation--Part II is being administered. Do not administer over the telephone.	☐ 1	☐ 2
i. Social Network (SH34)	☐	Required at one-month after randomization. Do not administer over the telephone.	☐ 1	☐ 2
j. Behavioral Evaluation--Part II	☐	Required at next regularly scheduled visit after an annual visit, if not already administered at annual visit, in participating centers. Cannot be administered over the telephone.	☐ 1	☐ 2
k. Activities of Daily Life (SH33)	☐	Required if Behavioral Evaluation--Part II is being administered.	☐ 1	☐ 2

REVIEW ITEMS 10 THROUGH 12, AND SCHEDULE NEXT CLINIC VISIT (ITEM 13) AT THE TERMINATION OF THIS VISIT, BEFORE THE PARTICIPANT LEAVES THE SHEP CLINIC. CHECK TO BE SURE THAT THE PARTICIPANT'S ID AND ACROSTIC ARE CORRECT--THE ACROSTIC SHOULD BE THE SAME AS THE ACROSTIC ON THE SH06. BE SURE THAT ALL REQUIRED SECTIONS OF THIS FORM ARE COMPLETE (IF REQUIRED) AND LEGIBLE. CHECK YELLOW COPY FOR LEGIBILITY, ALSO. ANY ITEMS OR PROCEDURES REQUIRED BUT NOT COMPLETED SHOULD BE EXPLAINED IN COMMENTS, ITEM 12.

11. Action required as a result of this visit: 1 ☐ None of 11a-11f required this visit.
    a. 1 ☐ Initial Notification of Morbid Event, SH20
    b. 1 ☐ SHEP Neurological Evaluation for Strokes, SH27
    c. 1 ☐ SHEP Neurological Evaluation for TIA, SH28
    d. 1 ☐ Dementia Referral, SH31
    e. 1 ☐ Depression Referral, SH32
    f. 1 ☐ Report of Unblinding, SH49
12. Comments on this visit: _____
13. Next clinic visit: [ ] [ ] [ ] (Month Day Year) at [ ] : [ ] (Hour Minute) 1 ☐ a.m. 2 ☐ p.m.
14. Signature of person reviewing this page: _____ [ ] Code

If the next scheduled visit is an annual visit, participant may take home the Annual Medical, Medication and Habits History (SH44).

PULSE AND BLOOD PRESSURE--If any pulse or blood pressure or the participant's weight is not obtained, enter all 9s in the appropriate spaces. If this is a telephone visit, leave cuff size and Item 15c blank.

15. a. Pulse: Beats in 30 seconds _____ x 2 = [ ] beats per minute.

b. Cuff Size:

1 ☐ Regular
2 ☐ Large arm
3 ☐ Thigh
4 ☐ Pediatric

Pulse Obliteration Pressure:

Observed Value: [ ]
Subtract Zero Level: - [ ]
Corrected Value: [ ]
Add Maximum Zero Level Plus 20: + [ ]
Peak Inflation Level: [ ]

Seated Readings:

	Systolic	Diastolic
First	[ ]	[ ]
Zero level	[ ]	[ ]
Corrected	[ ]	[ ]
+ Second	[ ]	[ ]
+ Zero level	[ ]	[ ]
+ Corrected	[ ]	[ ]
Sum of two corrected readings	[ ]	[ ]
Average of two corrected readings	[ ]	[ ]

Standing Readings:

One minute

Pulse: Beats in 15 seconds _____
x 4 = [ ] beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	[ ]	[ ]
Zero	[ ]	[ ]
Corrected	[ ]	[ ]

Three minutes

Pulse: Beats in 15 seconds _____
x 4 = [ ] beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	[ ]	[ ]
Zero	[ ]	[ ]
Corrected	[ ]	[ ]

(If standing blood pressure not done, skip to 15d.)

c. Did the participant volunteer any symptoms on standing? Yes ☐ 1 No ☐ 2 ↓

(1) Dizziness Yes ☐ 1 No ☐ 2
(2) Other (specify)? Yes ☐ 1 No ☐ 2 _____

SKIP to 15d.

d. Weight: [ ] pounds

e. Observer signature: _____ [ ] Code

COMPLIANCE EVALUATION

Interviewer: If any SHEP medication was started or increased at the last clinic visit, or if this is a semi-annual visit, the compliance evaluation (SH40) should be administered (refer to Items 9a, 9b and 10d). Do not administer if SHEP medications were not prescribed at the last visit. If required, administer the compliance evaluation and then return to this form.

GENERAL WELL-BEING - Interviewer: Questions in this section are to be asked at every visit; use phraseology that you are comfortable with.

16. Have you felt unwell in any way since your last clinic visit; has anything been bothering you? (Specify): _____ Yes ☐ 1 No ☐ 2 → Go to 18.

17. Are any of these problems different from the way things were at your last clinic visit? Yes ☐ 1 No ☐ 2

18. Since your last visit, have you seen a doctor for any reason? (Specify): _____ Yes ☐ 1 No ☐ 2

19. Since your last visit, have you been in the hospital for any reason? Yes ☐ 1 No ☐ 2 → Go to 20.

How many times? ☐

When? (Start with the first one after your last visit.)

(If more than 3 hospitalizations, list rest on blank sheet of paper.)

	Hospitalization #1	Hospitalization #2	Hospitalization #3
Hospital name			
Date of admission	Month ☐ Day ☐ Year ☐	Month ☐ Day ☐ Year ☐	Month ☐ Day ☐ Year ☐
Number of days	☐	☐	☐
Reason			

20. a. Since your last SHEP visit, have you had any sudden feeling of numbness, tingling or loss of feeling in either arm, hand, leg, foot or face? Yes ☐ 1 No ☐ 2 → SKIP to 21.

b. How many attacks of such numbness or tingling have you had? One ☐ 1 More than one ☐ 2

c. How long did each of the attack(s) usually last? Less than 24 hours ☐ 1 More than 24 hours ☐ 2

21. a. Since your last SHEP visit, have you had any sudden attacks of paralysis or loss of use of either arm, hand, leg or foot? Yes ☐ 1 No ☐ 2 → SKIP to 22.

b. How many attacks of such paralysis have you had? One ☐ 1 More than one ☐ 2

c. How long did the attack(s) usually last? Less than 24 hours ☐ 1 More than 24 hours ☐ 2

22. a. Since your last SHEP visit, have you had any sudden loss of eyesight or blurring of vision for a short period of time? Yes ☐ 1 No ☐ 2 → SKIP to 23.

b. What part of your vision was affected? Right eye only ☐ 1 Left eye only ☐ 2 Both eyes ☐ 3 Vision to the right side ☐ 4 Vision to the left side ☐ 5

c. How many attacks of loss of eyesight or blurring of vision have you had? One ☐ 1 More than one ☐ 2

d. How long did the attack(s) usually last? Less than 24 hours ☐ 1 More than 24 hours ☐ 2

23. a. Since your last SHEP visit, have you had any sudden attacks of changes in speech, loss of speech or inability to say words? Yes ☐ 1 No ☐ 2 → SKIP to 24.

b. How many attacks of loss of speech have you had? One ☐ 1 More than one ☐ 2

c. How long did the attack(s) usually last? Less than 24 hours ☐ 1 More than 24 hours ☐ 2

24. Since your last SHEP visit, have you had any of the following:

a. Dizziness Yes ☐ 1 No ☐ 2
b. Spinning sensation (vertigo) Yes ☐ 1 No ☐ 2
c. Loss of balance Yes ☐ 1 No ☐ 2
d. Difficulty walking Yes ☐ 1 No ☐ 2
e. Blackouts or fainting Yes ☐ 1 No ☐ 2
f. Frequent falls Yes ☐ 1 No ☐ 2

If none of 24a-f are answered "Yes," skip to 25.

g. About how many total attacks of all of these conditions do you think you ever had? One ☐ 1 More than one ☐ 2

h. How long did the attack(s) usually last? Less than 24 hours ☐ 1 More than 24 hours ☐ 2

25. Since your last SHEP visit, have you been told by a doctor or otherwise learned that you may have had a stroke? Yes ☐ 1 No ☐ 2

26. Thinking about the other medications that you might be taking now, or have taken since your last visit:

a. Have you stopped taking any medications? Yes ☐ 1 No ☐ 2
(Specify): _____

b. Have you increased or decreased any medications that you were taking? Yes ☐ 1 No ☐ 2
(Specify): _____

c. Have you started taking any new medications? Yes ☐ 1 No ☐ 2
(Specify): _____

27. Interviewer:
Did the participant bring all non-SHEP medications to the clinic at this visit?

Yes ☐ 1
No ☐ 2
Not on any non-SHEP medications ☐ 3

28. Interviewer:

a. Did the participant volunteer any complaints or problems in Items 16-25? Yes ☐ 1 No ☐ 2

↓

Skip to next section.

b. Are these problems that, in your opinion, may be related to study medications?

Yes ☐ 1
No ☐ 2
Not on SHEP medications ☐ 3

↓

SH42 required

SPECIFIC SIDE EFFECTS (SH42)

Interviewer: The Side Effects Quesionnaire (SH42) is required at the first required visit after SHEP medications are started or increased, in response to a "Yes" to Item 28b, and at interim visits for possible side effects. It is not required under any condition for participants who have been off of SHEP medications more than six months. If required, administer the SH42, and then return to this form.

POSSIBLE EVENTS

29. Are there any positive responses to Items 16-25 or on the Side Effects Questionnaire (SH42)? Yes ☐ 1 No ☐ 2 → Go to 33.

30. In the judgment of the SHEP clinician, are any of these positive or abnormal responses a result of:

		Yes	Possibly	No	
a.	Stroke	☐ 1	☐ 2	☐ 3	Arrange for SHEP
b.	Acute myocardial infarction	☐ 1	☐ 2	☐ 3	Neurological Examination
c.	Left ventricular failure	☐ 1	☐ 2	☐ 3	for Stroke (SH27) as soon as possible.
d.	Transient ischemic attack	☐ 1	☐ 2	☐ 3	Arrange for SHEP
e.	Other cardiovascular hospitalization (specify: _____)	☐ 1	☐ 2	☐ 3	Neurological Examination for TIA (SH28) as soon as possible.
f.	Hospitalization for reason other than above (specify: _____)	☐ 1	☐ 2	☐ 3	
g.	Intermediate or skilled care nursing home admission	☐ 1	☐ 2	☐ 3	

31. Was the participant hospitalized or seen by a physician for any event in 30a-30g?

Yes ☐ 1 → For possible strokes, acute myocardial infarctions, left ventricular failures, and transient ischemic attacks, obtain complete hospital/physician visit record for that event. For other hospitalizations and admissions to skilled or intermediate care nursing homes, obtain discharge summary or admission record only. Have participant sign consent to obtain medical records.

No ☐ 2

Not sure ☐ 3

For any event in 30a-30g checked "Yes" or "Possibly," fill out Form SH20, Initial Report of Morbid Event.

32. Does the participant think that any of these conditions are due to the SHEP medications? Yes ☐ 1 No ☐ 2 DK ☐ 3

33. Comments (note pertinent history and physical exam findings and diagnostic impressions): _____

_____

_____

_____

_____

34. Signature of person completing this section: _____ Code ☐

MEDICATION REVIEW

35. a. Were any SHEP blinded medications prescribed at the last visit? Yes □ 1 No □ 2 → Go to 36a.

b. Were all SHEP blinded medications discontinued since the last visit? Yes □ 1 No □ 2 DK □ 3 → Go to 36a.

c. Were there any other changes made in the SHEP blinded medications since the last visit? Yes □ 1 No □ 2 DK □ 3

(Specify_____)

36. a. Were open-label antihypertensive medications prescribed at the last visit (any source)? Yes □ 1 No □ 2 DK □ 3 → Go to 37a.

b. Were open-label antihypertensive medications prescribed since the last visit (any source)? Yes □ 1 No □ 2 DK □ 3

BLOOD PRESSURE REVIEW - Goal SBP: _____ BP today: _____ Last visit: _____

Please review the attached chart for treatment and scheduling decision based on blood pressure status.

37. a. Has the participant reached escape blood pressure at this visit? Yes □ 1 No □ 2 → Go to 38a. DK □ 3 →

b. List the escape blood pressure sequence:

	Month	Day	Year	SBP	DBP
Visit 1					
Visit 2					
Visit 3					

38. a. Will you be prescribing SHEP medications according to the prescribed SHEP blood pressure treatment regimen at this visit? Yes □ 1 No □ 2 DK □ 3

b. Will you be prescribing open-label antihypertensive medications at this visit? Yes □ 1 No □ 2 DK □ 3

If Item #38a is "Yes" and Item #38b is "No," skip to #39.

Reasons (check all that apply):

c. Participant has reached escape blood pressure at this visit or a previous visit Yes □ 1
d. Possible or probable side effects in the judgment of the SHEP clinician Yes □ 1
e. Perceived side effects in the judgment of the participant Yes □ 1
f. Stroke Yes □ 1
g. MI Yes □ 1
h. LVF Yes □ 1
i. Angina Yes □ 1
j. Other medical (specify) _____ Yes □ 1
k. Participant refusal or preference Yes □ 1
l. Private MD request Yes □ 1
m. Other (specify) _____ Yes □ 1

MEDICATION PRESCRIPTION AND SCHEDULING

---

39. Medication prescription last visit:

a. Step 1

C1 □ 1
C2 □ 2
½ C1 □ 3
Other C _____ □ 4
No Step 1 (go to 39c) □ 5

b. Step 1 bottle number [| |]

c. Step 2

A1 □ 1
A2 □ 2
Other A _____ □ 3
R Dose 1 □ 4
R Dose 2 □ 5
Other R _____ □ 6
No Step 2 (go to 39e) □ 7

d. Step 2 bottle number [| |]

e(1) Open-label drugs (specify drug and dose) Yes □ 1 No □ 2 DK □ 3

_____

↓ ↓

Go to 39f.

e(2) Source of open-label drugs

Prescribed by SHEP □ 1
Prescribed by other source □ 2
Both □ 3

f(1) K supplement Yes □ 1 No □ 2 DK □ 3

↓ ↓

Go to 39g.

f(2) Meq/day (unknown = 99) [|]

g. Uric acid drug (specify drug and dose) Yes □ 1 No □ 2 DK □ 3

_____

40. Medication prescription this visit: No change (go to 41) ☐ 1

a. Step 1

C1 ☐ 1
C2 ☐ 2
½ C1 ☐ 3
Other C _____ ☐ 4
No Step 1 (go to 40c) ☐ 5

b. Step 1 bottle number ☐☐☐

c. Step 2

A1 ☐ 1
A2 ☐ 2
Other A _____ ☐ 3
R Dose 1 ☐ 4
R Dose 2 ☐ 5
Other R _____ ☐ 6
No Step 2 (go to 40e) ☐ 7

d. Step 2 bottle number ☐☐☐

e(1) Open-label drugs (specify drug and dose) Yes ☐ 1 No ☐ 2 DK ☐ 3

_____

↓ ↓
Go to 40f.

e(2) Source of open-label drugs

Prescribed by SHEP ☐ 1
Prescribed by other source ☐ 2
Both ☐ 3

f(1) K supplement Yes ☐ 1 No ☐ 2 DK ☐ 3

↓ ↓
Go to 40g.

f(2) Meq/day (unknown = 99) ☐☐

g. Uric acid drug (specify drug and dose) Yes ☐ 1 No ☐ 2 DK ☐ 3

_____

41. Schedule:

Next quarterly ☐ 1
One month ☐ 2
1-2 weeks ☐ 3
1 week ☐ 4
Other (specify) _____ ☐ 5

42. Comments

43. Signature of Clinician completing this section: _____ ☐☐ Code

OTHER PROCEDURES

Interviewer: If the SHORTCARE (SH30), the Activities of Daily Life (SH33), or the Social Network Questionnaire (SH34) or the Behavioral Evaluation --Part II (SH35) are required at this visit, they should be administered at this time.

The participant may now be sent for any lab work that may be required at this visit. Document lab work on the front of this form (Items 10b and 10c.)

PLEASE REVIEW PAGE 1.

Combinations 1-8 assume DBP < 90 mm Hg at this visit:

	SBP [1] at Consecutive Visits On Same Step & Dose		On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2			
1	<=110 [4]			SD [5]	CD
2	111-goal	111-goal	N	NC	Q
3	111-189	111-189	Y	NC	Q
4	>goal-219	220-239	N	SU	2W
5	>goal-239	>goal-219	N	SU	1M
6	220-239	220-239	N Y	SU [5] OL [5]	2W CD
7	>=240 [4]			OL [5]	CD
8	Other			NC	SBP 111-219 ->1M SBP 220-239 ->2W

For DBP < 90 mm Hg this visit, skip Combinations 9-14.

	DBP [1] at Consecutive Visits On Same Step & Dose			On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2	Visit 3			
9	90-94	90-94		N	SU [5]	1M
10	90-94	95-114		N	SU [5]	1-2W
11	90-94	90-114	>= 90	Y	OL [5]	CD
12	95-114	95-114		N Y	SU [5] OL [5]	1-2W CD
13	115+ [4]				OL [5]	CD
14	Other				NC	DBP 90- 94 ->1M DBP 95-114 ->1-2W

[1] Average of two seated corrected readings
[2] OL = open label, SU = step up, SD = step down at clinician discretion
[3] W = weeks, M = month, Q = next quarterly, CD = clinician discretion
[4] Any single visit
[5] Escape blood pressure reached

If DBP >=90 mm Hg at this visit, treatment prescribed this visit should reflect the largest change in medication prescribed above for the appropriate blood pressure levels. For example, the choice between "No Change" and "Step Up" should be "Step Up"; the choice between "Step Up" and "Open Label" should be "Open Label". The next visit should be scheduled according to the shortest suggested interval.

For additional detail on specific blood pressure combinations, refer to the SHEP Manual of Operations, Chapter 3.

TABLE 2-2
Open-Label Antihypertensive Medications

Acebutolol
Adalat
Aldactazide
Aldactone
Aldoclor
Aldomet
Aldoril
Amiloride
Anhydron
Apresazide
Apresoline
Apresoline-Esidrix
Aquatensin
Arfonad
Atenolol
Bendroflumethiazide
Blocadren
Brevibloc
Bumex
Calan
Capoten
Capozide
Captopril
*Cardene (Nicardipine)
*Cardiazem-SR
Cardizem
Catapres
Catapres-TTS
Chlorothiazide
Chlorthalidone
Clonidine
Combipress
Corgard
Corzide
Demi-Regroton tablets
Deserpidine
Diltiazem
*Diltiazem-SR
Diucardin
Diulo
Diupres
Diuril
Diutensen
Diutensen-R
Dyazide
Dyrenium
Edecrin
Enalaprilat
Enduron
Enduronyl
Enduronyl Forte
Esidrix
Esimil
Eutonyl Filmtab tablets
Exna tablets
Furosemide
Guanabenz
Guanadrel
Guanethidine
Guanfacine
Harmonyl
Hydralazine
Hydrochlorothiazide
Hydro Diuril
Hydroflumethiazide
Hydromox
Hydromox-R
Hydropres
Hygroton
Hylorel
Hyperstat
Hytrin
Indapamide
Inderal
Inderal-LA
Inderide
Inderide-LA
Inversine
Ismelin
Isoptin
Labetalol
Lasix
Lisinopril
Loniten tablets
Lopressor
Lozol
Maxzide
Metahydrin
Metatensin
Methyldopa
Methylclothiazide
Metolazone
Metoprolol
Midamor
Minipress
Minizide
Minoxidil
Moderil
Moduretic
*Mycrox
Nadolol
Naqua
Naquival
Naturetin
*Nicardipine (Cardene)
Nifedipine
Nitropress
Nitrendipine (?Baypress)
Normodyne tablets
Normozide
Oretic
Oreticyl
Pargyline hydrochloride
Pindolol
Penbutolol
Polythiazide
Prazosin
Prinivil
*Prinzide 12.5
*Prinzide 25
Procardia
Propranolol
Raudixin tablets
Rauwolfia Serpentina
Rauzide
Regroton
Renese
Renese-R
Rescinnamine
Reserpine
Saluron
Salutensin
Salutensin-Demi
Sectral
Ser-Ap-Es
Serpasil
Serpasil-Apresoline
Serpasil-Esidrix
Spironolactone
Tenoretic
Tenormin
Terazosin
Thalitone
Timolide
Timolol
Trandate
Triamterene
Trichlormethiazide
Vasoretic
Vasotec
Vasotec I.V.
Verapamil
Visken
Wytensin
Zaroxolyn
Zestril

DRUGS THAT ARE NOT OPEN-LABEL THERAPY

Betopic
Betagan
Diamox
Neptazene
Nitrates
Timoptic

*New 4/89

2.6 Annual Visits

2.6.1 Description

As discussed in Section 2.5, all participants are required to be seen at one month, two months and quarterly after randomization. The annual visit takes place in the quarterly visit windows that include the randomization anniversary date. Extra efforts should be made to bring participants into the Clinic for these evaluations, but visits may take place in the participant's home or by telephone if absolutely necessary. It should be stressed to reluctant participants that the visit includes a comprehensive physical examination, an ECG (at some annual visits) and blood and urine analyses. If the visit must take place in the home or on the telephone, guidelines as to procedures for these visits is included in Section 2.6.2 and Section F.8.

The annual visits 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, and the behavioral evaluations. Blood chemistries (fasting at 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 follows:

Procedures	Frequency
Serum chemistries	All annual
Alkaline phosphatase	
Blood urea nitrogen	
Calcium	
Creatinine	
Glucose	
Potassium	
SGOT	
Sodium	
Uric acid	

Total serum cholesterol, HDL cholesterol, and triglycerides	Baseline, Year 1, Year 3, Final Annual (Fasting)
Hb/Hct, WBC (local)	All annual
Dipstick urinalysis (local)	All annual
ECG and two-minute rhythm strip	Baseline, Year 2 and Final Annual

Also, an SH09 must be completed for all participants not known to be deceased, when these participants would normally have had an annual visit. This enables SHEP to at least collect some vital status information on every participant, on an annual basis.

2.6.2 Reviewing the Annual Medical, Medication and Habits History (SH44)

This form is a combination and reduction of the two baseline take-home forms, the SH03 and SH04. It may have been taken home by the participant at a previous clinic visit, mailed to the participant or kept to fill in at the clinic at the time of the annual visit.

If some of these items are not completed at the time of the clinic visit, they should be completed prior to the beginning of the visit, by a clinic staff person using inquiries appropriate to the specific questions that were left blank. In some cases, the problem may be one of an inability to read, and the staff person will need to ask the question as written on the form. Regardless, the participant should have brought their medications to the clinic visit, and these should be checked against Items 33 and 35.

Some of the items require that a two or three-digit number be entered into boxes. For example:

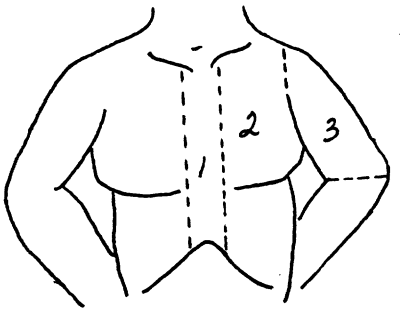
31b. How many (cigarettes) do you now smoke per day? ☐☐☐

The clinic staff person reviewing the form should make sure that these types of boxes are filled in as per instructions in Appendix F.

In addition, on page 3, Item 12h, several judgements must be made regarding the location of chest pain or discomfort (if any). If both 12a and 12b are answered "No", then no judgement needs to be made. If either is "Yes", then the location of the pain or discomfort should be indicated on the drawing, and documented in the box marked "Do not use --clinic use only" in the following manner:

12h(1)	This is "Yes" if there is an X in the sternum (upper, middle or lower). Otherwise, mark "No".
12h(2)	This is "Yes" if there is an X in the left anterior chest. Otherwise, mark "No".
12h(3)	This is "Yes" if there is an X in the left arm above the elbow. Otherwise, mark "No".

The areas described above are as per the following drawing:

RIGHT 

LEFT

For Items 36a-e (questions about current living status), if a participant is in a nursing home, the response should be "living with non-related paid help."

When the form is completed, positive responses to the medical questions should be highlighted for quick reference by the SHEP clinician.

Some visits may take place on the telephone. If possible, every effort should be made to get as much information as possible. In order to do this, it may be adviseable to mail the form to the participant ahead of time, and enclose a return envelope, requesting that the participant return it to the Clinic by the time of the visit. Alternatively, the form may be filled out as completely as possible over the telephone. If the entire form cannot be completed, it is imperative that major study endpoint and medication items by completed. These include the following items:

1 - 10	major diseases
14	myocardial infarction
17	left ventricular failure
18 - 22	TIA and stroke
24, 25	hospitalizations
33, 35	medications

These priority items are indicated for ease of reference on the form by a square around the item numbers.

If the Rose Questionnaire for angina (Item 12) is completed over the telephone, ascertain as closely as possible the location of chest pain or discomfort, if any.

2.6.3 Form SH09-SHEP Annual Clinic Visit

This form is to be used for all SHEP annual visits. Items 1 through 4 may be entered onto the form prior to the visit.

SHEP ID and acrostic (Items 1 and 2):

Be sure that these are legible and correct. The acrostic should always match what is on the participant's SH06 (Baseline Visit 1 Form).

Visit identification items (Items 3a-3c):

Item 3a, "Today's Date", is the date of the visit, and not the date that the form was prepared (if prepared ahead of time). Item 3b is the sequence number of the visit, previously described (Section 2.5.3). Item 3c is simply which annual visit--i.e., Year 1, Year 2, etc.

Place of Visit and Vital Status (Items 4a and b):

Put an X in the box that indicates where this visit took place. Any visit at which the participant is physically seen outside the SHEP Clinic (e.g., at the participant's home, other home or in the hospital or a nursing home) should be counted as a "home" visit. "Clinic," "Home," and "Telephone" assume that some SH09 information other than vital status has been ascertained.

For participants who are currently refusing to attend the clinic and who have refused telephone visits, some determination should be made of their vital status. This should be done during their normal annual visit window. An extra attempt should also be made to determine the vital status of participants who are lost to follow-up. Also, if a participant cannot attend an annual visit within the "entended" annual window, the annual visit is then missed, and an SH09 should be completed as described below. For these cases, where no information for the SH09 can be obtained, "No Visit" should be checked in Item 4a, and the vital status should be checked as appropriate in Item 4b. ("Today's Date," Item 3a, should be the date that the vital status was ascertained.) If "No Visit" is appropriate, leave the remainder of the form blank, except for Item 11, "Signature of person reviewing this page," and their two-digit ID code. Attempts should be made to determine vital status

until the end of the "extended" annual window (± 4 weeks from either end of the target window). At this time, if the vital status is still unknown, "Unknown" should be checked in Item 4b.

Time visit begins (Item 5):

Do not enter in this space the time that the participant arrives at the Clinic (this could be a long time before the visit actually begins). This should be the time (hour and minute) that visit activities actually begin (e.g., reviewing the take-home form and the original Participant Information Sheet, SH02).

The review of the take-home form and the Participant Information Sheet (SH02) should be the first thing done at these visits. The SH44 review is very similar to the baseline take-home form review and has been described in Section 2.6.2. For the SH02, simply ask the participant to briefly review both pages and indicate if anything has changed. Pay particular attention to participants who did not have a Social Security and/or Medicare Number at baseline. If he or she has since received a number, submit a change to the SH06 to reflect this new information; it is used to allow HCFA to find out if participants are hospitalized.

Items 6a-6k are listed in chart format, and indicate auxiliary procedures which are required at specific annual visits. Unless otherwise indicated in "Comments", procedures are required at every annual visit. Footnotes indicate procedures that may be omitted for home and telephone visits. This should be reviewed prior to the visit, and is completed at the end of the visit.

Pulse and blood pressure (Items 12a-12e):

These items are required, except at telephone visits (12d and 12e only are required at telephone visits). For telephone visits, the cuff size and Item 12c (symptoms on standing) may be left blank; fill the other items with 9s.

The pulse and blood pressure procedures should be carried out by a certified SHEP blood pressure observer, as described in the SHEP Blood Pressure Manual. If any pulse or blood pressure is not obtained, 9s should be entered onto the form in the appropriate boxes. If the standing blood pressure cannot be obtained for any reason, then Item 12c (symptoms on standing) may be skipped. If a visit must be completed in two sessions, the blood pressure and pulse may be done on both days at the Clinic discretion. However, the official blood pressure and pulse for that visit are the data from the first session.

If this visit is a telephone visit, then ask Item 12d. Ask if, since the participant's last visit in the SHEP Clinic, he or she has had their blood pressure taken. If so, when was it, and, if known, what were the readings. This includes readings taken by a doctor or nurse, at a health fair or other screening, and home blood pressure readings. Readings taken by the coin-operated type of machines do not count. If the date or the readings are unknown, fill the items with 9s.

The observer should then sign the form and enter their two-digit ID code in Item 12e.

ECG and Laboratory Procedures

The ECG and laboratory procedures which are required at this annual visit should be carried out after the blood pressure, according to Appendices C and D of this manual.

If a non-fasting blood sample is to be drawn, the Clinic may wait until the end of the visit to do this. Otherwise, the blood sample should be drawn at this time. (These procedures may be performed at any time during the visit that is suitable to the flow of the clinic visit, except that the blood pressure must be obtained prior to these procedures.)

Compliance Evaluation (Items 13-23):

Items 13-23 are compliance items repeated from the SH40. If SHEP blinded medications were not prescribed at the last visit, these items should not be done at all. If the visit is a home or telephone visit, the pill count (Item 23) should be skipped. Also, if a pill count cannot be completed at the scheduled clinic visit, no additional attempt should be made to obtain pill count information (e.g., do not ask the participant to count the pills and call the Clinic). Specific directions for the compliance evaluation may be found in Section 9.16 and in Chapter 6 of this manual.

General Well-Being (Items 24-31):

Questions in this section should be administered regardless of location of visit, any may be re-phrased by the interviewer.

These items constitute a general interval history and are for ascertaining both possible side effects and SHEP endpoints.

Except for Item 28, the screening questions for stroke and TIA are removed from here for the annual visit, and put onto the take-home form in the same detail that was asked at baseline.

If the participant responds "No" to Item 24 ("Have you felt unwell . . ."), then Item 25 should be skipped, as directed on the form. If the response is "Yes", then the interviewer should probe for details with a statement like, "Can you tell me about how you felt?" or, "Can you tell me what was wrong?". The interviewer should not suggest details in any way to the participant. Also, on a "Yes" response to Item 24, the interviewer should continue to Item 25, which asks if the problem is different from the way things were at the previous clinic visit.

Item 26 asks about visits that the participant has had with his/her own physician or usual source of care. This may be confusing for clinics providing primary care to their SHEP participants. A "Yes" response to this question should not include official SHEP treatment visits (i.e., visits scheduled for a reason provided for in the protocol, such as required visits, or any interim visits scheduled for any reason). If the participant has seen a doctor for non-SHEP reasons, the interviewer should probe for details as described for Item 24.

Item 27 asks about hospitalizations since the last clinic visit. If the participant responds "No", the interviewer should skip to Item 28. A "Yes" response to Item 27 requires further probing; for each hospitalization, the following information should be obtained:

- Hospital name
- Date of admission
- Number of days
- Reason--a diagnosis is requested, but if the participant does not know the actual diagnosis, the symptom(s) that led to the hospitalization are acceptable.

Emergency room visits and outpatient surgeries should not be counted or listed. If more than three hospitalizations are mentioned, list the rest on a blank sheet of paper. (<u>This extra sheet must be copied to send to the Coordinating Center with the hardcopy form</u>.

Item 28 inquires whether the participant has been told that he/she had a stroke, since the last clinic visit.

Item 29 inquires about non-SHEP medication changes since the last clinic visit (stop, increase, decrease, start). Both prescription and non-prescription medications should be considered. Medications that are changed in any way should be specified. The participant will have been instructed to bring all non-SHEP medications to the clinic at every visit. Whether or not this was done should be indicated in Item 30; if the participant reports that he/she is not taking any other medications, the "Not on any non-SHEP medications" should be checked.

Possible Side Effects (Items 31-62):

This sections is required at all annual visits, regardless of location of visit, except for participants who have been off of SHEP blinded medications for more than six months.

These items are an exact copy of those on the SH42; specific details are given in Sections 9.17 of this manual.

Clinician Review of Medication History (Items 63a-63v):

The clinician should then review the SH44 (completed previously at this visit) and complete Items 63a-63z. The SHEP blinded medications should not be indicated in 63a (any medication for blood pressure). In determing if the participant is on "Any medication for blood pressure . . . ," Item 63a, use Table 2-2 (List of Open-Label Antihypertensive Medication"). Some medications in Table 2-2 may fit into more than one category on the list (e.g., beta-blockers would also fit into Item 63d). Check all items as appropriate.

Item 63u (Estrogen) should include estrogen patches, but not estrogen creams.

Physical Examination (Items 64-78):

The physical examination has two purposes: (1) to provide good general medical care, and (2) to provide information on possible endpoints.

A SHEP clinician should perform the general physical examination as described in Appendix E of this manual, paying particular attention to the specific items listed. Height and weight should be measured first, as described in Appendix E. If this visit is a telephone or home visit, the participant should be asked to estimate his or her own weight and height; these should be entered into Items 64 and 65. (9s should be entered if the participant does not know their height and weight.)

The clinician should then sign the form and enter his or her ID code in Item 78.

Clinician's Judgment and Endpoint Review (Items 79-103):

After the physical examination, and while the participant is getting dressed, the clinician should review the medical history, physical exam (if completed), and ECG (if done), and complete Items 79-103.

For each disease or organ system, reference questions are listed to direct the clinician to items that are applicable from the Annual Medical, Medication and Habits History (SH44).

Since the physical examination data and the ECG information may be missing for telephone and home visits, only the main SHEP study endpoint items are definitely required for these visits:

80a, 80b	myocardial infarction
81a, 81b	coronary bypass
82	congestive heart failure
86a, 86b, 86c, 86d	vascular surgeries
89a, 89b, 89c	stroke
90	TIA
91	carotid endarterectomy
100	Other hospitalizations and admissions to intermediate or skilled care nursing home

These items are marked with a square around the item numbers; every effort should be made to obtain this information. Other items in the Clinician Judgment section may be marked "DK" for telephone and home visits, if the pertinent information is not obtainable.

The clinician should very carefully review this section for new events which require an Initial Notification of Morbid Event (SH20). These include new strokes, TIAs, left ventricular failures and myocardial infarctions, plus new other hospitalizations and new admissions to intermediate or skilled care nursing homes. Do not submit possible silent MIs as morbid events. If events are discovered which have not previously been reported on an SH20, this should be accomplished, and the pertinent records should be obtained with the participant's permission and signed consent. If a participant has had a TIA confirmed by the SHEP endpoint coders, new possible TIAs do not need to be submitted on a morbid event form.

The clinician reviewing this section should then sign the form in Item 103 and enter their two-digit ID code.

Medication Review (Items 104-106):

This section is to be filled out by the SHEP Clinician at each annual visit, regardless of place of visit.

Items #104a-c and #105a-b review the participant's medication status (SHEP and open-label therapy) at the last visit, and review possible changes since the last visit. Item #106 indicates reasons for not following the recommended SHEP blood pressure treatment regimen. Item #107 reviews the participant's current blood pressure status. Items #108-110 review the medication and scheduling decision.

In Items #104a-c, "SHEP blinded medications" refers to the C, A and R drugs normally used in the SHEP Clinics. If any SHEP medications, regardless of dose, were prescribed at the last visit, then Item #104a should be "Yes." If not, then Item #104a should be "No," and Items #104b-c should be skipped.

If SHEP medications were prescribed at the last visit, then we want to know if those medications were completely discontinued since the last visit--if so, mark Item #104b "Yes," and skip to Item #105a. This does not include simple noncompliers. An example that would fit the "Yes" category would be if a participant definitely is refusing to take SHEP medications since the last visit, or their private MD has discontinued SHEP medications. It should be noted here that we do not want to know about transient changes in SHEP medications (i.e., a temporary discontinuation for assessment of side effects), unless that change in medications lasts more than one month.

If SHEP medications were prescribed at the last visit and have not been completely discontinued, then Item #104c asks about other changes in SHEP medication since the last visit. It should be noted here that we do not want to know about transient changes in SHEP medications (i.e., a temporary reduction for assessment of side effects), unless that change in medications lasts more than one month. Any other changes should prompt a "Yes" response to this last item, with an explanation in the space provided.

"Last visit" refers to the visit with the next previous sequence number, regardless of type, reason or place of visit.

Items #105a-b ask about other medications which may affect the participant's blood pressure. Medications considered as "open-label" medications are listed in Table 2-2--if you have medications that you are unsure about, please contact the Coordinating Center as soon as possible. If open-label antihypertensives were prescribed at the last visit (either from SHEP or another source), then Item #105a should be "Yes" and you should skip to Item #106a. If not, or you don't know, then we want to know if open-label drugs have been prescribed since the last visit.

Blood Pressure Review (Items #106a-b):

The blood pressure review section documents protocol requirements for given levels of blood pressure at the last few visits, as well as escape blood pressure levels. Space is provided for the participant's goal blood pressure, today's blood pressure and the blood pressure at the last visit, for ease of reference. Details on the use of the blood pressure chart can be found in Chapter 3 of this manual.

Items #106a-b refer specifically to escape blood pressures (listed on the blood pressure chart). These items should be skipped for participants already on OLT. If the chart does not indicate that the participant is in an escape blood pressure sequence at this visit, then "No" should be checked, and Item #106b should be skipped. If the participant is in escape blood pressure, then the specific escape blood pressure sequence should be listed in Item #106b. "Visit 1," "Visit 2," and "Visit 3" correspond with the same terms in the blood pressure chart, with "Visit 1" being the earliest applicable visit. For all SBP escape sequences, the Visit 3 data should be left blank. If only one blood pressure is involved (e.g., SBP ≧240 mm Hg), the Visit 2 and Visit 3 data should be left blank.

Items #107a-m review (1) why a participant will not be on SHEP blinded medications, or (2) if on SHEP medications, why the prescribed treatment regimen will not be used, and/or (3) why a participant will start or continue open-label antihypertensive therapy. This would include, for example, a step-down for possible or probable side effects, or a participant being on open-label medications for any reason (escape blood pressure, stroke, etc.), or the participant refusing SHEP medication altogether. If the participant will be prescribed SHEP medications at this visit and that SHEP medication prescription will follow the recommendation on the blood pressure chart (e.g., if a step up is required, that a step up is accomplished, etc.), Item #107a is "Yes." If the participant will not be prescribed SHEP medications or the SHEP medication treatment recommendation is not accomplished, Item #107a is "No." If the participant will remain on SHEP medications, but you don't have a SHEP blood pressure at this visit (e.g., on telephone visits), you have no way of determining the recommended treatment--check "DK" in this case.

If the participant will be prescribed open-label antihypertensives (from any source) at this visit, then Item #107b is "Yes." Check Table 2-2 for the list of medications considered as "open-label antihypertensives." If none of those medications will be prescribed, then Item #107b is "No." If you cannot determine whether or not the participant is being prescribed open-label medications, then check "DK." Be sure to differentiate between problems that the SHEP clinician thinks may be side effects to the SHEP medication, and problems which are probably not side effects in the SHEP clinician's judgment but are thought to be side effects by the participant. Also, use the following guidelines in differentiating between "other medical," "participant refusal/preference," and "PMD request":

Other medical--Any reason such as arrhythmias, diabetes, gout, cancer or any other medical reason that a participant may be on OLT or have some non-routine SHEP medication decision. Does not include stroke, MI, LVF, or angina (noted elsewhere). This would not include side effects to study meds (this is included elsewhere) and would not include high BP in PMD office. It would include conditions that contraindicate study meds.

Participant refusal/preference--Would not include medical reasons; would include cases where the decision or recommendation was made by the participant and not by SHEP or the PMD.

PMD request--Does not include medical reasons as stated above. Does not include stroke, MI, LVF, or angina (noted elsewhere). High BP in PMD office would be included here.

Medication Prescription and Scheduling (Items #108-112):

A medication decision should then be made considering all parts of the Medication and Scheduling section.

The medications prescribed at the last visit should be indicated in Items #108a-e. If the participant is prescribed a Step 1 or Step 2 drug, check those in Items #108a and/or c, and fill in the appropriate bottle numbers in #108b and/or d. For Item #108e(1), refer to the list of open-label drugs in Table 2-2. Any drug on that list will prompt a "Yes" response to that item, and Item #108e(2) should be answered. It is possible that some open-label drugs may be prescribed by SHEP, and another open-label drug could be prescribed by a private MD; in that case, be sure to check "both" for Item #108e(2). If the participant was prescribed a potassium supplement at the last visit, indicate "Yes" in Item #108f(1), and indicate the dose in meq/day in Item #108f(2) (if unknown, list "99"). Similarly, if the participant was prescribed a uric acid drug at the last visit, indicate "Yes" in Item #108g and indicate the drug and dose in the space underneath the item. If any of Items #108e(1) or #108f(1) or #108g are not known (e.g., on a telephone visit), be sure to check "DK" for those items.

If the medication prescription will not be altered at this visit, check "No change" in Item #109 and skip to Item #110. Otherwise, complete all of Items #109a-g (not just those medications that are changed), as directed above.

Item #110 indicates when the participant should return for their next visit--these are directed in the blood pressure chart. "Other" reflects the clinician's discretion option.

Comments on the medication and scheduling decision should be made as appropriate in Item #111. The person completing this section should sign the form and enter their SHEP ID code in Item #112.

Behavioral Evaluations

The SHEP SHORTCARE (SH30, SH36), the Activities of Daily Life (SH33), the Social Network (SH34), and the Behavioral Evaluation -- Part II (SH35) are required at all annual visits except telephone visits. These should be administered by a trained interviewer according to the SHEP Behavioral Evaluation Manual. It should be noted that the annual Behavioral Evaluation -- Part II may be deferred until the first required visit after the annual visit; if this evaluation is deferred more than one month, then also defer the SHORTCARE and Activities of Daily Life.

Review of Visit (Items 6-11 on page 1):

When all procedures have been completed for this visit, page 1 should be reviewed carefully before the participant leaves the clinic. In Item 6, each procedure should be marked as "done" or "not done"; procedures that are required but not done should be explained in Comments, Item 8.

Item 7 asks about possible procedures and forms which may be required as a result of this visit. If none are required, check the box labelled "None of 7a-7f required this visit" and skip to Comments, Item 8. Otherwise, check off those that are indicated. All of these should be completed, if possible, or at least scheduled before the participant leaves. If necessary, ask the participant to sign an authorization to obtain medical or hospital records.

In Item 8, space is provided for any comments on this visit.

The next clinic visit should then be scheduled using the guidelines to scheduling provided with the form and also referring to the participant's target windows provided by the Coordinating Center.

The participant should always be provided with their SHEP medications, an appointment card, including the date, time and place of the next visit, and a reminder to bring their SHEP and other medications with them to the next clinic visit.

At this point, the visit is complete and the time of day should be entered in Item 10.

The person reviewing this section should then sign and enter their two-digit code in Item 11.

2.6.4 Auxiliary Forms for the Annual Visit

SH10 -- SHEP ECG Coding Form - submit ECGs and two-minute rhythm strips at Year 2 and Year 5

SH11 -- Local Laboratory Results (use for hematology and dipstick urinalysis results, and other local laboratory procedures; do not use for results from the Central Laboratory)--use one SH11 for all local lab results for a visit.

SH30 -- SHEP SHORTCARE Form

SH36 -- SHORTCARE Scoring Sheet

SH33 -- Activities of Daily Life

SH34 -- Social Network

SH35 -- Behavioral Evaluation -- Part II

SH62 -- Pill Count Worksheet

MetPath Request Slip (Central Laboratory)

SHEP ANNUAL MEDICAL, MEDICATION AND HABITS HISTORY

This Space for Clinic Use Only

Name: _____

SHEP ID: [ ] - [ ] - [ ] Acrostic: [ ]

Date of next Clinic Visit: [ ] Month [ ] Day [ ] Year at [ ] Hour : [ ] Minute a.m. ☐ 1 p.m. ☐ 2

DEAR PARTICIPANT:

PLEASE FILL OUT THIS FORM AS COMPLETELY AS POSSIBLE AND BRING IT WITH YOU TO THE CLINIC VISIT SCHEDULED ABOVE. IF YOU DO NOT UNDERSTAND SOME OF THE QUESTIONS, LEAVE THEM BLANK UNTIL YOUR CLINIC VISIT. WE WILL REVIEW THE WHOLE FORM WITH YOU AT THAT TIME.

IN THE PAST YEAR, HAS A DOCTOR TOLD YOU THAT YOU HAD ANY OF THE FOLLOWING?

1.	High blood pressure severe enough to lead to hospitalization?	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
2.	Heart attack (myocardial infarction, coronary occlusion or coronary thrombosis)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
3.	Angina (chest pain)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
4.	Other heart problems	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
5.	Stroke (cerebrovascular accident, CVA)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
6.	Memory problems or other problems of the brain	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
7.	Diabetes (high blood or urine sugar)	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
8.	Gout	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
9.	Cancer	Yes ☐ 1	No ☐ 2	Don't know ☐ 3
10.	Other major diseases (specify):	Yes ☐ 1	No ☐ 2	Don't know ☐ 3

_____

(PLEASE TURN OVER)

11. a. How many days in the past two weeks have you had to substantially reduce your social activities outside the home (meetings, shopping) because you did not feel well? ☐☐

b. How many days in the past two weeks have you had to substantially reduce your major work activities at home (house cleaning, laundry) because you did not feel well? ☐☐

c. How many days in the past two weeks have you had to substantially reduce your ordinary activities at home (cooking, dressing) because you did not feel well? ☐☐

d. How many days in the past two weeks did you spend most of the day in bed because you did not feel well? ☐☐

12. a. In the past year, have you had any pain or discomfort in your chest? Yes ☐ 1 No ☐ 2

↓

Skip to 12c

b. In the past year, have you had any pressure or heaviness in your chest? Yes ☐ 1 No ☐ 2

↓

Skip to 13 (next page)

c. Do you get this pain, discomfort, pressure or heaviness when you walk uphill or hurry? Yes ☐ 1 No ☐ 2

↓

Skip to 13 (next page)

d. Do you get it when you walk at an ordinary pace on the level ground? Yes ☐ 1 No ☐ 2

e. What do you do when you get this pain while you are walking?

Stop or slow down ☐ 1
Continue at same pace ☐ 2

f. Does it go away when you stand still? Yes ☐ 1 No ☐ 2

↓

Skip to 12h (next page)

g. How soon?

10 minutes or less ☐ 1
More than 10 minutes ☐ 2

15. a. Do you get a pain in either leg on walking? Yes □ 1 No □ 2 ↓ Skip to 16

b. Does this pain ever begin when you are standing still or sitting? Yes □ 1 No □ 2

c. Do you get this pain in your calf? (or calves?) Yes □ 1 No □ 2

d. Do you get it when you walk uphill or hurry? Yes □ 1 No □ 2 ↓ Skip to 16

e. Do you get it when you walk at an ordinary pace on the level ground? Yes □ 1 No □ 2

f. Does this pain ever disappear while you are still walking? Yes □ 1 No □ 2

g. What do you do if you get it when you are walking? Stop or slow down □ 1 Continue at same pace □ 2

h. Does it go away when you stand still? Yes □ 1 No □ 2 ↓ Skip to 16

i. How soon? 10 minutes or less □ 1 More than 10 minutes □ 2

---

16. a. Do you usually cough first thing in the morning in the winter? (If you cough with your first smoke or when first going outside, you should mark "yes." Do not respond "yes" for clearing of throat or a single cough.) Yes □ 1 No □ 2 ↓ Skip to 16c

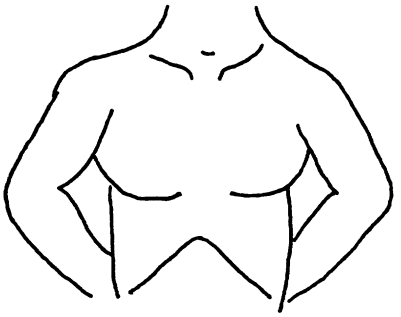
b. Do you usually cough during the day or at night in the winter? (Do not respond "yes" for a single cough.) Yes □ 1 No □ 2 ↓ Skip to 17 (next page)

c. Do you cough like this on most days for as much as 3 months each year? Yes □ 1 No □ 2

d. Do you usually bring up any phlegm (mucus) from your chest first thing in the morning in the winter? Yes □ 1 No □ 2

h. Where do you get this pain or discomfort?
(Mark the places with an "X" on the diagram.)

RIGHT SIDE



LEFT SIDE

Do not use--clinic use only.

(1)	Yes ☐ 1	No ☐ 2
(2)	Yes ☐ 1	No ☐ 2
(3)	Yes ☐ 1	No ☐ 2

---

13. In the past year, have you had a severe pain across the front of your chest lasting for half an hour or more? Yes ☐ 1 No ☐ 2

---

14. a. Have you had a heart attack (myocardial infarction, coronary thrombosis) in the past year? Yes ☐ 1 No ☐ 2 Don't know ☐ 3

↓ ↓

Skip to 15 (next page)

b. Were you hospitalized for any heart attacks in the past year? Yes ☐ 1 No ☐ 2

c. How many such attacks have you had? ☐☐

d. What were the dates of these heart attacks? (month/year) _____

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SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ Acrostic: ☐☐☐☐☐☐

(PLEASE TURN OVER)

e. Do you usually bring up any phlegm from your chest during the day or at night in the winter? Yes ☐ 1 No ☐ 2 ↓ Skip to 17

f. Do you bring up phlegm like this on most days for as much as 3 months each year? Yes ☐ 1 No ☐ 2

g. In the past year, have you had a period of increased cough and phlegm lasting for 3 weeks or more? Yes, once ☐ 1 Yes, more than once ☐ 2 No ☐ 3

---

17. a. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? Yes ☐ 1 No ☐ 2

b. Do you get short of breath walking with other people of your own age on level ground? Yes ☐ 1 No ☐ 2

c. Do you ever wake up at night gasping for breath? Yes ☐ 1 No ☐ 2

d. Do you get short of breath at night unless you sleep on two or more pillows? Yes ☐ 1 No ☐ 2

e. Have you ever had asthma? Yes ☐ 1 No ☐ 2 ↓ Skip to 18 (next page)

f. Have you had any asthma attacks in the past year? Yes ☐ 1 No ☐ 2

g. Do you take medication to control or treat asthma? Yes ☐ 1 No ☐ 2

Clinic Use Only

SHEP ID: [ ] - [ ] - [ ] Acrostic: [ ]

(PLEASE TURN OVER)

18. a. In the past year, have you had any sudden feeling of numbness, tingling or loss of feeling in either arm, hand, leg, foot or face?

Yes ☐ 1 No ☐ 2

↓

Skip to 19

b. How many attacks of such numbness or tingling have you had in the past year? (Check one.)

Only one	☐ 1
Two	☐ 2
Three to five	☐ 3
More than five	☐ 4

c. How long did each of the attack(s) usually last?

Less than 5 minutes	☐ 1
From 5 minutes to one hour	☐ 2
From 1-6 hours	☐ 3
From 6-24 hours	☐ 4
More than 24 hours	☐ 5

d. Did you see a doctor for the numbness, tingling, or loss of feeling?

Yes ☐ 1 No ☐ 2

---

19. a. In the past year, have you had any sudden attacks of paralysis or loss of use of either arm, hand, leg or foot?

Yes ☐ 1 No ☐ 2

↓

Skip to 20 (next page)

b. How many attacks of such paralysis have you had in the past year? (Check one.)

Only one	☐ 1
Two	☐ 2
Three to five	☐ 3
More than five	☐ 4

c. How long did the attack(s) usually last?

Less than 5 minutes	☐ 1
From 5 minutes to one hour	☐ 2
From 1-6 hours	☐ 3
From 6-24 hours	☐ 4
More than 24 hours	☐ 5

d. Did you see a doctor for this paralysis?

Yes ☐ 1 No ☐ 2

---

20. a. In the past year, have you had any sudden loss of eyesight or blurring of vision for a short period of time?

Yes ☐ 1 No ☐ 2 ↓

Skip to 21

b. What part of your vision was affected?

Right eye only	☐ 1
Left eye only	☐ 2
Both eyes	☐ 3
Vision to the right side	☐ 4
Vision to the left side	☐ 5

c. How many attacks of loss of eyesight or blurring of vision have you had in the past year?

Only one	☐ 1
Two	☐ 2
Three-five	☐ 3
More than five	☐ 4

d. How long did the attack(s) usually last?

Less than 5 minutes	☐ 1
From 5 minutes to one hour	☐ 2
From 1-6 hours	☐ 3
From 6-24 hours	☐ 4
More than 24 hours	☐ 5

e. Did you see a doctor for this vision problem? Yes ☐ 1 No ☐ 2

---

21. a. In the past year, have you had any sudden attacks of changes in speech, loss of speech or inability to say words?

Yes ☐ 1 No ☐ 2 ↓

Skip to 22 (next page)

b. How many attacks of loss of speech have you had in the past year?

Only one	☐ 1
Two	☐ 2
Three-five	☐ 3
More than five	☐ 4

c. How long did the attack(s) usually last?

Usually less than 5 minutes	☐ 1
From 5 minutes to one hour	☐ 2
From 1-6 hours	☐ 3
From 6-24 hours	☐ 4
More than 24 hours	☐ 5

d. Did you see a doctor for your speech problem? Yes ☐ 1 No ☐ 2

Clinic Use Only

SHEP ID: [ ] - [ ] - [ ] Acrostic: [ ]

(PLEASE TURN OVER)

22. In the past year, have you had any of the following:

a.	Dizziness	Yes ☐ 1	No ☐ 2
b.	Spinning sensation (vertigo)	Yes ☐ 1	No ☐ 2
c.	Loss of balance	Yes ☐ 1	No ☐ 2
d.	Difficulty walking	Yes ☐ 1	No ☐ 2
e.	Blackouts or fainting	Yes ☐ 1	No ☐ 2
f.	Frequent falls	Yes ☐ 1	No ☐ 2

23. a. Did you answer "yes" to any of the problems in Question 22? Yes ☐ 1 No ☐ 2 ↓

Skip to 24

b. About how many total attacks of all conditions checked do you think you had in the past year?

- Only one ☐ 1
- Two ☐ 2
- Three-five ☐ 3
- More than five ☐ 4

c. How long did the attack(s) usually last?

- Usually less than 5 minutes ☐ 1
- From 5 minutes to one hour ☐ 2
- From 1-6 hours ☐ 3
- From 6-24 hours ☐ 4
- More than 24 hours ☐ 5

d. Did you see a doctor for any of these spells? Yes ☐ 1 No ☐ 2

---

24. a. In the past year, have you had surgery to improve the blood flow in your arteries or vessels (endarterectomy, by-pass surgery)? (Do not include surgery for varicose veins.) Yes ☐ 1 No ☐ 2 ↓

Skip to 25 (next page)

b. Did you have surgery on your neck vessels (carotid artery)? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

c. Did you have surgery on your heart (coronary by-pass)? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

d. Did you have surgery on the aorta or leg arteries? Yes ☐ 1 No ☐ 2

Date(s) of surgery _____

---

25. a. Have you been hospitalized for any reason within the past year? Yes ☐ 1 No ☐ 2

Skip to 26

b. List the reason, the name and address of the hospital, and the month and year of the hospitalization.

	Reason	Month/Year	Name of Hospital, City and State
(1)			
(2)			
(3)			
(4)			
(5)			

(If more than 5 hospitalizations, list rest on a blank sheet of paper.)

26. In the past year, have you had a fracture of the:

a. Hip? Yes ☐ 1 No ☐ 2
When? _____

b. Spine? Yes ☐ 1 No ☐ 2
When? _____

c. Forearm? Yes ☐ 1 No ☐ 2
When? _____

Clinic Use Only

SHEP ID: ☐ - ☐☐☐☐ - ☐ Acrostic: ☐☐☐☐☐☐☐

(PLEASE TURN OVER)

27. a. About how many times would you say that you have fallen to the floor or ground for no obvious reason in the past three months?

None	☐ 1
Once	☐ 2
Twice	☐ 3
Three times	☐ 4
Four or five times	☐ 5
More than five times	☐ 6
Don't know	☐ 7

If "None," skip to 28

b. Did you have any injury from those falls that required a doctor's attention? Yes ☐ 1 No ☐ 2 Don't know ☐ 3

Describe injury: _____

---

28. Has any medicine you may be taking, or have taken in the past year, ever caused you to have a skin rash or other kind of allergic reaction? Yes ☐ 1 No ☐ 2

Describe medicine, reaction and circumstances:

_____

_____

_____

PERSONAL INFORMATION:

29. a. Which of the following most closely describes your current employment status?

Employed full time	☐ 1
Employed part time	☐ 2
Retired or not employed	☐ 3

b. If retired, in what month and year did you retire from your last paid employment (20 hours per week or more)?

Month ☐☐ Year ☐☐

30. What is your current marital status?

Married	☐ 1
Widowed	☐ 2
Separated	☐ 3
Divorced	☐ 4
Never married	☐ 5

31. a. Do you currently smoke cigarettes? Yes ☐ 1 No ☐ 2 ↓

Skip to 32 (next page)

b. How many do you now smoke per day? ☐☐

32. a. Which answer best describes how often you drink wine, beer, whiskey or liquor? (Check one.)

- Never drank ☐ 1
- I used to drink, but don't drink now ☐ 2
- 1 or 2 times a year or very occasionally ☐ 3
- Less than one per week or only at parties ☐ 4
- 1 to 2 times a week ☐ 5
- 3 to 4 times a week ☐ 6
- Nearly every day ☐ 7
- Every day ☐ 8

b. When you drink alcoholic beverages, how many do you usually drink in a day? (One drink = 1 can of beer, or a glass of wine or 1 shot of whiskey or liquor) ☐☐

33. a. Are you taking any medicines that require a prescription from a doctor? Yes ☐ 1 No ☐ 2 ↓

Skip to 34 (next page)

Name all of the medicines that are being prescribed for you by a doctor or a clinic.

	Medicine Name	What illness is medicine for?
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

b. Total number of prescription medicines being taken ☐☐

Clinic Use Only

SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ Acrostic: ☐☐☐☐☐☐☐☐

(PLEASE TURN OVER)

34. Have you stopped taking any prescription medications in the past two weeks?

Yes ☐ 1 No ☐ 2

↓

Skip to 35 (next page)

Please list them below

	Medicine Name	What illness is medicine for?
1.	_____	
2.	_____	
3.	_____	

Why did you stop taking the medicines?

Medicine No. 1		Check if Yes
1.	The doctor advised me to stop	☐ 1
2.	The prescription ran out	☐ 1
3.	I felt better	☐ 1
4.	I couldn't remember to take them	☐ 1
5.	I couldn't be bothered	☐ 1
6.	They made me feel sick	☐ 1
7.	I didn't think they were working	☐ 1
8.	A friend told me to stop	☐ 1
9.	Don't know	☐ 1
10.	Other:	☐ 1

_____

_____

Medicine No. 2		Check if Yes
1.	The doctor advised me to stop	☐ 1
2.	The prescription ran out	☐ 1
3.	I felt better	☐ 1
4.	I couldn't remember to take them	☐ 1
5.	I couldn't be bothered	☐ 1
6.	They made me feel sick	☐ 1
7.	I didn't think they were working	☐ 1
8.	A friend told me to stop	☐ 1
9.	Don't know	☐ 1
10.	Other:	☐ 1

_____

_____

Medicine No. 3		Check if Yes
1.	The doctor advised me to stop	☐ 1
2.	The prescription ran out	☐ 1
3.	I felt better	☐ 1
4.	I couldn't remember to take them	☐ 1
5.	I couldn't be bothered	☐ 1
6.	They made me feel sick	☐ 1
7.	I didn't think they were working	☐ 1
8.	A friend told me to stop	☐ 1
9.	Don't know	☐ 1
10.	Other:	☐ 1

_____

_____

35. a. Are you presently taking any medicines or diet supplements that you buy in a drugstore, supermarket or health food store without a prescription?
For example, aspirin, laxatives, vitamins, antacids.

Yes ☐ 1 No ☐ 2 ↓

Skip to 36 (next page)

What kind?

	Brand Name	What illness do take it for?
1.		
2.		
3.		
4.		
5.		

(If more than 5, list on a blank sheet of paper.)

b. Total number of non-prescription medicines being taken ☐☐

Clinic Use Only

SHEP ID: ☐☐☐ - ☐☐☐☐ - ☐☐ Acrostic: ☐☐☐☐☐☐☐

(PLEASE TURN OVER)

36. What are your current living arrangements? (Check all that apply.)

a.	Living alone (skip to 37)	☐ 1
b.	Living with spouse	☐ 1
c.	Living with other related individuals	☐ 1
d.	Living with non-related friends	☐ 1
e.	Living with non-related paid help	☐ 1

37. a. In the past year, have you changed where you go for medical care? Yes ☐ 1 No ☐ 2

b. If yes, would you object to us sending your blood pressure results to the person or clinic that usually supplies your health care?

Yes	☐ 1
No	☐ 2
Don't know	☐ 3
I do not have a personal physician or clinic that supplies health care	☐ 4

New Clinic Name or Doctor: _____

Address: _____

_____

Telephone: _____

Thank you for completing this form. Please remember to bring this form and any prescription medications that you are now taking with you for your clinic visit which is scheduled on the date shown on the front page.

SHEP ANNUAL CLINIC VISIT

1. SHEP ID: [ ] - [ ] - [ ] 2. Acrostic: [ ]

3. a. Today's Date: [ ] Month [ ] Day [ ] Year b. Seq. #: [ ] c. Year (1-6): [ ]

4a. Place of visit:
- 1 ☐ Clinic (skip to 5)
- 2 ☐ Home (skip to 5)
- 3 ☐ Telephone (skip to 5)
- 4 ☐ No visit

b. Vital status:
- 1 ☐ Alive
- 2 ☐ Dead
- 3 ☐ Unknown

5. Time visit begins: [ ]:[ ] 1 ☐ a.m. 2 ☐ p.m.

PRIOR TO INITIATING PROCEDURES FOR THIS VISIT

☐ Collect, complete and review take-home Annual Medical and Medication and Habits History, SH44

☐ Review and update original Participant Information Sheet, SH02

COMPLETE THE SECTION BELOW AT THE TERMINATION OF THIS VISIT BEFORE PARTICIPANT LEAVES; BE SURE THAT EVERY ITEM ON EACH PAGE IS COMPLETE AND LEGIBLE. THE SHEP ID AND ACROSTIC SHOULD MATCH THOSE ON THE SH06. CHECK YELLOW COPY FOR LEGIBILITY, ALSO. ANY ITEM THAT IS NOT COMPLETE ON THIS FORM, OR REQUIRED BUT NOT DONE, SHOULD BE EXPLAINED IN COMMENTS, ITEM 8.

Procedure		Auxiliary Form	Comment	Done this Visit?
6. a.	Annual Medical and Medication and Habits History	SH44		Yes ☐ 1 No ☐ 2
b.	ECG and two-minute rhythm strip [1,2]	SH10	Year 2 and Final Annual only	Yes ☐ 1 No ☐ 2
c.	Dipstick urinalysis, local [1,2]	SH11		Yes ☐ 1 No ☐ 2
d.	Blood sample, local [1,2]	SH11	Hematology required; also, local re-check of Central Laboratory results; as required in clinician's judgment.	Yes ☐ 1 No ☐ 2
e.	Fasting blood sample, central [1,2]		Year 1, Year 3, and Year 4	Yes ☐ 1 No ☐ 2
f.	Non-fasting blood sample, central [1,2]		Years 2 and 5; allowed at Years 1, 3, and 4 if fasting sample not possible.	Yes ☐ 1 No ☐ 2
g.	SHORTCARE/CES-D [2]	SH30, SH36		Yes ☐ 1 No ☐ 2
h.	Activities of Daily Life [2]	SH33		Yes ☐ 1 No ☐ 2
i.	Social Network [2]	SH34		Yes ☐ 1 No ☐ 2
j.	Behavioral Evaluation--Part II[2]	SH35	May be deferred until next required visit. If deferred, also defer SHORTCARE and Activities of Daily Life.	Yes ☐ 1 No ☐ 2

[1] May omit for home visits.
[2] May omit for telephone visits; SH33 and SH34 should be completed if participant is willing.

7. Action required as a result of this visit: 1 ☐ None of 7a-7f required
   - a. 1 ☐ Initial Notification of Morbid Event, SH20
   - b. 1 ☐ SHEP Neurological Evaluation for Strokes, SH27
   - c. 1 ☐ SHEP Neurological Evaluation for TIA, SH28
   - d. 1 ☐ Dementia Referral, SH31
   - e. 1 ☐ Depression Referral, SH32
   - f. 1 ☐ Report of Unblinding, SH49

8. Comments on this visit: _____

9. Next clinic visit: [ ] Month [ ] Day [ ] Year at [ ]:[ ] Hour Minute 1 ☐ a.m. 2 ☐ p.m.

10. Time visit is completed: [ ]:[ ] 1 ☐ a.m. 2 ☐ p.m.

11. Signature of person reviewing this page: _____ [ ] Code

PULSE AND BLOOD PRESSURE--If any pulse or blood pressure is not obtained, enter all 9s in the appropriate spaces. If this is a telephone visit, complete only items 12d and 12e; leave cuff size and Item 12c blank.

12. a. Pulse: Beats in 30 seconds _____ x 2 = [ ] beats per minute.

b. Cuff Size:

1 ☐ Regular
2 ☐ Large arm
3 ☐ Thigh
4 ☐ Pediatric

Pulse Obliteration Pressure:

Observed Value: [ ]
Subtract Zero Level: - [ ]
Corrected Value: [ ]
Add Maximum Zero Level Plus 20: + [ ]
Peak Inflation Level: [ ]

Seated Readings:

	Systolic	Diastolic
First	[ ]	[ ]
Zero level	[ ]	[ ]
Corrected	[ ]	[ ]
+ Second	[ ]	[ ]
+ Zero level	[ ]	[ ]
+ Corrected	[ ]	[ ]
Sum of two corrected readings	[ ]	[ ]
Average of two corrected readings	[ ]	[ ]

Standing Readings:

One minute

Pulse: Beats in 15 seconds _____
x 4 = [ ] beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	[ ]	[ ]
Zero	[ ]	[ ]
Corrected	[ ]	[ ]

Three minutes

Pulse: Beats in 15 seconds _____
x 4 = [ ] beats per minute.

Blood Pressure:	Systolic	Diastolic
Reading	[ ]	[ ]
Zero	[ ]	[ ]
Corrected	[ ]	[ ]

(If standing blood pressure not done, skip to 12e.)

c. Did the participant volunteer any symptoms on standing? Yes ☐ 1 No ☐ 2

(1) Dizziness? Yes ☐ 1 No ☐ 2
(2) Other (specify)? Yes ☐ 1 No ☐ 2
_____

↓
SKIP to 12e.

d. To the participant, for telephone visits only:

Since the last time that you came to the SHEP clinic, have your had your blood pressure taken? Yes ☐ 1 No ☐ 2 DK ☐ 3

↓ No → Skip to 12e.

When was the last time? ☐☐ Month ☐☐ Year

What was your blood pressure at that time? (Interviewer: If participant does not know last blood pressure, fill in with 9s.) ☐☐☐ SBP ☐☐☐ DBP

e. Observer: _____ ☐☐ Code

PARTICIPANT SHOULD NOW BE SENT FOR ECG AND TWO-MINUTE RHYTHM STRIP, URINE SAMPLES, AND BLOOD SAMPLES, IN THAT ORDER, AS REQUIRED AT THIS ANNUAL VISIT. CHECK PAGE 1 FOR REQUIRED PROCEDURES.

COMPLIANCE EVALUATION--If participant was not prescribed any of the SHEP medications at last visit, skip to 24.

---

13. Have you missed taking your SHEP medicines anytime in the past 7 days? Yes ☐ 1 No ☐ 2

↓ No → Go to 17.

14. Which days did you miss? (Circle days mentioned.)

M T W ~~Th~~ F S S → Total days missed ☐

15. Why did you miss taking the medicines?
(Push for answers, but do not mention specific categories.)

		Mentioned	Not Mentioned
a.	Wasn't feeling well	1 ☐	2 ☐
b.	Medicine made participant ill (Specify) _____	1 ☐	2 ☐
c.	Just forgot	1 ☐	2 ☐
d.	Away from home/didn't have medicine	1 ☐	2 ☐
e.	Ran out of medicine	1 ☐	2 ☐
f.	Didn't want to take (Reason) _____	1 ☐	2 ☐
g.	Doctor (usual source of care) told me to stop	1 ☐	2 ☐
h.	Other (Specify) _____	1 ☐	2 ☐

16. What did you do when you missed taking your SHEP medicines?
(Push for answers, but do not provide specific categories.)

		Mentioned	Not Mentioned
a.	Waited and doubled up the next dose	1 ☐	2 ☐
b.	Did nothing/took usual dose next time	1 ☐	2 ☐
c.	Reports missed dose(s) at next clinic visit	1 ☐	2 ☐
d.	Called SHEP clinic	1 ☐	2 ☐
e.	Recorded missed dose(s)	1 ☐	2 ☐
f.	Took it later	1 ☐	2 ☐
g.	Other (specify) _____	1 ☐	2 ☐

If participant is not currently being prescribed C1 or C2, skip to 20.

17. How many times a day do you take your C1/C2?
(Interviewer: Circle correct Step 1 drug.)

Every other day ☐ 1
Once per day ☐ 2
Other_____ ☐ 3
(Specify)

18. How many do you take each time?

One ☐ 1
Other_____ ☐ 2
(Specify)

19. When do you take it?

Morning when getting up ☐ 1
Other _____ ☐ 2
(Specify)

If participant is not currently being prescribed A1, A2 or R, skip to 23.

20. How many times a day to your take your A1/A2/R?
(Interviewer: Circle correct Step 2 drug.)

Once per day ☐ 1
Twice per day ☐ 2
Other_____ ☐ 3
(Specify)

21. How many do you take each time?

One ☐ 1
Other_____ ☐ 2
(Specify)

22. When do you take it?

Morning when getting up ☐ 1
Morning when getting up, and late afternoon or bedtime ☐ 2
Other _____ ☐ 3
(Specify)

Item 23 for interviewer only. Skip pill count for home and telephone visits.

23. a. Was a pill count done at this visit?

Yes ☐ 1 No ☐ 2 ↓

Skip to 24.

b. Step 1 result: ____ . ____ %

c. Step 2 result: ____ . ____ %

If participant reports missing doses, or pill count result (if done) is less than 80% for either Step 1 or Step 2, or participant is not taking drugs properly, reinforce instructions on how to take SHEP medications.

Interviewer: Questions in this section may be rephrased; use phraseology that you are comfortable with.

24. Have you felt unwell in any way since your last clinic visit; has anything been bothering you? (Specify): _____ Yes ☐ 1 No ☐ 2 → Go to 26.

25. Are any of these problems different from the way things were at your last clinic visit? Yes ☐ 1 No ☐ 2

26. Since your last visit, have you seen a doctor for any reason? (Specify): _____ Yes ☐ 1 No ☐ 2

27. Since your last visit, have you been in the hospital for any reason? Yes ☐ 1 No ☐ 2 → Go to 28.

How many times? ☐

When? (Start with the first one after your last visit.)

(If more than 3 hospitalizations, list rest on blank sheet of paper.)

	Hospitalization #1	Hospitalization #2	Hospitalization #3
Hospital name			
Date of admission	☐☐ Month ☐☐ Day ☐☐ Year	☐☐ Month ☐☐ Day ☐☐ Year	☐☐ Month ☐☐ Day ☐☐ Year
Number of days	☐☐	☐☐	☐☐
Reason			

28. Since your last SHEP visit, have you been told by a doctor or otherwise learned that you may have had a stroke? Yes ☐ 1 No ☐ 2

29. Thinking about the other medications that you might be taking now, or have taken since your last visit:

a. Have you stopped taking any medications? (Specify): _____ Yes ☐ 1 No ☐ 2

b. Have you increased or decreased any medications that you were taking? (Specify): _____ Yes ☐ 1 No ☐ 2

c. Have you started taking any new medications? (Specify): _____ Yes ☐ 1 No ☐ 2

30. Interviewer: Did the participant bring all non-SHEP medications to the clinic at this visit? Yes ☐ 1 No ☐ 2 Not on any non-SHEP medications ☐ 3

POSSIBLE SIDE EFFECTS--May not be re-phrased. If the participant has been off of SHEP medications more than six months, skip to Item 63.

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
31. Unusual coldness or numbness of the hands or feet?	Yes □ 1 → No □ 2					
32. Unusual skin rash or bruising?	Yes □ 1 → No □ 2					→ (f) Is an acute skin rash present on physical exam? Yes □ 1 Possibly □ 2 No □ 3
33. Any feelings of unsteadiness or imbalance?	Yes □ 1 → No □ 2					
34. Faintness or light headedness when you stand up quickly?	Yes □ 1 → No □ 2					→ (f) Is there an observable postural drop in blood pressure? Yes □ 1 No □ 2
35. Loss of consciousness or passing out	Yes □ 1 → No □ 2					
36. Falls?	Yes □ 1 → No □ 2					
37. Fractures?	Yes □ 1 → No □ 2					→ (f) Hip? Yes □ 1 No □ 2 (g) Spine? Yes □ 1 No □ 2 (h) Forearm? Yes □ 1 No □ 2
38. Unusual pain in any joint?	Yes □ 1 → No □ 2					→ (f) Are there physical signs of acute arthritis? Yes □ 1 Possibly □ 2 No □ 3
39. Muscle weakness or cramping?	Yes □ 1 → No □ 2					
40. Excessive thirst?	Yes □ 1 → No □ 2					
41. Loss of appetite?	Yes □ 1 → No □ 2					
42. Nausea or vomiting?	Yes □ 1 → No □ 2					
43. Unusual indigestion?	Yes □ 1 → No □ 2					
44. Change in bowel habits?	Yes □ 1 → No □ 2					

POSSIBLE SIDE EFFECTS (Continued)--May not be re-phrased.

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
45. Tarry black stools or red blood in the stools?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
46. Heart beating unusually fast or skipping beats?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
47. Heart beating unusually slow?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	→ (f) Is an arrhythmia present on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
48. Episodes of chest pain or heaviness in the chest?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
49. Headaches so bad you had to stop what you were doing?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
50. Stuffy nose?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
51. Unusual shortness of breath or wheezing?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	→ (f) Is there evidence for bronchospasm on auscultation of the chest? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
52. Unusual tiredness or loss of pep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
53. Swelling of the ankles?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	→ (f) Is there evidence of CHF on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
54. Feeling so depressed (sad or blue) that it interfered with your work, recreation or sleep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
55. Any trouble with your memory or concentration?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
56. Nightmares?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	

POSSIBLE SIDE EFFECTS (Continued)--May not be re-phrased.

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
57. Any changes in your sexual activity?	Yes □ 1 → No □ 2	☐	☐	☐	☐ →	(f) Loss of interest Yes □ 1 No □ 2 (g) Decline in frequency? Yes □ 1 No □ 2 (h) Loss of enjoyment? Yes □ 1 No □ 2 (i) Functional impairment? Yes □ 1 No □ 2
58. Trouble going to sleep, or waking early and having trouble getting back to sleep?	Yes □ 1 → No □ 2	☐	☐	☐	☐	
59. Waking up in the night more frequently to urinate?	Yes □ 1 → No □ 2	☐	☐	☐	☐	
60. More worry or anxiety than usual?	Yes □ 1 → No □ 2	☐	☐	☐	☐	
61. Weakness or numbness on one side, or unexpected difficulties talking or thinking?	Yes □ 1 → No □ 2	☐	☐	☐	☐ →	(f) Is there evidence of a stroke on physical exam? Yes □ 1 Possibly □ 2 No □ 3
62. Other relevant symptoms: Specify: _____ _____ _____	Yes □ 1 → No □ 2	☐	☐	☐	☐ →	(f) Are there other relevant signs on physical exam? Yes □ 1 Possibly □ 2 No □ 3 Specify: _____ _____

CLINICIAN REVIEW OF MEDICATION HISTORY--To be completed by clinician using information from the Annual Medical and Medication and Habits History, SH44. Medications may fit into more than one category.

63. Is the participant taking any of the drugs listed below?

		Current (last 2 weeks)	Not Current or Not Sure
a.	Any medication for blood pressure, or any drugs with antihypertensive action (see list in Manual of Operations)	□ 1	□ 2
b.	Digitalis	□ 1	□ 2
c.	Nitrates, including nitroglycerine, or other coronary vasodilator	□ 1	□ 2
d.	Propranolol or other beta blockers for other than treatment of blood pressure (excluding eye drops containing beta-blockers)	□ 1	□ 2
e.	Eye drops containing beta-blockers	□ 1	□ 2
f.	Anti-arrhythmic drugs	□ 1	□ 2
g.	HMG CoA reductase inhibitors (e.g., Lovastatin, Mevicor)	□ 1	□ 2
h.	Other lipid-lowering drugs, including clofibrate, cholestryramine, colestipol, nicotinic acid, etc.	□ 1	□ 2
i.	Agents for gout, including probenecid, allopurinol or colchicine	□ 1	□ 2
j.	Insulin	□ 1	□ 2
k.	Oral hypoglycemic agents	□ 1	□ 2
l.	Anticoagulants	□ 1	□ 2
m.	Antibiotics or anti-infection agents	□ 1	□ 2
n.	Cortisone or other gluco corticoids	□ 1	□ 2
o.	Amphetamines or other stimulant	□ 1	□ 2
p.	Flurazepam or other sedative	□ 1	□ 2
q.	Anti-depressants	□ 1	□ 2
r.	Librium, valium or other antianxiety agents	□ 1	□ 2
s.	Other psychotropic agents	□ 1	□ 2
t.	Potassium supplementation other than dietary recommendations	□ 1	□ 2
u.	Estrogen	□ 1	□ 2
v.	Anturane® (Sulfinpyrazone) at least 4 weeks	□ 1	□ 2
w.	Persantine® (Dipyridamole) at least 4 weeks	□ 1	□ 2
x.	Aspirin at least 4 weeks	□ 1	□ 2
y.	Non-steroidal anti-inflammatory drugs	□ 1	□ 2
z.	Any experimental drug	□ 1	□ 2

PHYSICAL EXAMINATION--The clinician should perform a general physical examination, paying particular attention to the specific items listed below, entering comments for each indicated abnormality. For home and telephone visits, the participant should be asked to estimate their own height and weight; the remainder of the physical examination may be omitted.

64. Weight in pounds: [, ,] 65. Height in inches: [,]

	Area Examined		Comments
66.	SKIN	Abnormal □ 1 Normal □ 2	
67.	HEAD, EARS, NOSE, THROAT	Abnormal □ 1 Normal □ 2	
68.	EYES Fundi: Other (Specify)?	a. Abnormal □ 1 Normal □ 2 Not Visualized □ 3 b. Yes □ 1 No □ 2	

PHYSICAL EXAMINATION (Continued)

	Area Examined			Comments
69.	NECK			
	Raised jugular venous pressure?	a.	Yes ☐ 1 No ☐ 2	
	Carotid bruits?	b.	Yes ☐ 1 No ☐ 2 ↓	
		c.	Right only ☐ 1 Left only ☐ 2 Bilateral ☐ 3	
	Carotid pulses absent or markedly diminished?	d.	Yes ☐ 1 No ☐ 2 ↓	
		e.	Right only ☐ 1 Left only ☐ 2 Bilateral ☐ 3	
	Thyroid abnormality?	f.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	g.	Yes ☐ 1 No ☐ 2	
70.	LYMPH NODES		Abnormal ☐ 1 Normal ☐ 2	
71.	CHEST, LUNGS			
	Bilateral rales that do not clear with coughing?	a.	Yes ☐ 1 No ☐ 2	
	Respiratory rate 20+?	b.	Yes ☐ 1 No ☐ 2	
	Wheezing?	c.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	d.	Yes ☐ 1 No ☐ 2	
72.	HEART			
	PMI more than 2 centimeters lateral to midclavicular line?	a.	Yes ☐ 1 No ☐ 2	
	Any murmur?	b.	Yes ☐ 1 No ☐ 2	
	Third heart sound?	c.	Yes ☐ 1 No ☐ 2	
	Fourth heart sound?	d.	Yes ☐ 1 No ☐ 2	
	Pulse irregular?	e.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	f.	Yes ☐ 1 No ☐ 2	
73.	BREASTS		Abnormal ☐ 1 Normal ☐ 2	
74.	ABDOMEN			
	Liver span 10 cm or more?	a.	Yes ☐ 1 No ☐ 2	
	Abnormal abdominal pulse?	b.	Yes ☐ 1 No ☐ 2	
	Any masses?	c.	Yes ☐ 1 No ☐ 2	
	Bruit?	d.	Yes ☐ 1 No ☐ 2	
	Other (Specify)?	e.	Yes ☐ 1 No ☐ 2	

Area Examined			Comments
75. EXTREMITIES			
Pitting ankle edema?	a.	Yes □ 1 No □ 2	
Femoral bruit?	b.	Yes □ 1 No □ 2	
Any peripheral pulses absent or markedly diminished (specify location)?	c.	Yes □ 1 No □ 2	
Other (Specify)?	d.	Yes □ 1 No □ 2	
76. NEUROLOGICAL (UA = unable to assess)			
Gait			
Left hemiparetic?	a.	Yes □ 1 No □ 2 UA □ 3	
Right hemiparetic?	b.	Yes □ 1 No □ 2 UA □ 3	
Walking on toes			
Left weakness?	c.	Yes □ 1 No □ 2 UA □ 3	
Right weakness?	d.	Yes □ 1 No □ 2 UA □ 3	
Walking on heels			
Left weakness?	e.	Yes □ 1 No □ 2 UA □ 3	
Right weakness?	f.	Yes □ 1 No □ 2 UA □ 3	
Stationary 30 seconds			
Eyes closed?	g.	Can do □ 1 Cannot do □ 2 UA □ 3	
Eyes open (only if unable to do with eyes closed)	h.	Can do □ 1 Cannot do □ 2 UA □ 3	
Cranial nerves			
Facial weakness left?	i.	Yes □ 1 No □ 2 UA □ 3	
Facial weakness right?	j.	Yes □ 1 No □ 2 UA □ 3	
Visual field deficit			
Left side?	k.	Yes □ 1 No □ 2 UA □ 3	
Right side?	l.	Yes □ 1 No □ 2 UA □ 3	
Motor wrist extensors			
Weakness left?	m.	Yes □ 1 No □ 2 UA □ 3	
Weakness right?	n.	Yes □ 1 No □ 2 UA □ 3	
Coordination			
Left hand patting?	o.	Slowed □ 1 Normal □ 2 UA □ 3	
Right hand patting?	p.	Slowed □ 1 Normal □ 2 UA □ 3	
Reflexes			
Assymetry of Patellar tendon	q.	L>R □ 1 Equal □ 3 R>L □ 2 UA □ 4	
Babinski sign left?	r.	Yes □ 1 No □ 2 UA □ 3	
Babinski sign right?	s.	Yes □ 1 No □ 2 UA □ 3	
Other			
Any speech or language problems (specify)?	t.	Yes □ 1 No □ 2	

77. OTHER PHYSICAL FINDINGS (SPECIFY):

78. Clinician's signature: _____ Code

CLINICIAN'S JUDGMENT AND ENDPOINT REVIEW--To be completed by the clinician using information from the participant's history and from the physical examination. These are clinical data for study endpoint determination as well as analysis at the Coordinating Center and they should reflect the clinician's interpretation of the findings. The study endpoint questions are identified with ⊛. These questions must all be covered prior to termination of this visit. Pertinent items on the Medical History (SH44) are listed with the section headings. The "DK" option should be used only for home and telephone visits when pertinent information is not available.

Angina Pectoris - SH44 Items 3, 12

79. On the basis of your history and/or physical exam, do you believe that the participant has angina pectoris? Yes □ 1 No □ 2 DK □ 3 ⊛

Note: The Rose Questionnaire for angina (from SH44) is positive if:

Either 12a or 12b is "Yes,"
and either 12c or 12d is "Yes,"
and 12e is "Stop or slow down,"
and 12f is "Yes,"
and 12g is "10 minutes or less,"
and either 12h(1) is "Yes," (X placed in sternum upper, middle or lower) or both 12h(2) and 12h(3) are "Yes"
(X in both left anterior chest and in left arm).

Myocardial Infarction (MI) - SH44 Items 2, 13, 14, 24, 25

80. a. On the basis of the ECG and/or your history and physical examination, do you believe the participant has had a myocardial infarction in the past year? Yes □ 1 No □ 2 DK □ 3 ⊛

↓ ↓

SKIP to 81.

b. When was the most recent possible myocardial infarction? Month Year

81. a. Is there a history of coronary bypass in the past year? Yes □ 1 No □ 2 DK □ 3 ⊛

↓ ↓

SKIP to 82.

b. Month and year of surgery: Month Year

Congestive Heart Failure - SH44 Item 17

82. On the basis of your history and/or physical examination, do you believe that the participant has had congestive heart failure during the past year?
□ 1 Yes, controlled
□ 2 Yes, not controlled
□ 3 No
□ 4 DK

ECG

83. Was an ECG performed this visit? Yes □ 1 No □ 2
→ SKIP to 85.

84. Are any of the following present?

a. Atrial fibriliation or flutter? Yes □ 1 No □ 2
b. Second or third degree A-V block? Yes □ 1 No □ 2
c. VPBs--multifocal, pairs or runs, or more than 10% of beats? Yes □ 1 No □ 2
d. Bradycardia (<50 beats/min.)? Yes □ 1 No □ 2

85. Does the participant currently have a pacemaker? Yes □ 1 No □ 2 DK □ 3

Vascular System - SH44 Items 15, 18, 24, 25

86. a. Is there a history of vascular surgery in the past year? Yes □ 1 No □ 2 DK □ 3
→ SKIP to 87.

b. Aortic, iliac, popliteal or femoral bypass or graft? Yes □ 1 No □ 2

c. Angioplasty? Yes □ 1 No □ 2
Which vessel(s)? _____

d. Other (Specify) _____ Yes □ 1 No □ 2

87. On the basis of your history and/or physical examination, does the participant have arterial disease with tissue necrosis or related loss of an extremity? Yes □ 1 No □ 2 DK □ 3

Note: The Rose Questionnaire for intermitent claudication (from SH44) is positive if:

15a is "Yes"
and 15b is "No"
and 15c is "Yes"
and either 15d or 15e is "Yes"
and 15f is "No"
and 15g is "Stop or slow down"
and 15h is "Yes"
and 15i is "10 minutes or less"

Pulmonary - SH44 Items 16, 17

88. On the basis of the history and/or physical examination, does the participant have:

a. Chronic bronchitis? Yes □ 1 No □ 2 DK □ 3
b. Emphysema? Yes □ 1 No □ 2 DK □ 3

Stroke/TIA - SH44 Items 5, 18-25

89. a. On the basis of your history and/or physical examination, and keeping the SHEP criteria in mind, do you believe the participant has had a stroke in the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3 → SKIP to 90.

b. When was the most recent episode of probable stroke (not TIA)? ____ Month ____ Year

c. Are any residual effects still present? Yes ☐ 1 No ☐ 2 DK ☐ 3

If not already accomplished, arrange for SHEP Neurological Evaluation for Stroke (SH27) as soon as possible.

---

90. On the basis of your history and/or physical examination, do you believe that the participant has had transient cerebral ischemic attacks within the past year?

☐ 1 Yes, based on history and presence of carotid bruit
☐ 2 Yes, based on history of two or more TIA in same location
☐ 3 Yes, based on other combinations of evidence
☐ 4 No
☐ 5 DK

If "Yes, based on history and presence of carotid bruit" or "Yes, based on history of two or more TIA in same location," or "Yes, based on other combinations of evidence," arrange for SHEP Neurological Evaluation for TIA (SH28) as soon as possible if not already accomplished.

---

91. Is there a history of carotid endarterectomy in the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3

Contraindications and Allergies to Study Drugs

92. On the basis of your history and/or physical examination, does this participant have any contraindication or allergy to chlorthalidone? Yes ☐ 1 No ☐ 2 DK ☐ 3

93. On the basis of your history and/or physical examination, does this participant have any contraindication or allergy to atenolol? Yes ☐ 1 No ☐ 2 DK ☐ 3

94. On the basis of your history and/or physical examination, does this participant have any contraindication or allergy to reserpine? Yes ☐ 1 No ☐ 2 DK ☐ 3

Falls and Fractures

95. Do you believe that, in the past year, the participant has had a fracture of:

a. Hip? Yes ☐ 1 No ☐ 2 DK ☐ 3

b. Spine? Yes ☐ 1 No ☐ 2 DK ☐ 3

c. Forearm? Yes ☐ 1 No ☐ 2 DK ☐ 3

96. Do you believe that the participant has had a problem with frequent falls in the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3

Other

97. Alcohol--on the basis of your history and/or physical examination, do you believe the participant currently drinks 6 or more drinks/day, or that alcoholism or alcoholic liver disease have been present in the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3

98. Dementia--on the basis of your history and physical examination, do you believe the participant definitely has any form of dementia? Yes ☐ 1 No ☐ 2 DK ☐ 3

99. a. Has the participant had cancer (except basal cell cancer) diagnosed within the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3

↓ ↓

SKIP to 100.

b. What was (were) the primary sites?

_____

_____

100. Other than possible stroke, TIA, left ventricular failure, myocardial infarction and vascular surgeries, was the participant hospitalized or admitted to an intermediate or skilled care nursing home in the past year? Yes ☐ 1 No ☐ 2 DK ☐ 3

101. On the basis of your history and/or physical examination is there any other life-threatening disease, or any other reason which might seriously impair the individual's participation in the SHEP over the next year? Yes ☐ 1 No ☐ 2 DK ☐ 3

Specify: _____

102. Comments: _____

_____

_____

103. Clinician's signature: _____ ☐ Code

For new possible strokes, acute myocardial infarctions, left ventricular failures, and transient ischemic attacks, obtain complete hospital/physician visit record for that event. For new other hospitalizations and new admissions to skilled or intermediate care nursing homes, obtain discharge summary or admission record only. Have participant sign consent to obtain medical records. Fill out Form SH20, Initial Report of Morbid Event.

MEDICATION REVIEW

104. a. Were any SHEP blinded medications prescribed at the last visit? Yes ☐ 1 No ☐ 2 → Go to 105a.

b. Were all SHEP blinded medications discontinued since the last visit? Yes ☐ 1 → Go to 105a. No ☐ 2 DK ☐ 3

c. Were there any other changes made in the SHEP blinded medications since the last visit? Yes ☐ 1 No ☐ 2 DK ☐ 3

(Specify_____)

105. a. Were open-label antihypertensive medications prescribed at the last visit (any source)? Yes ☐ 1 → Go to 106a. No ☐ 2 DK ☐ 3

b. Were open-label antihypertensive medications prescribed since the last visit (any source)? Yes ☐ 1 No ☐ 2 DK ☐ 3

BLOOD PRESSURE REVIEW - Goal SBP: _____ BP today: _____ Last visit: _____

Please review the attached chart for treatment and scheduling decision based on blood pressure status.

106. a. Has the participant reached escape blood pressure at this visit? Yes ☐ 1 No ☐ 2 → Go to 107a. DK ☐ 3 →

b. List the escape blood pressure sequence:

	Month	Day	Year	SBP	DBP
Visit 1					
Visit 2					
Visit 3					

107. a. Will you be prescribing SHEP medications according to the prescribed SHEP blood pressure treatment regimen at this visit? Yes □ 1 No □ 2 DK □ 3

b. Will you be prescribing open-label antihypertensive medications at this visit? Yes □ 1 No □ 2 DK □ 3

If Item #107a is "Yes" and Item #107b is "No," skip to #108.

Reasons (check all that apply):

c. Participant has reached escape blood pressure at this visit or a previous visit Yes □ 1
d. Possible or probable side effects in the judgment of the SHEP clinician Yes □ 1
e. Perceived side effects in the judgment of the participant Yes □ 1
f. Stroke Yes □ 1
g. MI Yes □ 1
h. LVF Yes □ 1
i. Angina Yes □ 1
j. Other medical (specify) _____ Yes □ 1
k. Participant refusal or preference Yes □ 1
l. Private MD request Yes □ 1
m. Other (specify) _____ Yes □ 1

MEDICATION PRESCRIPTION AND SCHEDULING

---

108. Medication prescription last visit:

a. Step 1
C1 □ 1
C2 □ 2
½ C1 □ 3
Other C _____ □ 4
No Step 1 (go to 108c) □ 5

b. Step 1 bottle number [ ]

c. Step 2
A1 □ 1
A2 □ 2
Other A _____ _____ □ 3
R Dose 1 □ 4
R Dose 2 □ 5
Other R _____ □ 6
No Step 2 (go to 108e) □ 7

d. Step 2 bottle number [ ]

e(1) Open-label drugs (specify drug and dose) Yes □ 1 No □ 2 DK □ 3
↓ ↓
Go to 108f.

_____

e(2) Source of open-label drugs
Prescribed by SHEP □ 1
Prescribed by other source □ 2
Both □ 3

f(1) K supplement Yes □ 1 No □ 2 DK □ 3
↓ ↓
Go to 108g.

f(2) Meq/day (unknown = 99) [ ]

g. Uric acid drug (specify drug and dose) Yes □ 1 No □ 2 DK □ 3

_____

109. Medication prescription this visit: No change (go to 110) □ 1

a. Step 1

C1 □ 1
C2 □ 2
½ C1 □ 3
Other C _____ □ 4
No Step 1 (go to 109c) □ 5

b. Step 1 bottle number [ ]

c. Step 2

A1 □ 1
A2 □ 2
Other A _____ □ 3
R Dose 1 □ 4
R Dose 2 □ 5
Other R _____ □ 6
No Step 2 (go to 109e) □ 7

d. Step 2 bottle number [ ]

e(1) Open-label drugs (specify drug and dose) Yes □ 1 No □ 2 DK □ 3

_____

↓ ↓
Go to 109f.

e(2) Source of open-label drugs

Prescribed by SHEP □ 1
Prescribed by other source □ 2
Both □ 3

f(1) K supplement Yes □ 1 No □ 2 DK □ 3

↓ ↓
Go to 109g.

f(2) Meq/day (unknown = 99) [ ]

g. Uric acid drug (specify drug and dose) Yes □ 1 No □ 2 DK □ 3

_____

110. Schedule:

Next quarterly □ 1
One month □ 2
1-2 weeks □ 3
1 week □ 4
Other (specify) _____ □ 5

111. Comments

112. Signature of Clinician completing this section: _____ [ ] Code

BEHAVIORAL EVALUATIONS

The participant should now be administered:

- SHEP SHORTCARE (SH30, SH36)
- Activities of Daily Life (SH33)
- Social Network (SH34)
- Behavioral Evaluation--Part II (SH35)

PLEASE REVIEW PAGE 1

Combinations 1-8 assume DBP < 90 mm Hg at this visit:

	SBP [1] at Consecutive Visits On Same Step & Dose		On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2			
1	<=110 [4]			SD [5]	CD
2	111-goal	111-goal	N	NC	Q
3	111-189	111-189	Y	NC	Q
4	>goal-219	220-239	N	SU	2W
5	>goal-239	>goal-219	N	SU	1M
6	220-239	220-239	N	SU [5]	2W
			Y	OL [5]	CD
7	>=240 [4]			OL [5]	CD
8	Other			NC	SBP 111-219 ->1M SBP 220-239 ->2W

For DBP < 90 mm Hg this visit, skip Combinations 9-14.

	DBP [1] at Consecutive Visits On Same Step & Dose			On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2	Visit 3			
9	90-94	90-94		N	SU [5]	1M
10	90-94	95-114		N	SU [5]	1-2W
11	90-94	90-114	>= 90	Y	OL [5]	CD
12	95-114	95-114		N	SU [5]	1-2W
				Y	OL [5]	CD
13	115+ [4]				OL [5]	CD
14	Other				NC	DBP 90- 94 ->1M DBP 95-114 ->1-2W

[1] Average of two seated corrected readings
[2] OL = open label, SU = step up, SD = step down at clinician discretion
[3] W = weeks, M = month, Q = next quarterly, CD = clinician discretion
[4] Any single visit
[5] Escape blood pressure reached

If DBP >=90 mm Hg at this visit, treatment prescribed this visit should reflect the largest change in medication prescribed above for the appropriate blood pressure levels. For example, the choice between "No Change" and "Step Up" should be "Step Up"; the choice between "Step Up" and "Open Label" should be "Open Label". The next visit should be scheduled according to the shortest suggested interval.

For additional detail on specific blood pressure combinations, refer to the SHEP Manual of Operations, Chapter 3.

CHAPTER 3

TREATMENT PROTOCOL

3.1 General Description

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 more than 20 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.

3.2 Drug Names

The following drugs will be used in the treatment program: chlorthalidone, atenolol, and reserpine and their matching placebos. They will be labeled as follows:

Drug	Label
Chlorthalidone, 12.5 mg or matching placebo	C1
Chlorthalidone, 25 mg or matching placebo	C2
Atenolol, 25 mg or matching placebo	A1
Atenolol, 50 mg or matching placebo	A2
Reserpine, .05 mg or matching placebo	R

3.3 Initiation of C1 at Baseline Visit 2

Individuals who are eligible and, after orientation to the study, agree to participate by signing the consent form, will be randomized by telephone with the Coordinating Center. 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. All randomized participants will be started on a low dose of chlorthalidone (12.5 mg/day) or matching placebo. If any section of the Baseline Visit 2 (e.g., blood sample or behavioral evaluation) must be rescheduled, that procedure should be rescheduled as soon as possible and drugs should be withheld until that procedure has been accomplished.

3.4 The Stepped Care Treatment Plan

Following randomization, a participant should be given the C1 drug and scheduled to return to the clinic in four weeks for the first routine follow-up visit. Thereafter, the participant will be prescribed the SHEP medications and scheduled to return for additional routine visits based on his or her levels of SBP and DBP.

Guidelines for making medication decisions and scheduling routine follow-up visits may be found in Table 3-1 (detail table) and Table 3-2 (summary table). Table 3-1 lists each possible SBP combination at two visits, and DBP combinations at two or three visits, and describes the routine medication and scheduling decision to be made in each situation. If the DBP is 90+ mm Hg at the routine follow-up visit, the decisions must involve both SBP and DBP; in this case, the maximum change in medications and the shortest visit interval should be used, as described on the table. Table 3-2 (the summary table) is found on the last page of each main clinic visit form (SH08 and SH09), and combines into "other" all SBP and DBP patterns that do not require a change in the SHEP medication prescription; patterns that allow a quarterly visit schedule are listed separately on these tables.

In summary, if a participant is at or below goal at two consecutive routine follow-up visits on the same Step and Dose of SHEP medications, he or she will remain on that Step and Dose and be scheduled to return at the next quarterly visit. If the participant is above goal at two consecutive routine follow-up visits on the same Step and Dose of SHEP medications, he or she will be stepped up to the next higher Dose or the next Step will be added, until the maximum Step and Dose (Step 2 Dose 2) is reached. The normal sequence of doses and medications for the entire sequence would be: C1, C2, C2+A1 (R dose 1), C2+A2 (R dose 2), as described below. Doses higher than C2, A2, or R2 (e.g., C2 twice a day) are not allowed. Also, A and R cannot be prescribed together.

The C1 drug (chlorthalidone 12.5 mg/day or placebo) is the first medication to be prescribed (at Baseline Visit 2, after randomization). For participants needing to step up after two consecutive routine follow-up visits above goal, the medication will be changed to C2 (chlorthalidone 25 mg/day or placebo). Subsequent step-ups to Step 2 would then be to add A1 (atenolol 25 mg/day or placebo); normally, the participant would remain on the C2 drug if a Step 2 drug is prescribed. If contraindications to atenolol exist at the point of Step 2 initiation, or intolerable side effects to atenolol develop, participants will receive R (reserpine or placebo) in doses of 0.05 or 0.1 mg/day as a secondary Step 2 drug in an analogous manner.

Other reasons for stepping up medications would be if a participant is at escape blood pressure (see Section 3.5), or if it is otherwise necessary in the SHEP clinician's judgment.

Table 3-3 is an exercise listing various SBP and DBP combinations at two or three clinic visits, with the correct medication and scheduling decision outlined. Blank copies of this exercise may be obtained from the Coordinating Center for local training purposes.

3.4.1 Maximum SHEP Medications

Maximum SHEP medications is defined as the highest SHEP dose that is not medically contraindicated. This includes bona fide clinically confirmed side effects. Persons refusing higher doses of SHEP medications or who complain on non-confirmed side effects or who for any other reason cannot be stepped up according to the protocol are not at maximum dose. Their visit frequency may be modified if appropriate, using Item #41 of the SH09 (Item #110 on the SH09). However, persons who achieve escape BP level who for any reason cannot be stepped up, should be placed on open-label therapy.

3.4.2 Exceptions to the Stepped Care Treatment Plan

As of April 1988, the following exceptions have been made to the stepped care treatment plan as described above:

* Any participant on maximum SHEP medications, with DBP less than 90 mm Hg, who has SBP above goal but <190 mm Hg on two consecutive visits, may be scheduled for the next quarterly visit.
* Participants who have remained at or below goal for at least one year, and have a visit at which they are above goal, should return in one month. If they are then below goal, the quarterly visit schedule may resume.

3.5 Management of Blood Pressure Escape

An escape blood pressure is defined as an SBP or DBP alert level that indicates a special action; SBP and DBP escape criteria are included in Tables 3-1 and 3-2 (footnote [5]) and are summarized below. (An SBP of 110 mm Hg, while actually classified as a potential side effect, nevertheless allows a step down of SHEP medications.) Determinations of SBP and DBP escape should not be made using standing blood pressures.

An average SBP reading 240 mm Hg or above on a single visit qualifies as an escape pressure, and individual therapy should be initiated. If the participant is not on maximum SHEP medications, an SBP of 220 mm Hg or above requires a return in two weeks; if the SBP is still 220 mm Hg or above, the next drug dose or step should be initiated. If the participant is on maximum drug dosage and SBP is 220 mm Hg or above 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 is 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 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 or 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 participants 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.

If a participant is on open-label therapy due to escape blood pressure (except SBP less than 110 mm Hg), that participant should <u>not</u> be approached later about discontinuing their open-label medications or restarting SHEP medications.

TABLE 3-1

DETAIL OF SHEP TREATMENT PROTOCOL

This table assumes DBP < 90 mm Hg at this visit:

	SBP [1] at Consecutive Protocol Visits on Same Step and Dose		On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2			
1	<=110 [4]			SD [5]	CD
2	111-goal	[6]		NC	1M
3	111-goal	111-goal		NC	Q
4	111-goal	>goal-219	N	NC	1M
			Y	NC	SBP<190 --> Q SBP>=190 --> 1M
5	111-goal	220-239		NC	2W
6	>goal-219	[6]		NC	1M
7	>goal-219	111-goal	N	NC	1M
			Y	NC	SBP<190 x 2 -->Q Other --> 1M
8	>goal-219	>goal-219	N	SU	1M
			Y	NC	SBP<190 x 2 --> Q Other --> 1M
9	>goal-219	220-239	N	SU	2W
			Y	NC	2W
10	220-239	[6]		NC	2W
11	220-239	111-goal		NC	1M
12	220-239	>goal-219	N	SU	1M
			Y	NC	1M
13	220-239	220-239	N	SU [5]	2W
			Y	OL [5]	CD
14	>=240 [4]			OL [5]	CD

For DBP >= 90 mm Hg at this visit, also refer to the following:

	DBP [1] at Consecutive Protocol Visits on Same Step and Dose			On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2	Visit 3			
1	<90	90-94			NC	1M
2	<90	95-114			NC	1-2W
3	90-94 [6]				NC	1M
4	90-94	90-94		N	SU [5]	1M
				Y	NC	1M
5	90-94	95-114		N	SU [5]	1-2W
				Y	NC	1-2W
6	90-94	90-114	>=90	Y	OL [5]	CD
7	95-114 [6]				NC	1-2W
8	95-114	90-94			NC	1M
9	95-114	95-114		N	SU [5]	1-2W
				Y	OL [5]	CD
10	115+ [4]				OL [5]	CD

[1] Average of two seated readings
[2] OL = open label, SU = step up, SD = step down at clinician discretion, NC = no change
[3] W = weeks, M = month, Q = next quarterly, CD= clinician discretion
[4] Any single visit
[5] Escape BP reached
[6] First visit at current step and dose

If DBP >=90 mm Hg this visit, treatment prescribed this visit should reflect the largest change in medication prescribed in these charts for the appropriate blood pressure levels. For example, the choice between "No change" and "Step up" should be "Step up"; the choice between "Step up" and "Open label" should be "Open label". The next visit should be scheduled according to the shortest suggested interval.

Participants who have remained at or below goal for at least one year, and have a visit at which they are above goal, should return in one month. If they are then below goal, the quarterly visit schedule may resume.

TABLE 3-2

SUMMARY OF SHEP TREATMENT PROTOCOL
(Combines Patterns That Do Not Require A Change in SHEP Medications)

Combinations 1-8 assume DBP < 90 at this visit:

	SBP [1] at Consecutive Visits On Same Step & Dose		On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2			
1	<=110 [4]			SD [5]	CD
2	111-goal	111-goal	N	NC	Q
3	111-189	111-189	Y	NC	Q
4	>goal-219	220-239	N	SU	2W
5	>goal-239	>goal-219	N	SU	1M
6	220-239	220-239	N	SU [5]	2W
			Y	OL [5]	CD
7	>=240 [4]			OL [5]	CD
8	Other			NC	SBP 111-219 -> 1M SBP 220-239 -> 2W

For DBP < 90 mm Hg this visit, skip Combinations 9-14.

	DBP [1] at Consecutive Visits On Same Step & Dose			On Maximum SHEP Meds?	Prescription This Visit [2]	Schedule [3]
	Visit 1	Visit 2	Visit 3			
9	90-94	90-94		N	SU [5]	1M
10	90-94	95-114		N	SU [5]	1-2W
11	>= 90	>= 90	>= 90	Y	OL [5]	CD
12	95-114	95-114		N	SU [5]	1-2W
				Y	OL [5]	CD
13	115+ [4]				OL [5]	CD
14	Other				NC	DBP 90- 94 -> 1M DBP 95-114 ->1-2W

[1] Average of two seated corrected readings
[2] OL = open label, SU = step up, SD = step down at clinicial discretion
[3] W = weeks, M = month, Q = next quarterly, CD = clinician discretion
[4] Any single visit
[5] Escape blood pressure reached

Participants who have remained at or below goal for at least one year, and have a visit at which they are above goal, should return in one month. If they are then below goal, the quarterly visit schedule may resume.

If DBP >=90 mm Hg at this visit, treatment prescribed this visit should reflect the largest change in medication prescribed above for the appropriate blood pressure levels. For example, the choice between "No Change" and Step Up" should be "Step Up"; the choice between "Step Up" and "Open Label" should be "Open Label". The next visit should be scheduled according to the shortest suggested interval.

TABLE 3-3

BLOOD PRESSURE REVIEW EXAMPLES
(Assume Goal SBP = 146 mm Hg)

	Routine Visits at Same Step and Dose						
	Visit 1	Visit 2	Visit 3	Max Meds	Medication Decision	Scheduling Decision	Item Numbers from Chart*
1.	176/82	180/78		N	Step up	1 month	SBP #5, skip DBP
2.	176/82	180/78		Y	No change	Quarterly	SBP #3, skip DBP
3.	140/72	138/72		N	No change	Quarterly	SBP #2, skip DBP
4.	140/72	142/92		N	No change	1 month	SBP #2, DBP #14
5.	140/90	142/92		N	Step up	1 month	SBP #2, DBP #9
6.	140/90	142/92		Y	No change	1 month	SBP #3, DBP #14
7.	140/90	142/92	142/92	Y	Open label	Discretion	SBP #3, DBP #11
8.	226/88	246/90		N	Open label	Discretion	SBP #7, DBP #14
9.	222/86	224/86		N	Step up	2 weeks	SBP #6, skip DBP
10.	160/90	162/96		N	Step up	1-2 weeks	SBP #5, DBP #10

*Refer to MOO Table 3-2.

3.6 Deviations from the Routine Plan of Therapy

At any time during the trial, SHEP drugs may be discontinued, decreased or increased, or a required change may not be accomplished, or open-label therapy might be initiated for any of the following reasons:

- escape blood pressure attained and participant is already on maximum study medications
- major side effects
- morbid event
- request of participant's private physician
- other reason, in the clinician's judgment, that SHEP drugs should not be prescribed according to protocol

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.

It should be noted that initiation of open-label therapy by a private MD does not necessarily mean that the participant should be taken off of SHEP meds, unless the participant, private MD or Clinic MD indicate that this should be the case.

Table 3-1 and Table 3-2 (which is repeated on the SH08 and SH09) are guides to specific deviations due to blood pressure and when they are required. Deviations from the routine plan of therapy are documented on the SH08 (SHEP Clinic Visit) or SH09 (SHEP Annual Visit).

3.7 Re-challenging Participants Not on the Routine Plan of Therapy

It may be possible to approach participants who are on open-label therapy and/or not on SHEP medications about getting back into the routine plan of therapy. Indeed, it is imperative that this be done whenever possible, to ensure that SHEP's final data are as clear as possible at the end of the trial.

If a participant is on open-label therapy due to escape blood pressure (except SBP less than 110 mm Hg), that participant should not be approached later about discontinuing their open-label medications or restarting SHEP medications.

For post-MI and post-stroke participants, restarting SHEP medications (including the waiting time post-event) is left to the judgment of the SHEP clinician and the participant's private MD. The participant must be above SHEP goal SBP, and may be on other open-label drugs with antihypertensive action.

If a participant is not on any medication at all (no open-label and no SHEP), and SHEP medications are restarted, the SHEP clinician should use their best judgment regarding the scheduling of the follow-up visits. Many participants will resist restarting SHEP medications if they must come in monthly. The visits should not be less frequent than quarterly, if possible.

For participants discontinuing open-label in order to return to the routine plan of therapy, the clinician should use their best judgment as far as the method and schedule of tapering and stopping the open-label therapy.

3.8 Unblinding Study Medications

The unblinding of SHEP participants and their physicians should be vigorously discouraged and kept to an absolute minimum. Emergency situations may arise, however, where it is in the best interest of the participant to identify the treatment drug. For these cases, the label of the drug bottle contains the code for the drug in that particular bottle. An unblinded list has been provided to each Clinical Center, and each center has a designated person who is responsible for this list. (This designated person is not responsible for the medical care of SHEP participants.) In addition, identification of all study drugs can be obtained at the Coordinating Center.

The following principles apply to requests for unblinding. They should be carefully read and rehearsed by all staff members likely to be involved:

1) Under usual circumstances, unblinding should be vigorously discouraged and kept to an absolute minimum.

2) If the SHEP or private physician, the participant, or other interested party is concerned about the occurrence of what might be a serious adverse drug effect, the participant can usually be given optimum care by discontinuation of the study drug without unblinding.

3) If the physician feels that open-label treatment is in the best interest of the participant, this can be done by simultaneously discontinuing the study medication and initiating open treatment without unblinding.

4) Except where immediate knowledge of the study drug is essential, all cases where official unblinding is contemplated should be discussed in advance with the Chairman of the Steering Committee (Kenneth G. Berge, M.D.) or with the Deputy Director of the Coordinating Center (Barry R. Davis, M.D., Ph.D.).

5) If unblinding is requested by someone unrelated to the SHEP (e.g., an anesthesiologist or surgeon), the project physician should try to ascertain if such knowledge is essential. If in his judgment it is not, he should make every reasonable effort to persuade the person requesting the information of this view. In most cases it can be pointed out that knowledge of the study drug will in no way alter contemplated medical or surgical treatment and that discontinuation of the study drug is sufficient. If it is still necessary that the participant's medication be identified, arrangement should be made for someone other than SHEP personnel to unblind and communicate this information to the person requesting it. Anyone becoming aware of the identity of the drug should be urged to preserve the confidentiality of this information.

6) If the treatment should be disclosed to the participant or SHEP personnel, and the participant is in the placebo group, it is not necessary for the participant to continue taking the placebo. The participant should, however, continue receiving every other aspect of the follow-up procedures (interview, physical exam, lab, ECG, etc.) on the same schedule.

7) Every case of unblinding should be followed promptly by a Report of Study Drug Disclosure (SH49) documenting the circumstances and reasons for this action (see Section 9.30, this manual).

CHAPTER 4

ASSESSMENT AND MANAGEMENT OF SIDE EFFECTS

4.1 Introduction

Minor side effects are defined as effects of the SHEP drugs that may be unpleasant or distressing to the participant, but that do not require reducing the dose or discontinuing the drug; minor side effects are not harmful to the participant.

Major side effects, on the other hand, are effects that are of sufficient severity to warrant reducing or discontinuing the drug, either because they are intolerable or because they are judged to be potentially harmful to the participant.

Correct assessment of all side effects is vital to the success of the study because the ultimate cost/benefit ratio of drug treatment for hypertension in the elderly may hinge on how well the drugs are tolerated. For this reason, the procedures for carrying out the assessment are highly standardized and should be followed carefully.

Management of side effects is based on the philosophy of protecting the safety of the participant while at the same time making every effort to adhere to the stepped-care treatment program. In those instances where deviations from the treatment protocol are necessary in the judgment of the clinic physician, these deviations should be as brief as possible. The procedures for managing side effects reflect these philosophies. Suggested approaches to some of the more notable potential problems are specified in some detail. Other, less common

problems are not described, reflecting the philosophy that each clinic physician will need the flexibility to use his or her own judgment for handling the wide variety of situations that may develop, in a fashion that will maintain both the safety of the participant and the integrity of the trial.

4.2 Assessment of Symptoms

It is important to obtain reliable information on all side effects, and a placebo-controlled double-blind trial offers the opportunity to do so. Our approach is to differentiate between side effects that are volunteered by the participant and those that are elicited as a result of specific questions, and, thus, suggested to the participant. To this end, the "side effects" information is obtained in two parts--a general well-being (interval history) and a detailed assessment for possible side effects.

4.2.1 General Well-Being

These questions, which are administered at every visit, are used to ascertain the general well-being of the participant. Open-ended questions such as, "Have you felt unwell in any way since your last clinic visit?", "Since your last visit, have you seen a doctor for any reason?", and, "Since your last visit, have you been in the hospital for any reason?" are designed to elicit problems from, rather than suggest specific problems to, the participant. If the participant reports any problems, details are probed.

4.2.2 Side Effects

If a positive response is obtained to specific questions on the general well-being section, or Step 1 or Step 2 medication has been started or increased at the last clinic visit, then these questions will be administered. They contain a standard set of queries concerning specific side effects that are associated with the drug use. The interviewer should ask each item as it is written on the form rather than a general queston. For example, "Since your last visit, have you been troubled by skin rash or unusual bruises?", etc. The items may not be rephrased. Always record the participant's response, regardless of whether in the interviewer's opinion it is reasonable or not. (It is recognized that inquiring about the same side effects at each visit may guide the participant toward future symptomatology; however, the participant's response should always be reported on the form.) Some positive answers suggest short, directed, physical examinations pertinent to the side effect in question.

4.3 Blood Tests

Biochemical tests, including those tests listed below, will be performed at the Central Laboratory at baseline and at annual intervals during the trial. In addition, serum potassium is measured by the Central Laboratory on the next visit after initiating Step I medication or increasing the dosage of Step I medication. These same tests may be obtained at any point in the trial, using local laboratory facilities, at the discretion of the clinic therapist; other blood tests that are deemed advisable may also be ordered locally.

4.3.1 Local Laboratory Analyses - SH11

This form is to be filled out whenever a blood sample, urine sample, or other test is done for local analysis. The serum potassium required at visits after starting or increasing Step I medications is not a local analysis. Details on filling out the SH11 are contained in Section 9.2 of this manual. This form is not to be used for reporting Central Laboratory analyses to the Coordinating Center.

4.3.2 Alert Levels from the Central Laboratory - SH13

This form is used to record abnormal laboratory test results received by telephone from the Central Laboratory. Details on filling out the SH13 are contained in Section 9.3 of this manual.

Values that are considered to be "alert levels" by the Central Laboratory are:

Alkaline phosphatase	No alert
Blood urea nitrogen	Less than 3.0, more than 80.0 mg/dl
Calcium	Less than 7.0, more than 14.0 mg/dl
Cholesterol (total)	No alert
Creatinine	More than 6.0 mg/dl
Glucose	Less than 40, more than 300 mg/dl
HDL cholesterol	No alert
Potassium	Less than 3.2, more than 6.0 mmol/l
SGOT	More than 400 IU/L
Sodium	Less than 120, more than 150 mmol/l
Triglycerides	No alert
Uric acid	No alert

4.4 Management of Side Effects

4.4.1 General Precepts

Every effort should be made to prevent interruptions of treatment except for bonafide, major side effects. These are few with the drugs employed in the study. Hence, minor and non-specific side effects such as fatigue, weakness, tiredness, drowsiness, dry mouth, impotence or decreased libido, and nasal stuffiness are not usually sufficient reasons for discontinuing the assigned regimen. Impotence or decreased libido will not always be considered minor and must therefore be dealt with individually.

When drug therapy is initiated, the participant is briefed on the possibility of side effects from the study drugs and is reassured that these side effects are not harmful. If there are side effects that are judged to be minor or not drug-related, the clinician should use all of his or her skills to reassure the participant and maintain effective dosage. The clinician should emphasize that the side effects are not unusual and that they are likely to become less bothersome with time, and that every effort should be made to tolerate them. It is also stressed to the participant that the study drugs may be ineffective in less than full dosage.

If major side effects that may be drug-related occur, such as postural hypotension, severe depression, asthma or bronchospasm, active peptic ulcer, Raynaud's phenomenon, extrememe drowsiness or nasal congestion, major dermatitis, blood dyscrasia, etc., then the study medication may be stepped down to progressively lower levels. If deemed clinically necessary or advisable by the clinic physician, the

medication may also be discontinued. Whenever medication is reduced or discontinued, consideration should be given to a rechallenge with the prior dosage if the blood pressure remains above goal and if the physician and participant are both willing.

In those instances where dosage is reduced, every attempt is made to lower it as little as is necessary and for as short a time as possible. The participant should be told that a temporary lowering of the dosage may be sufficient to eliminate the side effect, and that a later restoration of the full dosage may be tolerable. The clinician should ascertain and record the effect of the dosage change upon the undesirable side effects.

Whenever possible, full dosage may be subsequently restored. A review by Clinical Center staff of the status of participants who are on reduced medication should be made at least monthly. These participants may be brought in for extra visits in an attempt to increase their dosage level if their SBP is not at goal. If the participant does not tolerate the unpleasantness of the side effect despite all efforts on the part of the clinician, then the offending agent may have to be discontinued permanently.

In the event of major side effects from Step I medication, such that it is permanently discontinued, two situations may rise. If the participant has not yet received any Step 2 medication and atenolol is not contraindicated, the participant may start on this. If the participant has already begun to receive a Step 2 medication, this may be continued and the individual may remain an active participant even though he is receiving no Step 1 treatment.

In the event of major side effects from A1 or A2, R may be substituted. In the event of major side effects from both of the Step 2 medications, the medications will be discontinued and the participant followed routinely on Step 1 medication, unless the participant reaches escape blood pressure.

4.4.2 Specific Conditions

4.4.2.1 Allergy:

Development of an allergy (such as purpura, asthma, or a generalized rash) to Step 1 or Step 2 medication requires that the medications be discontinued. Such participants will often be suitable for subsequent rechallenge. Ultimately, they may need to be withdrawn permanently from the medication of that step and managed as described above.

4.4.2.2 Hypokalemia:

Serum potassium is measured in the Central Laboratory at baseline, annually, and after starting or increasing the dosage of Step 1 medication. It is measured in the local lab as a follow-up if an abnormal result is reported from the Central Laboratory. Also, additional tests from the local laboratory may be ordered at any time the clinician deems it appropriate.

If the potassium level is between 3.2 and 3.5 meq/l once, potassium should be re-checked locally 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. Potassium supplementation is indicated if, on two consecutive scheduled visits, serum potassium is less than 3.5 meq/l.

Oral potassium supplementations will be Micro-K in 10 meq tables. 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)

4.4.2.3 Hyperuricemia:

If the uric acid level rises above 9.9 mg/dl, a uric-acid lowering drug may be prescribed at the discretion of the clinic physician.

If the participant develops acute gout while receiving Step 1 medication, the gout should be treated by the clinic physician using an appropriate regimen. Probenecid should be started, and continued prophylactically after the acute gout has resolved, even if the uric acid level drops below 9.9 mg/dl. Step 1 medication need not be withdrawn unless the gout cannot be controlled by this treatment.

4.4.2.4 Symptomatic hypotension:

If a participant's SBP drops to 110 mm Hg or below, medication may be stepped down according to the SHEP clinician's judgment, and the participant should return in one week. A subsequent SBP above goal will require that medications be stepped up.

4.4.2.5 Low pulse rate:

It is recommended that if the participant's pulse is less than 50 beats per minute, the Step 2 medicine should not be started or increased until the case is discussed with a SHEP physician; it would be at the SHEP MD's discretion whether or not to start or increase the Step 2 medication. Any time a participant's pulse is less than 40 beats per minute, this could be considered as an alert to the SHEP MD to check the participant.

4.4.2.6 Sodium <130:

If a central serum sodium is <130, recheck locally. If still <130, consider taking off C meds and follow on normal sodium diet and recheck. If sodium is subsequently ≧130, cautiously restart C at lowest dose.

4.4.2.7 Glucose >200, ≦300:

If a central serum glucose is above 200 mg/dL, but not above 300 and the participant is not symptomatic, monitor locally with no change in meds at intervals not to exceed 8 weeks (urine should be checked at the same time). Diabetes treatment should be handled by the participant's private MD.

4.4.2.8 Glucose >300 or urine sugar 3+:

If a central serum glucose is above 300 mg/dL, or the urine sugar is 3+, the C meds should be stopped; A or R may be continued. Refer to the participant's MD for diabetes control. If the SBP is 160+ and diabetes remains uncontrolled, the SHEP clinician should consider stopping study meds and initiating OLT. If the SBP is 160+ and diabetes is controlled, a cautious trial of the C meds may be attempted.

4.4.2.9 Changes in lipid levels:

Lipid changes do not require immediate action. These should be referred to the private MDs. We should neither encourage nor discourage the addition of lipid-lowering agents.

General dietary recommendations may be made, using guidelines as provided in the SHEP orientation booklet.

4.4.2.10 Changes in creatinine levels:

Changes in creatinine do not require immediate action. Increases should be watched--if they do not remain stable, the participant should be encouraged to visit their private MD.

4.4.2.11 Other:

Other side effects that develop are a matter for the judgment of the clinic physician who has the twin objectives of assuring the safety of the participant and of maintaining the treatment protocol wherever possible.

CHAPTER 5

STUDY ENDPOINTS

5.1 Diagnostic Categories to be Recorded

The following events will be monitored during the SHEP:

- Stroke of any kind (fatal and nonfatal)
- Sudden unexplained death (within 1 hour)
- Rapid unexplained death (1 to 24 hours)
- Myocardial infarction (acute or silent, fatal and nonfatal)
- Left ventricular failure (fatal and nonfatal)
- Other cardiovascular death
- Non-cardiovascular death
- Transient ischemic attack
- Other cardiovascular event associated with hospitalization
- Angina pectoris
- Significant arrhythmias
- Left ventricular hypertrophy
- Intermittent claudication
- Renal dysfunction
- Aortic aneurysm
- Coronary bypass surgery
- Carotid surgery
- Other arterial surgery, including angioplasty
- Fractures
- Other overnight hospitalizations
- First admission to intermediate or skilled care nursing home
- Depression
- Dementia (including multi-infarct dementia)
- Disability days
- Days of limited activity

5.2 Discovery of a Possible Event

All participants will have a complete physical examination, medical history review and routine laboratory work at all annual examinations. A standard 12-lead electrocardiogram and two-minute rhythm strip will be done at Year 2 and the Final Annual Visit. In addition, the participant's general well-being and a short interval history will be ascertained at every visit (see Form SH08, Section 2.5.3 and Form SH09, Section 2.6.3 of this manual). Additional tests may be ordered by the SHEP clinician as indicated. SHEP diagnoses will be based on these results.

All participants in the SHEP are asked to call the Clinical Center if they are hospitalized. They will have been given an identification card saying that they are participating in the SHEP, that they are on drug treatment for systolic hypertension, and that the Clinical Center should be notified when they are hospitalized.

The participant may also be diagnosed by a physician other than the study physician; the participants will have been asked to notify the center if any neurological or other cardiovascular diagnosis is made by their physician. In addition, at each visit to the clinic, the clinician will inquire whether the individual has been seen by a physician between visits and what diagnoses were made, if any.

The Clinical Center may receive notification of a death, hospitalization or other event through the participant's family or friends. Monitoring of the HCFA files, which will be done through the Coordinating Center, may also prove to be an aid in SHEP event discovery.

5.3 Monitoring and Recording Events

5.3.1 A Synopsis of Monitoring and Recording

For all deaths, suspected nonfatal strokes, acute myocardial infarctions, left ventricular failures or TIAs, and for other hospitalizations and admissions to skilled or intermediate care nursing homes, an initial report is to be promptly submitted. Thereafter collection of the required documentation should begin at once. The required documentation is designed to make the most accurate determination possible regarding the cause of death or the nature of the morbid event. The text below presents the documentation usually considered necessary. That documentation, plus any other pertinent information, should be sent as a packet to the Coordinating Center as soon as possible, preferably within six weeks. Any deviations from what is specified should be noted and explained. Monthly reports and listings will be generated by the Coordinating Center indicating events that are incomplete longer than 60 days from the Initial Report, with an indication of the missing documentation.

In general, for events which occur in hospital or for which a participant is treated in hospital (or nursing home) a preliminary diagnosis is usually available and most, or all, of required documentation may be relatively easily available. Events that occur without hospitalization present more of a problem. The fraction discovered may be smaller and more uncertain. Discovery will depend primarily on the participant or his family reporting suspicious circumstances, a visit to a physician, other suggestive information obtained during a clinic visit.

5.3.2 Monitoring and Recording of Fatal Events

The death of any SHEP participant that occurs following randomization must be reported to the Coordinating Center within 48 hours of learning of the event, on Form SH22 (Initial Notification of Death). As soon as possible (preferably within six weeks), Form SH23 (Final Report of Death) and all available* information necessary or useful for determining the diagnosis should be provided to the Coordinating Center. When available,* this information should include a copy of the death certificate, terminal hospital record (if hospitalized)† and autopsy report. In the event that the death occurred out-of-hospital, relevant information should be obtained from the attending physician (Form SH25), and a narrative history should be obtained by interviewing the next of kin and other witnesses (Form SH26). Forms SH25 and SH26 may also be filled out for some in-hospital deaths, at the discretion of the Clinic Principal Investigator. If the death was certified by the coroner or medical examiner, then a copy of that record should be obtained and sent to the Coordinating Center with the autopsy report.

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*Here and throughout this chapter, all requested information is to be provided if available, i.e., if available with any reasonable effort. An attempt has been made to request the minimum needed for effective adjudication; however, if some of the requested documents cannot be obtained after diligent effort, their absence should not delay the submission of the other information to the Coordinating Center. If missing information subsequently becomes available, it should be submitted promptly.

†If that record is excessive (e.g., more than 30 pages), the critical information bearing on the event in question including physician notes, nurses notes, laboratory data, and blood pressure graphics should be sent.

If stroke was considered as the possible cause of death, include all notes by neurologists, CT Scan (films), MRI (films), and reports of X-rays or other studies of head, CSF data, and any other pertinent information.

If myocardial infarction or left ventricular failure was considered as the possible cause of death, include all notes by cardiologists, all ECGs, echocardiograms, chest X-ray reports, cardiac enzyme data, and any other pertinent information.

It may be necessary to obtain permission from the next-of-kin to get copies of these documents. Instructions for completing these forms may be found in Sections 9.7, 9.8, 9.10 and 9.11 of this manual.

A summary of the required documentation may be found in Table 5-1.

5.3.3 Monitoring and Recording of Non-fatal Events

5.3.3.1 General

All relevant non-fatal events experienced by randomized SHEP participants must be reported to the Coordinating Center within 48 hours of learning of the event. To this end, Form SH20 (Initial Notification of Morbid Event) should be filled out whenever there has been a possible stroke, acute myocardial infarction, left ventricular failure, possible TIA, overnight hospitalization for any other reasons, or admission to a skilled or intermediate care nursing home. These may be ascertained during a SHEP clinic visit or by other notification.

For possible strokes and TIAs, neurological evaluations directed to those endpoints should be carried out by the SHEP neurologist as soon as possible (see Section 5.3.3.2). Any participant who has had a possible TIA which is subsequently confirmed by the Working Group (see Section 5.5.3) need not be evaluated for subsequent possible TIAs, nor should any event forms be filed. Clinics will be notified of confirmed TIAs after each semiannual coding meeting.

If the participant was hospitalized for suspected stroke, acute myocardial infarction, left ventricular failure or TIA, a complete hospital record should be obtained.

If stroke was considered, include all notes by neurologists, CT Scan (films), MRI (films), and reports of X-rays or other studies of head, CSF data, and any other pertinent information.

If myocardial infarction or left ventricular failure was considered, include all notes by cardiologists, all ECGs, echocardiograms, chest X-ray reports, cardiac enzyme data, and any other pertinent information.

For all other hospitalizations and admissions to skilled or intermediate care nursing home, only the discharge summary or other documentation of hospitalization or admission dates and diagnoses should be obtained.

If the participant was not hospitalized, but has seen their non-SHEP physician, a letter should be sent to the physician (with the participant's permission) requesting information about any medical diagnoses, neurological evaluation, CT scan (films), or MRI (films).

If other information is necessary, in the judgment of the Principal Investigator, interviews may be accomplished with the participant, family, or personal physician (see SH24, Section 9.9 of this manual). This is particularly useful for events which do not involve a hospitalization.

Form SH21 (the Final Report) and its supporting documentation should then be completed and forwarded to the Coordinating Center, preferably within six weeks of the Initial Notification.

Directions for filling out the above forms and submitting them to the Coordinating Center may be found in Sections 9.5, 9.6 and 9.7 of this manual.

A summary of the required documentation may be found in Table 5.1

TABLE 5-1

DOCUMENTATION REQUESTED FOR SHEP EVENTS

Key Items (*)--Events returned to the Coordinating Center by the Coding Group, requesting additional information, will most often request these missing items. If any of the key information is impossible to obtain, an appropriate note with explanation should be made on the Final Report. It is expected that every effort will be made to obtain these items.

ATTENTION: BE SURE THAT ALL RECORDS SENT TO THE COORDINATING CENTER ARE LEGIBLE.

NONFATAL STROKES * = key items

SH20 -- required in all cases

SH21 -- required in all cases

*SH24 -- especially in cases when the participant is not hospitalized; if judged to be unnecessary, an appropriate note should be made on the SH21

Entire hospital record, if applicable, particularly:

All notes by neurologists
CSF data if available
*CT scan or MRI (films) with SH14--a written report of the result may be included with the records, but may not take the place of the actual film and SH14
Results of other X-rays or studies of the head

*SH27 -- SHEP Neurologic Evaluation for Stroke--if your consulting neurologist is unable to see the participant, the SH27 should still be completed as far as possible with information from the medical record, indicating that the participant was not seen.

*If a CT/MRI film is not available with a hospital record, or the participant was not hospitalized, a CT/MRI scan should be obtained by SHEP as soon as possible.

TABLE 5-1

DOCUMENTATION REQUESTED FOR SHEP EVENTS
(Continued)

TRANSIENT ISCHEMIC ATTACK		* = key items
SH20	--	required in all cases
SH21	--	required in all cases
*SH24	--	It is especially important to have a good description of the possible event--i.e., why the Clinic staff suspects that a TIA may have occurred--especially in cases when the participant is not hospitalized; if judged to be unnecessary, an appropriate note should be made on the SH21.
*SH28	--	SHEP Neurologic Evaluation for TIA--often the only medical evaluation available for possible TIAs; very important
Entire hospital record, if applicable		

ACUTE MYOCARDIAL INFARCTION AND LEFT VENTRICULAR FAILURE (LVF/CHF)		* = key items
SH20	--	required in all cases
SH21	--	required in all cases
*SH24	--	especially in cases when the participant is not hospitalized; if judged to be unnecessary, an appropriate note should be made on the SH21
Entire hospital record, if applicable, particularly:		
*Photocopies of all ECGs done in the hospital		
*Reports of cardiac exzymes		
*X-rays of the chest (narrative is sufficient)		
All notes by cardiologists		
Echocardiogram reports		

TABLE 5-1

DOCUMENTATION REQUESTED FOR SHEP EVENTS
(Continued)

OTHER OVERNIGHT HOSPITALIZATIONS	* = key items

SH20 -- required in all cases

SH21 -- required in all cases

Discharge summary--required in all cases

DEATHS	* = key items

SH22 -- required in all cases

SH23 -- required in all cases

*Death certificate

*Autopsy report if done

*Record from terminal hospitalization, including items described above as applicable to major nonfatal events.

SH25 -- Interview with Participant's Private Physician
SH26 -- Interview with Next of Kin or Witness to Death

→ Should be done for all out-of-hospital deaths; may also be done for in-hospital deaths at the discretion of the Clinic PI

5.3.3.2 Neurologic examination for possible strokes and TIAs

The SHEP system for diagnosis of stroke or TIAs is designed to obtain the best evidence and judgments available on the basis of a complete and detailed neurological examination performed as soon as possible after the event.

If a stroke or TIA is suspected during a visit to the clinic, either by history or by examination by SHEP staff, then a detailed neurological examination and evaluation should be carried out by the SHEP neurologist as soon as possible and reported on Form SH27 for stroke (see Section 9.12), or Form SH28 for TIA (see Section 9.13).

Permission should be obtained from the participant or family to have a member of the SHEP staff examine and evaluate all hospitalized participants with a diagnosis of stroke, TIA, dementia, brain tumor or other neurological diagnosis suggestive of a SHEP event. This examination should be done by a consulting neurologist or the SHEP staff physician (if expert in neurological evaluation) as soon as possible after admission to the hospital, and should be recorded on Form SH27 for possible strokes or Form SH28 for possible TIAs (see Sections 9.12 and 9.13 of this manual).

If the participant could not be examined in the hospital by a SHEP neurologist, and the participant is unable to come to the Clinic for evaluation, a home examination may be attempted.

For possible strokes, if the participant cannot be examined or refuses to be examined, then Form SH27 (Neurologic Evaluation for Stroke) should be completed as far as possible by the SHEP consulting neurologist, using available medical records and contact with other physicians.

For suspected strokes, if a CT scan or MRI was not done, the clinic staff should arrange for one as soon as possible.

5.4 Central Reading of the CT Scan and/or MRI (CT/MRI)

Since the CT/MRI is such an important test to confirm stroke or rule out other diseases, an effort will be made to obtain CT/MRI 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/MRI be done early if none has yet been done. If the participant had an early CT/MRI and it was normal, the neurologist may obtain a follow-up CT/MRI. If the participant has been discharged from the hospital and no CT/MRI was done, or no lesion was demonstrated, a CT/MRI should be done with the participant's permission.

The CT/MRI will be collected by each Clinical Center coordinator and sent to the Coordinating Center with Form SH14 (see Section 9.4 of this manual). The reading of the CT/MRI will be accomplished by two independent readers (C.V.G. Krishna Rao, Maryland; L. Anne Hayman, Houston) using a standardized protocol. The readers would be blinded to the clinical opinion or presumed location of the stroke.

Using a standardized algorithm for comparison, the Coordinating Center will compare the two independent readings. If they are comparable, Dr. Rao's coding will be used. If they are not comparable, Dr. Price (Maryland) will review the CT/MRI and both sets of readings, selecting one for use in endpoint coding.

The results of the reading would be used, along with other available information, by the Endpoint and Toxicity Subcommittee in the determination of whether or not a stroke occurred and in the determination of stroke type.

5.5 Adjudication

All deaths, suspected strokes, acute myocardial infarctions, left ventricular failures and TIAs will be adjudicated according to the rules set forth below. All other overnight hospitalizations (including cardiovascular causes other than MI or LVF) will be coded at the Coordinating Center on the basis of the diagnoses appearing on the hospital discharge summary.

5.5.1 Adjudication Working Group

The Adjudication Working Group of the Toxicity and Endpoint Subcommittee will consist of seven subcommittee members and will include two neurologists, two cardiologists, and three other physicians. For any given possible event, three members of the Working Group will be asked to adjudicate. Possible nonfatal strokes and TIAs will be reviewed by one neurologist and two other physicians. Possible MIs and LVFs will be reviewed by one cardiologist and two other physicians. Deaths will be reviewed by one neurologist, one cardiologist and one other physician. No member of the group will review events from his own Clinic.

5.5.2 Preparing Event Data at the Coordinating Center

The completed individual case packets for adjudication which the Clinical Center sends to the Coordinating Center will be checked for completeness and legibility by the Coordinating Center. When the Coordinating Center finds a case incomplete, it is to contact the Clinical Center and report the deficiency. If it can be corrected, the case is to be held in the Coordinating Center until the additional information can be obtained. If the deficiency seems unimportant the Coordinating Center may decide to submit the incomplete case to the Working Group; however, if this is done a note as to the deficiency is to be included. If the case lacks important or critical information five months after the event, the chairman of the Working Group is to be contacted for a decision as to whether to wait longer for documentation or to submit the case as it is for discussion at the next semi-annual Working Group meeting (see Section 5.5.3). Obviously there will be cases with less than the desired amount of data on which a final adjudicated diagnosis will have to be made.

5.5.3 Final Adjudication by Working Group

Copies of all complete legible case reports will be submitted to the Working Group for adjudication at its regular semiannual (more often, if necessary) meeting. At this Working Group meeting, three members of the Working Group shall review each case (see 5.5.1). Final diagnoses of accepted study events (or of no event) require unanimous concurrence of the three reviewers of a case. If there is no unanimous decision by the three reviewers, the case is to be considered by the entire Working Group present at the meeting and a majority of them shall make the final diagnosis, subject to the limitations that a neurologist must be present whenever the diagnosis of stroke is being considered and must concur in that diagnosis. Although a decision can be put off until the next meeting in order to obtain additional information, a decision must eventually be reached. To be considered in making the final diagnosis, all information from the Clinical Center must be in writing. No possible or probable diagnoses will be accepted as final adjudication. All finally adjudicated cases will be recorded by the Coordinating Center for analysis.

5.6 Diagnostic Categories and Definitions

Three categories of events will be classified: strokes (fatal and non-fatal); non-stroke cardiovascular events and conditions (fatal and non-fatal), and other events.

5.6.1 Stroke (fatal and non-fatal)

Stroke is defined as 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. The final diagnosis of stroke will be made by the Adjudication Working Group of the Endpoint and Toxicity Subcommittee based on the opinion of the consulting neurologist that a stroke has occurred and the satisfaction of the appropriate algorithms. It will include strokes occurring during surgery.

We will attempt to categorize strokes as thrombotic, embolic or hemorrhagic, including subtypes using the following stroke algorithm.

STROKE ALGORITHM

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. Hemorrhagic Stroke

1. Blood in subarachnoid space or intraparenchymal hemorrhage 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 hemorrhagic or ischemic infarction. Satisfies criteria for stroke.

Hemorrhagic Strokes are further divided into Subarachnoid Hemorrhage (SAH); Intraparenchymal Hemorrhage (IPH) and Indeterminate Type Hemorrhagic Stroke.

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.

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

Ischemic Strokes are further divided into Lacunes (L), Embolic (Emb), Atherosclerotic (ATL) and Other-Unknown Type Ischemic Infarction (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, embolic 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.
- Bell's 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 inconsistencies 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.

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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 5-1

STROKE ALGORITHM

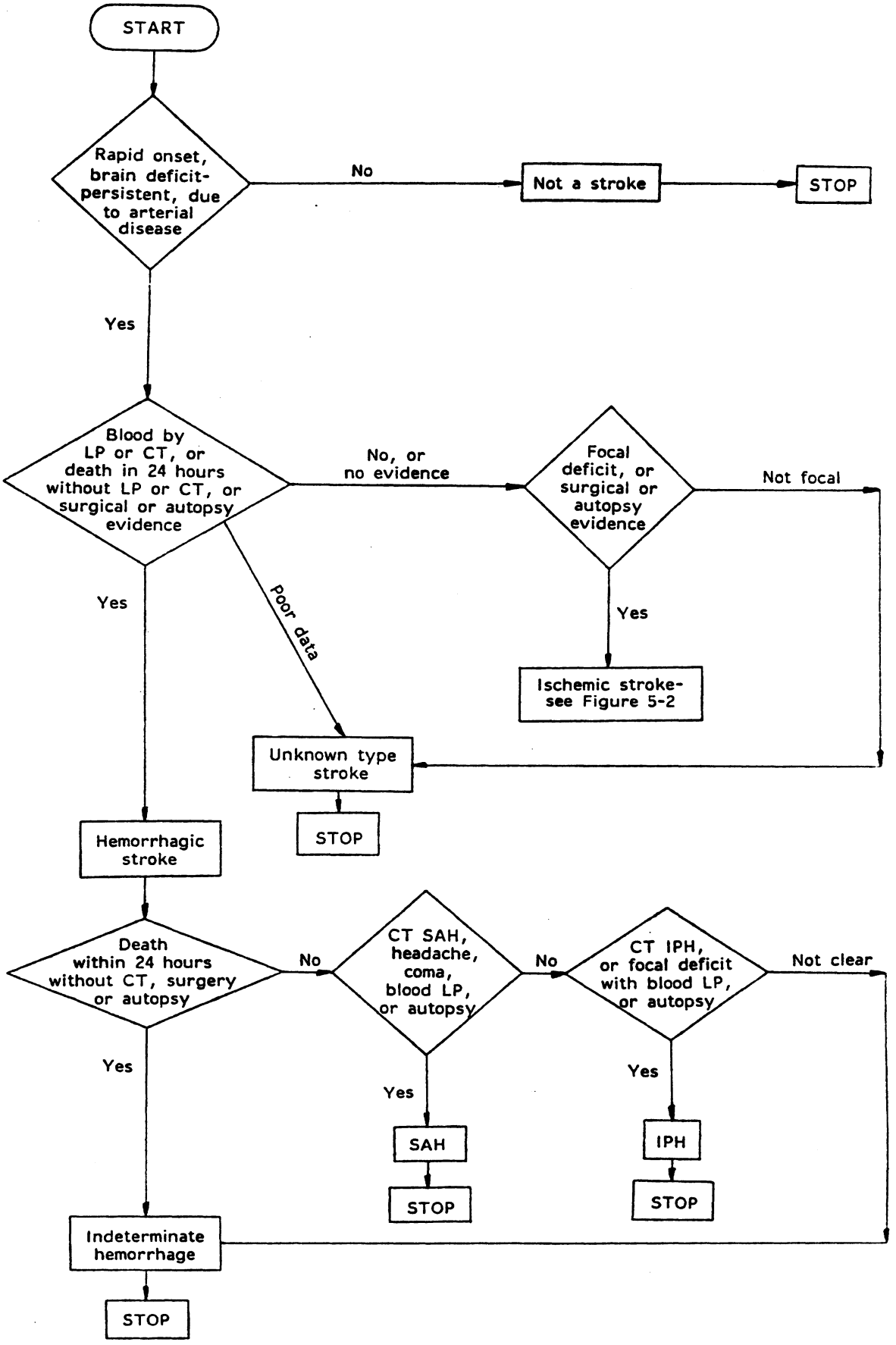
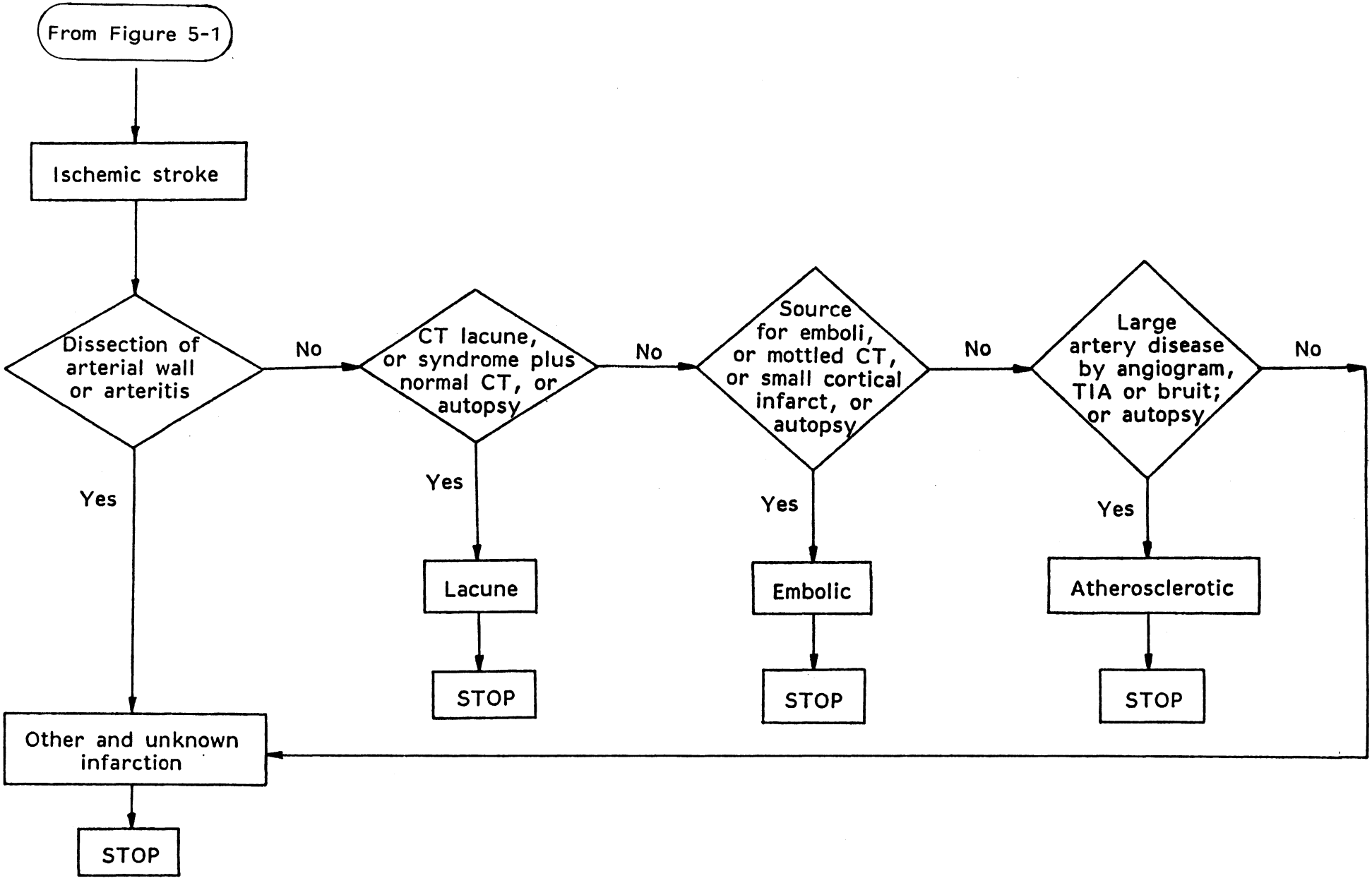


FIGURE 5-2

STROKE ALGORITHM
(Continued)



5.6.2 Non-stroke Cardiovascular "Events" and "Conditions"

Non-stroke cardiovascular events will be symptomatic and hence can be assigned a definite time of occurrence. These events are listed below:

Sudden unexplained death

Rapid unexplained death

Acute myocardial infarction

Left ventricular failure

Other cardiovascular death

Transient ischemic attack

Coronary bypass surgery

Carotid surgery

Angioplasty

Other arterial surgery

Nonfatal cardiovascular conditions differ from the events listed above because they will not be recognized by their symptoms. They will be diagnosed on the basis of (1) annual Rose Questionnaire, (2) annual creatinine determination, (3) ECG done in the Clinic (comparing baseline to second or final annual visit or done during hospitalization), or (4) annual physical examination; hence their precise time of occurrence cannot be accurately fixed. They will be assumed to have occurred at the mid-point between the two limiting examinations. These conditions include:

Myocardial infarction without symptoms ("silent")

Angina pectoris

Peripheral vascular disease (intermittent claudication)

Significant arrhythmia

Left ventricular hypertrophy

Renal dysfunction

Aortic aneurysm

No participant shall have more than one event or condition of record; however, a tabulation will be kept of all events and conditions. The event or condition of record shall be the one that places highest in the hierarchy below without regard to when it occurred as long as it occurred between randomization and termination of the study:

Stroke of any kind

Sudden unexplained death

Rapid unexplained death

MI (with or without symptoms)--fatal or nonfatal

Left ventricular failure

Other cardiovascular death

Transient ischemic attack

Angina pectoris

Significant arrhythmia

Left ventricular hypertrophy

Renal dysfunction

Aortic aneurysm

Coronary bypass surgery

Carotid surgery

Other arterial surgery

Noncardiovascular death

Death from unknown cause

5.6.2.1 Acute Myocardial Infarction (suspected from symptoms)

Acute myocardial infarction may be suspected by the SHEP staff if the participant reports hospitalization for heart attack, or reports being told by his or her physician that a heart attack occurred, or if the participant reports chest pain typical of myocardial infarction.

Diagnosis will be made by a new significant Q-wave (plus Minnesota code 1-1-1 to 1-1-7, 1-2-1 to 1-2-5 and 1-2-7) in any ECG done because symptoms suggested myocardial infarction, but not on the basis of an ECG done without any suggestive symptom. Documents of all hospitalizations for cardiac events together with all ECGs will be studied by the Endpoint and Toxicity Subcommittee to observe if a new significant Q-wave has appeared.

In the absence of new significant Q-waves, a diagnosis of MI will be made in the presence of :

- A history of typical symptoms consistent with acute myocardial infarction (timing and relief of pain by specific medications are deliberately omitted from the definition because such information is so commonly missing from the hospital record.)

PLUS

- Significant elevation of serum enzymes:

  (a) CPK-MB present, or above upper limit of normal (depending on how local lab records) within 36 hours of onset of acute symptoms of MI

  - OR -

  (b) Reversal of LDH1/LDH2 ratio within 5 days of the onset of acute symptoms of MI

  - OR -

(c) CPK total at least 1.25* times the upper limit of normal for the laboratory that performed the test (in the absence of other possible causes for elevation of the CPK total and with CPK-MB missing, not done, or done more than 36 hours after onset of symptoms)

- OR -

(d) SGOT, LDH, or other cardiac enzymes at least 1.25* times the upper limit of normal for the laboratory that performed the test (in the absence of other possible causes for elevation of the enzymes and with CPK-MB missing, not done, or done more than 36 hours after the onset of symptoms).

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*The level of increase in enzymes required is an empirical/clinical one. Studies have varied [without documentation] in the level of increased enzyme levels required from 1.25 to 2X.

5.6.2.2 Fatal myocardial infarction--requires at least one of the following categories:

- Death certificate having an underlying or immediate cause compatible with CHD plus pre-terminal hospitalization with a definite or suspected diagnosis of acute myocardial infarction within 4 weeks prior to death (see (Section 5.6.2.1)).

- OR -

- Acute myocardial infarction diagnosed by autopsy.

5.6.2.3 Sudden Unexplained Death

Sudden death requires the presence of all three characteristics listed below:

- Death witnessed as occurring within one hour after the onset of severe cardiac symptoms or within one hour after the subject was last seen without symptoms.
- No known non-atherosclerotic process (acute or chronic) or other event that could have explained such a sudden death according to relative, physician, hospital records.
- No documentation of acute myocardial infarction in four weeks prior to death (see Section 5.6.2.1).

5.6.2.4 Rapid Unexplained Death

- Death witnessed as occurring between one and twenty-four hours after the onset of severe cardiac symptoms or between one and twenty-four hours after the subject was last seen without symptoms.

- No known non-atherosclerotic process (acute or chronic) or other event that could have explained such a sudden death according to relative, physician, hospital records.
- No documentation of acute myocardial infarction in four weeks prior to death (see Section 5.6.2.1).

5.6.2.5 Left Ventricular Failure

The diagnosis of LVF requires one of the following:

- Paroxysmal nocturnal dyspnea, or
- Dyspnea at rest, or
- New York Heart Classification III, or
- Orthopnea

In addition, one of the following must be present:

- Râles
- Ankle edema (2+ or greater)
- Tachycardia of 120 beats/minute or more after 5 minutes at rest
- Cardiomegaly by chest X-ray
- Chest X-ray characteristic of congestive failure
- S_3 Gallop
- Jugular venous distention

This diagnosis should be made with great care in anyone with severe pulmonary disease manifested by:

- C.O.P.D., including:
  - (a) positive chronic bronchitis questionnaire
  - (b) plus smoking history of 10 pack years or greater
  - (c) and X-ray confirmation

- Pneumonia
- Other severe lung disease documented by X-ray or other tests.

5.6.2.6 Other Cardiovascular Death requires:

- Presumed myocardial infarction or other presumed cardiovascular cause that did not meet criteria for definite diagnosis (see Section 5.6.2.1); death certificate consistent with myocardial infarction or other cardiovascular cause, without other underlying or immediate cause and without criteria for a definite diagnosis of myocardial infarction.

- OR -

- Presumed sudden or rapid unexplained death that did not meet criteria for a definite diagnosis (see Sections 5.6.2.3 and 5.6.2.4); this requires (1) a and c and d, or (2) b and c and d of the following:

  (a) Previous history of MI or definite or possible MI by SHEP record.

  - OR -

  (b) Autopsy reporting severe atherosclerotic coronary artery disease without acute myocardial infarction.

  - AND -

  (c) No known nonatherosclerotic process (acute or chronic) or other event that could have explained such a sudden death according to relative, physician, hospital records.

(d) No documentation of definite acute MI in four weeks prior to death.

- OR -

- Death certificate or information from hospital records or other reliable source consistent with other cardiovascular causes of death (ICD 390-458 exclusive of any of the aforementioned causes)

5.6.2.7 Transient ischemic attack

The final diagnosis of TIA will be made by the Adjudication Working Group of the Endpoint and Toxicity Working Group, based upon the opinion of the consulting neurologist that a TIA has occurred, and the satisfaction of the criteria in this section.

A participant has the diagnosis of transient ischemic attack if he has one or more episodes of focal neurologic deficit lasting more than 30 seconds and no longer than 24 hours with rapid evolution of the symptoms to the maximal deficit in less than 5 minutes with complete resolution and no immediately preceeding head trauma. There should be no evidence of clonic jerking, conjugate eye deviation, prolonged Jacksonian march, scintillating scotoma, headache with nausea and vomiting. Conditions to be ruled out include seizures, hypoglycemia, migraine, drug intoxication, tumor, infection, orthostatic hypotension and generalized cerebral ischemia. Discovery of an infarct by CT in a location compatible with the symptoms, even if the symptoms cleared in less than 24 hours shall be diagnosed as a stroke. Focal symptoms means they can be either localized at least to either the left carotid, right carotid or vertebral basilar system.

Left carotid system TIAs produce one or more of the following symptoms or signs:

1. Loss of vision in the left eye (amaurosis fugax) or, rarely, right field of vision.
2. Motor defect (weakness, paralysis or clumsiness of the right arm, leg and/or face).
3. Sensory symptoms (loss of feeling; numbness or paresthesias) involving the right side
4. Aphasia--speech, language, reading, writing may be involved singly or together.
5. Dysarthria may accompany the above symptoms.

Right carotid system TIAs produce one or more of the following symptoms or signs:

1. Loss of vision of the right eye (amaurosis fugax) or, rarely, left field of vision.
2. Motor defect (weakness, paralysis or clumsiness of the left arm, leg and/or face).
3. Sensory symptoms (loss of feeling, numbness or paresthesias) involving the left side.
4. Dysarthria may accompany the above symptoms.

Vertebro-basilar system TIAs produce one or more of the following symptoms:

1. Motor defect (weakness, paralysis or clumsiness) of any combination of arms, legs and face, left or right.
2. Sensory defect (loss of feeling, numbness or paresthesia) involving left or right or both sides.

3. Loss of vision by fields left, right or both

4. Ataxia, loss of balance, vertigo, diplopia, dysphagia, and dysarthria do not meet the criteria for transient ischemic attacks when they occur alone or in combination except when accompanied by the above symptoms 1, 2, or 3.

Sensory symptoms involving only one location (arm or foot), not accompanied by other symptoms do not constitute enough to diagnose TIA.

5.6.2.8 Silent myocardial infarction (found at routine ECG on second or final annual visit, or on hospital ECGs)

Diagnosis will be made by the presence of a new significant Q-wave (plus Minnesota code 1-1-1 to 1-1-7, 1-2-1 to 1-2-5 and 1-2-7) not present on previous ECG.

This determination will be made by the Coordinating Center, using the Baseline, Year 2 and/or Final Annual ECG as coded by the ECG Coding Center in Minneapolis, Minnesota.

Also, if a participant is hospitalized, and has an ECG which shows MI, but had no symptoms, this will be counted as an MI event by the endpoint coders.

5.6.2.9 Angina Pectoris

The determination of angina pectoris will be based on central scoring of the Rose Questionnaire completed by participants at baseline (SH04) and annual clinic visits (SH44).

The Rose Questionnaire for angina will be positive if all of the following conditions are met:

Baseline (SH04)	Annual (SH44)	Description
42a or 42b is "Yes"	12a or 12b is "Yes"	participant has had pain, discomfort, pressure or heaviness in chest
42c or 42d is "Yes"	12c or 12d is "Yes"	pain (etc.) occurs when the participant walks uphill or hurries, or occurs when walking at an ordinary pace on level ground
42e is "Stop or slow down"	12e is "Stop or slow down"	participant stops or slows down when the pain (etc.) occurs
42f is "Yes"	12f is "Yes"	the pain (etc.) goes away when the participant stands still
42g is "10 minutes or less"	12g is "10 minutes or less"	the pain goes away in 10 minutes or less
42h(1) is "Yes" OR both 42h(2) and 42h(3) are "Yes"	12h(1) is "Yes" OR both 12h(2) and 12h(3) are "Yes"	the pain (etc.) is either in the sternum (upper, middle, or lower) or in both the left anterior chest and the left arm

5.6.2.10 Peripheral Vascular Disease (intermittent claudication) will be based on central scoring of the Rose Questionnaire completed by participants at baseline and annual clinic visits.

The Rose Questionnaire for intermittent claudication will be positive if all of the following conditions are met:

Baseline (SH04)	Annual (SH44)	Description
45a is "Yes"	15a is "Yes"	participant has pain in either leg on walking
45b is "No"	15b is "No"	the pain does not begin while the participant is standing still or sitting
45c is "Yes"	15c is "Yes"	the pain is felt in the calves
45d or 45e is "Yes"	15d or 15e is "Yes"	the pain occurs when the participant walks uphill or hurries or walks at an ordinary pace on the level
45f is "No"	15f is "No"	the pain may disappear while the participant is still walking
45g is "Stop or slow down"	15g is "Stop or slow down"	the participant stops or slows down if the pain occurs while walking
45h is "Yes"	15h is "Yes"	the pain goes away when the participant stands still
45i is "10 minutes or less"	15i is "10 minutes or less"	the pain goes away in 10 minutes or less

5.6.2.11 Significant arrhythmias

Significant arrhythmias will be determined at the Coordinating Center using the Baseline, Year 2, and/or Final Annual ECG as coded by the ECG Coding Center in Minneapolis, Minnesota.

Significant arrhythmias are:

- Multifocal VPBs present on ECG and/or two-minute rhythm strip
- VPBs in pairs or runs present on ECG and/or two-minute rhythm strip
- Number of VPBs at least 10% of beats on two-minute rhythm strip

(To be completed. Need other significant arrhythmias and Minnesota Code for all arrhythmias.)

5.6.2.12 Left ventricular hypertrophy (LVH)

LVH will be determined at the Coordinating Center using the Baseline, Year 2, and/or Final Annual ECG as coded by the ECG Coding Center in Minneapolis, Minnesota.

a) definite: the presence of Minnesota codes 3-1 plus any of 4-1 to 4-3 OR 5-1 to 5-3

b) increased voltage only (3-1)

c) left atrial hypertrophy (terminal P-V1 duration x depth $\geq$ 0.04)

5.6.2.13 Renal dysfunction

The diagnosis of renal dysfunction requires a serum creatinine level of $\geq$3 mg% done in the Central Laboratory on an annual examination.

5.6.2.14 Aortic aneurysm

The diagnosis of aortic aneurysm requires an incidental finding of an abdominal aorta wider than 2 cm on X-ray, definite diagnosis of aortic dissection, or an autopsy diagnosis of aortic aneurysm.

5.6.2.15 Coronary by-pass surgery, carotid surgery, angioplasty, and other arterial surgery

Coronary by-pass surgery and other arterial surgeries will be ascertained by self-report at each clinic visit, and by the annual medical history questionnaire. In addition, these may be picked up during endpoint coding.

5.6.3 Other Events

Non-cardiovascular events (both fatal and non-fatal) include:

- Non-cardiovascular death
- Overnight hospitalizations for non-cardiovascular reasons
- Intermediate or skilled care nursing home admission
- Depression
- Dementia (including MID)
- Fractures
- Disability days
- Days of limited activity

An intermediate or skilled care nursing home will meet the following criteria:

Intermediate Care Facility (ICF)

ICF provides 24 hour accommodations, board, shelter, supervision of diets, monitoring of medications, housekeeping, social and recreational programs, protective care during short-term illness, or recuperation and supervision of health care under the direction of a physician.* In addition, ICF provides personal care and supervision for persons not capable of fully independent living who do not need continuous medical or nursing services. This includes individuals who require assistance with activities of daily living, such as bathing, dressing, feeding, transferring, walking, administering medications and injections, and/or who require dressing changes and catheter care.

Skilled services are provided intermittently rather than daily. Plan of care and basic health and nursing care services are provided under the daily supervision of a licensed nurse as well as under the direction of a physician.

Care is aimed at support, maintenance, and protection. Medicare will not pay for Intermediate Care.

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*Note: This type of care is provided in a Residential Care Facility which is designed for the semi-independent patient able to walk alone or with a gait device (cane, walker, crutch).

Skilled Nursing Facility (SNF)

SNF provides all of the above services plus daily supervision by skilled nursing or rehabilitative personnel under the direction of a physician. This type of facility provides for complicated or unstable conditions, acute (rather than chronic) conditions with potential for improvement, generally during initial teaching phase. It also provides total care for bedridden or terminally ill patients, intravenous care, tube feedings, and IPPB treatments.

Emphasis in a skilled nursing facility is on rehabilitation or restorative care for stroke and fracture patients needing physical, speech, and occupational therapies.

Medicare will provide payment for such services only while daily skilled services are needed to restore patient to his/her previous or improved level of functioning.

CHAPTER 6

ASSESSING COMPLIANCE

6.1 Introduction

In a study of this kind, it is necessary to monitor the participants' adherence to the study protocol so that statements can be made about the two groups with this variable properly weighed. Medication adherence and clinic attendance are monitored for making this evaluation, the results of which are reviewed by the Recruitment and Adherence Subcommittee.

6.2 Medication Adherence

Adherence to the drug protocol is systematically monitored by making a count of pills taken by the participant between visits, by questioning the participant, and by qualitative assessment of urine chlorthalidone at predetermined times throughout the course of follow-up. The results of these measurements are reviewed by the Data and Safety Monitoring Board, the Project Office, the Coordinating Center, and the Recruitment and Adherence Subcommittee.

6.2.1 Urine Chlorthalidone Determinations

Urine specimens obtained at Years 1 and 4 will be analyzed for the presence of chlorthalidone in order to make some assessment of participants' adherence to the prescribed drug regimen and to detect chlorthalidone usage in the placebo group.

The urine chlorthalidone determinations were discontinued on February 28, 1988.

The specimen is analyzed centrally at the METPATH Laboratory and the results are transmitted directly to the Coordinating Center. All such data are reviewed periodically by the Data and Safety Monitoring Board and will not be available to study investigators until Phase III.

The urine chlorthalidone determination is requested using the MetPath Requisition Form.

6.2.2 Pill Count and Interview

Monitoring of medications will be done at clinic visits after starting or increasing any study drug, and semiannually, by two methods:

1. Direct pill counts (SH40 and SH62)
2. Questioning the participant about how regularly he/she has been taking his/her medicines (SH40)

The results of these measures are reviewed centrally as well as locally.

Specific directions for the pill count and the interview are found in Sections 9.21 and 9.29 of this manual.

If adherence problems occur (pill count less than 80%, or by self-report), several mechanisms may be suggested to the participant as reminders to take their medicines:

1. A special time and place to take medicines (e.g., medicines on breakfast table with dosage taken at time participant starts breakfast).
2. Participant-kept record of compliance
3. Reminding the participant of the medical complications which could possibly occur by taking study medication (A1 or A2) sporadically

If non-adherence to medications persists as a problem, a conference should be held, including a spouse or other appropriate family member, to see if family mechanisms can be activated to remind the participant to take his/her medicine regularly.

6.3 Adherence to Visit Schedule

During the follow-up phase of this trial participants are required to attend the clinic at regular three-month intervals. Attendance of scheduled visits is documented by the completion of the Clinic Visit Documentation (SH08) and appropriate ancillary forms.

Clinics are advised to keep more detailed records of individual participant's clinic attendance. It is important to locally monitor the quality of follow-up interviews and examinations. For example, interviews obtained over the telephone or in the participant's home should be so noted on the SH08. Also, participants consenting to only a portion of the follow-up procedures, for example, the interview only, should be flagged. Local summary reports of these kinds of follow-up visits are important to the clinic staff in knowing what kinds of adherence problems exist among their study population.

6.4 Promotion and Maintenance of Adherence

The following section contains guidelines for the Clinical Centers in establishing a high degree of adherence to the SHEP protocol, both in the area of medication adherence and in clinic attendance.

a) Participant-Staff Relationship

The key element in successfully maintaining a participant in long-term treatment is the development of a personal relationship between the individual participant and individual members of the staff. Impersonal form letters or phone calls from someone not known to the participant are far less likely to succeed in keeping him/her returning or bringing him/her back into the trial. This personal element in participant contacts cannot be overemphasized.

b) Continuity of Care

Participants should be scheduled for repeat visits on a specific day and clinic session so that they can be seen by the same clinic staff members, if possible. At clinics with more than one physician involved in seeing participants, each participant should have his/her regular SHEP physician whom he/she sees consistently where possible.

c) Clinic Environment

The clinic environment should be warm and pleasant, and oriented to the comfort of the participant. Personal note can be made of events in the life of the participant--these can be commented on at the next visit. If possible, provide lunch periodically. For some SHEP pilot study clinics, holiday get-togethers provided an opportunity for the participants and clinic staff to get to know each other on a more personal basis.

d) Participant-Staff Communications

Good communication is essential, and consistency is the key word to communication. The same person should be caring for the participant at each visit. If the participant is not relating well to one SHEP physician, switch to a different one for better rapport. In addition to consistency among staff in what is communicated to the participant, instructions should be clear and interactions should be friendly and individualized. Discussions about diet, physical examination findings, lab values and the like will help instill a realization in the participant that the SHEP staff is diligently monitoring his/her state of health for the purpose of improving the participant's health, not just as a subject in a scientific study. The participant should be helped to understand the beneficial nature of his/her participation in this program.

e) Convenience and Accessibility of Care

Examples of factors in the accessibility of care include Clinic location, availability of transportation, and convenient Clinic hours. In general, the responsibility for making visits easily adhered to belongs to each Clinical Center and is critical to the ultimate success of the study. Depending on local circumstances, different approaches may be used, but no participant should be unable to attend the Clinic because of transportation, hours of Clinic operation, or any similar reason. If necessary, participants should be reimbursed for transportation or child care expenses. Pre-arranged parking should be available if at all possible.

Appointments should be scheduled at times and on days that do not interfere with the participant's working schedule if he or she is employed. All Clinical Centers should have at least some clinic sessions on evenings or weekends, outside of usual working hours.

f) Time in Clinic

One element which may be of vital importance in keeping participants returning for interviews over a prolonged period of time may be the amount of time that it takes to be seen on each Clinic visit. Thus it would seem essential that total Clinic visit time on all visits be kept to a minimum. It is especially important to keep waiting times to a minimum. If waiting is necessary, explain the situation and offer the option of seeing another physician or rescheduling, if possible. Excessive waiting times at local laboratories may also lead to adherence problems. Try to instill a feeling in these departments that the SHEP participants are as important as any other participants. Visit with the participant and have coffee and the daily newspaper available.

g) Appointment Reminders

Participants (like the rest of us) do tend to forget. Therefore, appointment reminders should be used to prompt participants to come for Clinic visits. (See Appendix F, Section 2.)

h) Interim Contact

During the period between the Initial Contact and Baseline Visit 2, a participant may have second thoughts or develop apathy toward the study. It is crucial at this point that Clinic staffs intensify efforts aimed at getting the participant into the Clinic for these first visits. These visits demand that the participant interrupt his or her normal routine and make a trip to the Clinic. Participants with otherwise good intentions may find this an unwelcome task. This is the first test of their willingness and/or ability to comply with the required follow-up visits.

The first visit often presents special problems simply in its newness to the participant. Once the route to the Clinic site and the personnel and procedures within have become familiar, subsequent visits should not evoke any such anxiety. It is suggested that Clinic staff aid the participant in overcoming any reluctance to attend the first follow-up visit by any means locally feasible. For example, the participant could be invited to drop by the clinic at sometime before his or her scheduled visit just to learn its location, survey its interior, and meet the staff. Maps may also be distributed to the participant, showing the location of the SHEP clinic.

It is important that Clinic staff at least telephone the participant to express interest and concern and to elicit assurance that the first clinic appointment will be kept.

During follow-up, interim telephone contact is encouraged, particularly with participants who are having problems with the medication or who have started or increased the SHEP medication at the previous visit. Three months between contacts with the SHEP Clinic may be too long. A telephone contact will display a caring attitude by the Clinic staff as well as provide some "long-distance" supervision. Try to avoid giving the participant a feeling that he or she is being "checked on." A good system is usually to ask the participant at a visit if he/she would object to a telephone call before the next visit. Ask what time of the day and which day of the week that he/she prefers to be called. Never leave a message asking a participant to call back. However, the participant should be encouraged to call if he/she has any questions or problems.

i) Participant Identity with SHEP

The clinics should focus on promoting participant identity with the SHEP. Regular communication is important. Some possibilities include:

1. Newsletters sent to the participants in the trial sharing information of interest
2. Holiday cards
3. Other written communication; e.g., notices of special events.
4. Group events; e.g., educational programs
5. Letter from a significant person outside the SHEP (e.g., congressman or governor) pointing out the importance of SHEP and the need for full cooperation on the part of each participant. Information on the progress of the study could be included as a motivator.

j) Involvement of Family Members

Family members' involvement should be encouraged. The spouse should be informed about why the study is done, its general design and the study medication. The importance and need for full cooperation from each study participant should be stressed. The spouse could, for example, be invited to attend the Clinic visits, especially the initial visits, or any group meetings that are held during the course of the study. Compliance with the study medication is more likely to be good if the family members get a feeling of involvement. It is conceivable that they will then also call if something happens to the participant.

k) Medication Adherence

Centers may purchase individual pillboxes to give to the participants as a means of making the transporting of the pills more convenient. Participants should be encouraged to keep a supply of study medication at places where he or she will most likely be when medication is due to be taken; i.e., at home in the kitchen or bathroom.

Several other ideas have already been suggested in Section 6.2.2.

l) Staff Meetings

Regular staff meetings should be held to keep the SHEP physician informed regarding individual and overall adherence problems and to plan strategies for improvement. An adherence chart should be developed and reviewed for each participant and kept with the participant's record. Notes on Clinic visit summaries can be used to indicate adherence problems. The SHEP physician should be readily available and willing to take personal action or give assistance when adherence problems make his or her involvement advisable.

m) Participant ID Cards

Every participant in SHEP should be given an identification card bearing the name of the study. A telephone number for medical advice 24 hours a day, with the instruction that the number be called in case of any medical emergency should also appear on the card. The C1 bottle number may also be useful on this card. All participants should be requested to carry this identification at all times and present it whenever care is sought at a hospital, an emergency room or a doctor's office, for a major medical problem, in addition to scheduled Clinic visits.

n) SHEP Relationship with Private Source of Care

Good communications and maintenance of a positive relationship with the participant's privately attending physician or other outside source of care is important. He or she should be kept advised of the participant's clinical course by continual reports of laboratory findings, physical examination findings, and other pertinent information. The private physician should be told of any clinical problems encountered. A good rapport with the private physician and his/her support and cooperation with the SHEP protocol is essential to a high degree of compliance.

o) Re-education

A periodic review of the purposes of the study can be a strong motivation. Discuss the purpose of the placebo, double blind, when to call the SHEP physician, and length of planned follow-up (this is easily forgotten).

6.5 Management of Negative Adherence

The following sections address the issue of poor compliance to the study protocol by individual participants. Some suggestions are given to aid in rectifying problems such as chronic or occasional inattendance at the Clinic. Standard procedures are also given for handling and documenting these cases.

6.5.1 Missed Visits

Participants not attending the clinic during the required time frame are considered to have missed a visit. Careful documentation and monitoring of missed visits is important in the specific as well as the overall management of these cases. As a minimum, the following procedures should be implemented in each Clinical Center:

a) Establishment of a clerical system that provides an immediate alert to a missed visit.

b) Immediate contact (usually by telephone) with the participant, upon missing the visit.

c) If the reason for the missed visit can be rectified by some action on the part of the Clinic, and if that action is within the realm of services that the staff is able to provide, then such action should be taken.

d) Rescheduling of the visit, if at all possible, within the same window, should be attempted. If an examination cannot be scheduled due to a participant's refusal, every effort should be made to obtain a telephone interview. Otherwise, an appointment should be scheduled to occur as soon as possible.

e) Establishment of a mechanism by which Clinic attendance for each participant can be charted and monitored locally.

f) If a visit is missed because the participant is refusing (verbally or by continued non-attendance), the staff should activate some means to elicit compliance. These means are open-ended and limited only by the imagination, reality, ethics, and the law.

An SH51 (Report of Missed Quarterly or Annual Visit) should be filed when a quarterly or annual visit does not take place in the clinic, at home, or on the telephone.

6.5.2 Refusals

Some participants randomized into the study may not be actively participating, i.e., not taking SHEP medication and/or not attending the SHEP Clinic. This may be due to any of a number of reasons, including transportation problems, or to the private physician or participant deciding against participation (see SH51). Regardless of the reason, these participants should be followed for the duration of the study, and the Clinic staff must make contact every three months. It may be possible to complete an interview over the telephone. These contacts are intended to first, ascertain possible SHEP events, and second, to remind the participant that he or she is still eligible to participate in the Program. Further details on telephone interviews may be found in Appendix F, Section 8.

6.5.3 Negative Medication Adherence

Participants are often concerned with "side effects." If this occurs:

a) Enlist the aid of a private physician--it is possible that the participant will be more willing to take the advice of an "objective" outsider.

b) Enlist the aid of the Principal Investigator. Some possible "side effects" have emotional consideration, i.e., impotence--assurance and encouragement from the PI may result in willingness to cooperate.

c) It is necessary for the PI to become familiar with the participant's needs as well as the study Protocol. (Use of progress notes and flow charts help in this process.)

d) Distinguish between effects that are frequent and minor and those that require immediate or serious attention. (Both the SHEP physician and the Coordinator can do this.)

e) Look back at symptoms before participant enrolled in SHEP (on Baseline Visit 2 form)--remind the participant if these were present at that time.

f) Explain that "side effects" may be due to other medication the participant is taking. (The SHEP physician should reinforce the Coordinator in these explanations.)

g) Suggest tapering off medication and trying again if participant insists medication is cause of "symptoms."

h) Use 7-day pillboxes and other ideas presented in this chapter to help make medication taking routine.

i) Ask participant to repeat instructions--be sure instructions are clear.

CHAPTER 7

QUALITY CONTROL

7.1 Certification and Re-certification

7.1.1 Blood Pressure Procedures

Certification of blood pressure observers is described in the SHEP Blood Pressure Manual. All SHEP blood pressure observers must be certified prior to reading blood pressures for the SHEP; this includes the successful completion of:

- videotape test
- live evaluation
- written test

Re-certification will be annual, in February or March. Persons hired and certified within 90 days prior to the annual re-certification do not need to be re-certified until the next year.

Scoring of the videotape test will be done by the Coordinating Center. The results of the completed tests may be telephoned to Mrs. Barbara Raslan or Mrs. Donna Spross at (713) 792-4280 for scoring.

7.1.2 ECG Procedures

Certification for ECG procedures is described in Appendix C of this manual. Each potential ECG technician will submit one complete standard ECG and two-minute rhythm strip, using the form provided in Appendix C, and following the procedures in that section. These should be submitted as specified on that form.

Re-certification procedures are not required; however, the quality of ECG tracings is continuously monitored by the ECG Reading Center and the Coordinating Center.

7.2 Equipment Maintenance

7.2.1 General

Each Clinical Center is responsible for the proper operation and maintenace of its equipment. Maintenance responsibility should be assumed by a specific person who has been assigned as a Quality Control Officer, and all staff should be instructed to report any real or suspected equipment problems to that person promptly.

All checks, inspections, cleanings and problems indicated will be documented and recorded by date in a permanent log and/or electronically. Problems and solutions should also be recorded. This log will be inspected during periodic site visits, or a copy may be requested by the Coordinating Center at periodic intervals.

7.2.2 Random-Zero and Standard Sphygmomanometers

The interval and procedures for maintaining the SHEP sphygmomanometers are specified in the SHEP Blood Pressure Manual, under separate cover.

7.2.3 ECG Machines

(To be completed.)

7.2.4 Weight Scales and Laboratory Equipment

Once each year weight scales at the Clinical Center should be calibrated and certified by the local Division of Weights and Measures of the Public Service Department. This is necessary because defects in the mechanical aspects of the scale may not be noted unless multiple loads covering the entire range of the scale are measured. A record of this certification should be kept on file in the local Clinical Center. In addition, local checks should be made at least every other week with a standard 50-pound weight.

Temperature of refrigerators should be checked weekly using a thermometer.

Centrifuge speeds will be checked every six months or when insufficient sample problems are being experienced.

7.3 On-going Quality Control Efforts

7.3.1 Clinical Center Activities

Specific quality control activities to be carried out at the Clinical Center include:

- Certification/recertification of field and clinic staff in study procedures, by centrally-trained supervisors.
- Scheduling and monitoring of regular equipment maintenance.
- Regular observation and monitoring of specific clinical procedures.
- Monitoring and editing of study data through the distributed data processing system.
- Reporting of quality control concerns/problems to Coordinating Center personnel for prompt resolution.

Certification and re-certification efforts, and equipment maintenance, are described in Sections 7.1 and 7.2.

The Clinic Coordinator and/or Quality Control Officer should regularly observe the various Clinical Center procedures to be sure that they are being carried out properly and with consideration for the SHEP participant. Corrective action should be taken immediately if problems are observed.

Some quality control of study data may also be carried out locally using the SHEP data entry system--invalid and incomplete forms may be taken care of prior to transmitting data to the Coordinating Center (refer to SHEP Data Entry System Manual). In addition, monitoring and/or error reports generated by the Coordinating Center will be transmitted to the Clinical Center through this system.

The Clinical Center staff are encouraged to communicate with the Coordinating Center for quality control or other concerns or problems.

7.3.2 Quality Control for the 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.

7.3.3 Coordinating Center Activities

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. For example, these reports will include data on:

- recruitment yield at each Clinical Center
- summaries of certifications and re-certifications
- blood pressure measurement errors, missed visits, and other monitoring reports
- problems observed or reported at site visits
- adverse reactions
- deviations from protocol

- missed visits, refusals, losses to follow-up
- adherence

It is the responsibility of Coordinating Center personnel to review these reports on a timely basis, to initiate procedures to remedy any problems as soon as possible, and, if necessary, to participate in site visits at the Clinical Centers, as well as to perform follow-up evaluations of actions taken.

7.3.4 Project Office/Steering Committee Activities

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.

The Behavioral Assessment Subcommittee will be responsible for quality control of the SHEP behavioral evaluations; these procedures are being developed.

7.3.5 Data and Safety Monitoring Board Activities

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. Unblinded data will be available to this group only during Phase II.

7.4 Changes to the Manual of Operations

Due to problems that may occur due to a procedural difficulty or ambiguity in this manual, changes to this manual may need to be made from time to time. When this is required, a notification and the revised pages will be sent to all Clinical Centers. All obsolete pages/sections should be filed for reference--do not discard.

If a major procedural or design problem occurs, the Executive Committee will be asked to make a recommendation, the change will be made as above, and the Steering Committee will be asked to approve at their regularly scheduled meeting.

7.5 Site Visits

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.

CHAPTER 8

DRUG HANDLING PROCEDURES

8.1 Source of Drugs

8.1.1 Centrally-supplied drugs

These include the three drugs used in the double-blind treatment program (see Chapter 3)--chlorthalidone, atenolol and reserpine, as well as the potassium supplement (see Chapter 4). Three pharmaceutical companies have agreed to donate these drugs for the duration of the study.

a) chlorthalidone, 12.5 and 25 mg, atenolol (Tenormin), 25 and 50 mg, and matching placebos--Stuart Phamaceuticals

b) reserpine, 0.05 mg, and matching placebo--Lemmon Company

c) potassium chloride, 10 mEq (Micro-K)--A. H. Robins Company

These companies have agreed to forego any promotional use of the relationship to SHEP until after the study is completed. Any acknowledgment of their role in SHEP should be first reviewed by the Steering Committee.

8.1.2 Locally-obtained drugs

Drugs for treating side effects need to be obtained locally. These include drugs for lowering uric acid and/or treating acute gout, and if donated supplies are depleted, Micro-K.

Also, open-label antihypertensive drugs for the treatment of blood pressure escape (or any other reason) need to be obtained locally.

8.2 Drug Distribution

8.2.1 Potassium supplements

To reduce the work load on the Drug Distribution Center, and since no special labeling is required, the Micro-K will be supplied directly to the clinics by the manufacturer, on approximately an annual basis. Each clinic will receive 50 bottles of 500 capsules initially. This size bottle will approximately cover a participant's maximum daily needs (for 4 capsules/day) between quarterly visits. Utilization of Micro-K will be monitored to determine when re-supply will be needed.

8.2.2 Blinded drugs

The blinded drugs are distributed by the United States Public Health Service Supply Service Center, Perry Point, Maryland (Mr. Tom Miller, Officer-in-charge). There are two types of shipments: a) an initial supply, which provides each participant with the drugs potentially needed for step-up during his first post-randomization year, and b) resupply, generally for maintenance purposes.

8.2.2.1 Initial supply

This will consist of a sequence of shipments to the clinics beginning in mid-March (C1 drugs) and ending in June 1985. This routine will be repeated in 1986. When each year's sequence is completed, each clinic will have a set of drugs, in bottles of 100, covering the maximum requirements for C and A drugs for 150 participants for a one-year period, and a set of R drugs for 30 participants for a one-year period. The numbers of bottles calculated for this purpose for each participant are as follows:

C1	4 bottles
C2	4 bottles
A1	3 bottles
A2	3 bottles
R	5 bottles

The supply of "R" drugs is based on the estimate that 50 percent of participants will require step 2 drugs and 40 percent of these will have contraindications to or intolerance of A drugs.

8.2.2.2 Re-supply

Each clinic has furnished the name and address of a person authorized to receive drugs. This is also the only person authorized to order drugs, unless the Coordinating Center and Project Office are notified otherwise. Clinics will be re-supplied on the basis of specific orders placed with Perry Point, on either a routine or emergency basis. Routine ordering is for the purpose of re-stocking the drugs needed for participants expected to remain on a maintenance regimen. This will generally include a C1 or C2 drug. This ordering should be carried out at approximately six-monthly intervals, and will utilize the attached drug requisition form, mailed to Perry Point. These four-part NCR forms will be provided by the Coordinating Center. Instructions for mailing these forms are at the bottom of each form. Turnaround will be approximately two weeks plus times-in-transit. Emergency ordering will be necessary occasionally due to lost drugs or BP escape. This can be done by express mail. However, Perry Point also has a Phone Entry Computer Ordering System (PECOS), which potentially can provide more rapid turn-around. Some clinics may wish to become authorized users of PECOS (see attached description).

8.3 Drug Dispensing

At time of randomization and assignment of a SHEP ID, each participant will also be given five 3-digit drug codes, selected from the following ranges:

Drugs	1st 150 randomized	2nd 150 randomized
C1	001-050	051-100
C2	101-150	151-200
A1	201-250	251-300
A2	301-350	351-400
R	401-410	411-420

Procedures for over 300 participants per clinic will be developed. Throughout SHEP, if the treatment protocol calls for dispensing of any of the five drugs, that participant is to receive a bottle labeled with the assigned code only. In general, a set of bottles of C and A drugs appropriately coded may be set aside for a given participant at the time of randomization (the "shoe-box" approach). The A bottles are replaced in the "shoe-box" by a set of R bottles at the time of step-up, if contraindications to atenolol are present, or subsequently, if intolerance develops. Since the codes are not uniquely assigned to a given participant, occasionally a bottle set aside for one participant may, in an emergency, be dispensed to another with the same code. These occasions should be kept to a minimum.

Each Clinic should have a means by which the person dispensing the drugs may keep track of how many bottles of each drug code have been received and dispensed, and to whom they were dispensed. Sample record-keeping forms (labelled SH60 and SH61) are attached here, but these exact formats are not required.

With the initial shipment of drugs from Perry Point each clinic will also receive a box of 51,000 non-childproof caps that fit the bottles of blinded drugs. The person dispensing the drugs should discuss with the participant whether replacement of the childproof cap is indicated, considering both any limitations of manual dexterity and the conditions under which the drugs are to be stored.

8.4 Discarding Old and Unused Drugs

As many institutions have established procedures for discarding old and unused drugs, no standard procedure will be outlined here. The Clinical Centers are not required to keep any old and unused medicines for accounting purposes.

SHEP DRUG C-1 REQUISITION FORM

Clinic Name and Address:

Voucher Number: _____

Clinic Number: _____

Name and Telephone Number of Clinic Contact:

Date of Requisition: _____

Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered
001		026		051		076	
002		027		052		077	
003		028		053		078	
004		029		054		079	
005		030		055		080	
006		031		056		081	
007		032		057		082	
008		033		058		083	
009		034		059		084	
010		035		060		085	
011		036		061		086	
012		037		062		087	
013		038		063		088	
014		039		064		089	
015		040		065		090	
016		041		066		091	
017		042		067		092	
018		043		068		093	
019		044		069		094	
020		045		070		095	
021		046		071		096	
022		047		072		097	
023		048		073		098	
024		049		074		099	
025		050		075		100	

NOTE: DO NOT fill in Voucher Number. Send white and yellow copies of this requisition to the HRSA Supply Service Center, Perry Point, Maryland 21902. Retain pink copy for your files until shipment is received. Send goldenrod copy to the SHEP Coordinating Center.

SHEP DRUG C-2 REQUISITION FORM

Clinic Name and Address:

Voucher Number: _____

Clinic Number: _____

Name and Telephone Number of Clinic Contact:

Date of Requisition: _____

Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered
101		126		151		176	
102		127		152		177	
103		128		153		178	
104		129		154		179	
105		130		155		180	
106		131		156		181	
107		132		157		182	
108		133		158		183	
109		134		159		184	
110		135		160		185	
111		136		161		186	
112		137		162		187	
113		138		163		188	
114		139		164		189	
115		140		165		190	
116		141		166		191	
117		142		167		192	
118		143		168		193	
119		144		169		194	
120		145		170		195	
121		146		171		196	
122		147		172		197	
123		148		173		198	
124		149		174		199	
125		150		175		200	

NOTE: DO NOT fill in Voucher Number. Send white and yellow copies of this requisition to the HRSA Supply Service Center, Perry Point, Maryland 21902. Retain pink copy for your files until shipment is received. Send goldenrod copy to the SHEP Coordinating Center.

SHEP DRUG A-1 REQUISITION FORM

Clinic Name and Address:

Voucher Number: _____

Clinic Number: _____

Name and Telephone Number of Clinic Contact:

Date of Requisition: _____

Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered
201		226		251		276	
202		227		252		277	
203		228		253		278	
204		229		254		279	
205		230		255		280	
206		231		256		281	
207		232		257		282	
208		233		258		283	
209		234		259		284	
210		235		260		285	
211		236		261		286	
212		237		262		287	
213		238		263		288	
214		239		264		289	
215		240		265		290	
216		241		266		291	
217		242		267		292	
218		243		268		293	
219		244		269		294	
220		245		270		295	
221		246		271		296	
222		247		272		297	
223		248		273		298	
224		249		274		299	
225		250		275		300	

NOTE: DO NOT fill in Voucher Number. Send white and yellow copies of this requisition to the HRSA Supply Service Center, Perry Point, Maryland 21902. Retain pink copy for your files until shipment is received. Send goldenrod copy to the SHEP Coordinating Center.

SHEP DRUG A-2 REQUISITION FORM

Clinic Name and Address:

Voucher Number: _____

Clinic Number: _____

Name and Telephone Number of Clinic Contact:

Date of Requisition: _____

Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered	Code	Number of Bottles Ordered
301		326		351		376	
302		327		352		377	
303		328		353		378	
304		329		354		379	
305		330		355		380	
306		331		356		381	
307		332		357		382	
308		333		358		383	
309		334		359		384	
310		335		360		385	
311		336		361		386	
312		337		362		387	
313		338		363		388	
314		339		364		389	
315		340		365		390	
316		341		366		391	
317		342		367		392	
318		343		368		393	
319		344		369		394	
320		345		370		395	
321		346		371		396	
322		347		372		397	
323		348		373		398	
324		349		374		399	
325		350		375		400	

NOTE: DO NOT fill in Voucher Number. Send white and yellow copies of this requisition to the HRSA Supply Service Center, Perry Point, Maryland 21902. Retain pink copy for your files until shipment is received. Send goldenrod copy to the SHEP Coordinating Center.

SHEP DRUG R REQUISITION FORM

Clinic Name and Address:

Voucher Number: _____

Clinic Number: _____

Name and Telephone Number of Clinic Contact:

Date of Requisition: _____

Code	Number of Bottles Ordered
401	
402	
403	
404	
405	
406	
407	
408	
409	
410	
411	
412	
413	
414	
415	
416	
417	
418	
419	
420	

NOTE: DO NOT fill in Voucher Number. Send white and yellow copies of this requisition to the HRSA Supply Service Center, Perry Point, Maryland 21902. Retain pink copy for your files until shipment is received. Send goldenrod copy to the SHEP Coordinating Center.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Health Resources and
Services Administration
Rockville MD 20857

December 3, 1984

HRSA FLYER 83.1
REVISED

UPDATE
TELEPHONE ORDERING SYSTEM FOR PERRY POINT CUSTOMERS

The Phone Entry Computer Ordering System (PECOS) announced in HRSA Flyer 83.1, January 1983 became functionable in mid-1983. Response has been good; currently 40% of all line items received are through PECOS.

Our dialogue with Perry Point customers during this initial period has disclosed a need for refinement of PECOS to provide additional options such as:

1. A method for the Indian Health Service to enter orders using more than 1 Common Accounting Number (CAN) when needed.

2. A means to enter PECOS orders through use of portable hand-held micro computer terminals in lieu of the telephone adaptor.

3. A means to use existing CRT equipment for entry of PECOS orders to Perry Point.

Item 1. above has already been accomplished. The attached (updated) PECOS Briefing Paper provides necessary information to permit use of multiple CAN numbers.

Procedures to implement changes 2. and 3. are currently being developed and will be the subject of a separate issuance in the near future.

Harry O. Knutson

TABLE OF CONTENTS

I. THE SYSTEM IN BRIEF

A. How PECOS Works

A customer uses any touch-tone telephone to access PECOS. For those facilities who do not have touch-tone telephones as standard equipment, Perry Point has available, for $36.00, a unit which readily converts a dial phone to permit this application. This unit may be requisitioned from Perry Point under "NSN 7510-00-000-1031, Soft Touch 2 Tone Dialer." The Soft Touch 2 Tone Dialer replaces the mouthpiece of conventional dial telephones and will work on all telephones except decorator phones, or GTE telephones. The brochure furnished with the Soft Touch 2 Tone Dialer has instructions requesting that you notify the telephone utility that you are installing a Soft Touch 2 Tone Dialer. It is suggested that you read these instructions and comply with the FCC rules.

PECOS prompts the customer by recorded voice on each step of the data entry. This eliminates the need for special training and the caller does not have to worry about forgetting the procedure.

PECOS is operational 24 hours a day, and orders are accepted even though the Perry Point facility closes at 5:00 P.M. Eastern Time. Further, customers can arrange to place their orders when the ordering official has free time or is less subject to being interrupted. The only real change to the information presently needed for requisitioning supplies will be the addition of an "authorizing Identification Number" to identifiy each person that places an order electronically. This "ID No." is a security feature necessary when you have the capability to enter an order directly into the computer.

Many facilities will require a "hard copy" to document obligation of funds. To meet this requirement, the Supply Service Center will mail to the consignee, within 72 hours of receipt of the order, 2 advance information copies of the shipping document showing the actual materials to be shipped. One of these documents will be clearly stamped "Obligating Document, Route to Ordering Office." Please note that with PECOS a confirming requisition is not utilized.

B. Some Benefits to Customers

Numerous advantages are realized by customers utilizing electronic transmission. Some of the advantages are:

1. Procurement lead time is reduced approximately 10 days.

2. The reduction in procurement lead time permits inventory levels to be reduced accordingly and substantial dollar savings are realized.

3. You know that your order has been received and entered into the computer. Perry Point frequently receives requests for the status of of orders placed by mail only to discover that the order has not yet been received.

4. Order preparation time, typing, etc. is reduced. Note that the only feature on ordering that is not constant is the stock number and the quantity.

5. All orders placed using this system automatically receive priority handling in that conventional orders received by mail must be processed manually prior to computer entry.

C. Identification Numbers (ID)

For security purposes, an ID is necessary for all orders entered into PECOS. Each authorized person is assigned a unique ID PECOS can easily accommodate individuals having authority to place orders for more than one facility. Each individual, regardless of how many customer numbers (stations) are involved, is assigned one ID Number.

D. Special Instructions

In order to enable customers to provide special instructions with an order, the followig codes are to be used whenever one or more special insructions are applicable.

PECOS SPECIAL MESSAGE CODES

CODE #	MESSAGE
520	Routine Order
521	Medical Emergency-Ship ASAP
525	Supply Emergency - Expedite
527	Ship Order by Air Freight

CODE #	MESSAGE
529	Ship Order By Parcel Post
531	Inside Delivery Required
532	Ship Order By Overnight
533	Ship Order By Roadway Express
535	Ship Order By Yellow Freight
537	Ship Order Via Sky Courier
540	Do Not Backorder-Fill or Kill
595	Call For Special Instructions

The following Codes are for Alaska only:

553	Ship To The Following Address- All Trans Alaska Freight Inc. 655 South Edmonds Street Seattle, WA 98108
560	Ship To The Following Address- All Trans Alaska Freight Inc. 655 South Edmonds Street Seattle, WA 98108 ********** * FREEZABLE MATERIAL * * PLACE IN HEATED VANS * * TO PREVENT DAMAGE * **********

E. Data Entry Instructions

It is important to note that PECOS cannot accept Alpha characters. Two possible data entry steps where customers could have the occasion to utilize Alpha charactes are as follows:

1. When entering the Appropriation No., required by Step 4 of Part II if your Appropriation is for "no year funds" and the third digit is an "X", substitute the number "9" for the "X" and we will understand that this is "no year funds."

2. For those stations who utilize Alpha-Numeric purchase orders, it will be necessary when placing an order electronically, that your purchase order number be restricted to numeric characters.

F. Verification of Entries

In the event that you want your data entries repeated as provided for by Step 9 of Part II, and you have entered 99, PECOS will repeat each step of the entry process. There will be a slight pause after each entry has been repeated at which time you will be required to either verify the accuracy of the entry, or signal that a correction will be made, as follows:

1. To confirm that the data entry is correct, enter the pound (#) sign.

2. To correct an entry, enter the asterisk (*) and then re-enter data followed by the #.

A # advances the system to the next step, whereas the * erases any entry back to the preceding #. Please note that your ID number will not be repeated for verification, once accepted.

II. USING THE SYSTEM - INSTRUCTIONS

In order to use PECOS, simply dial FTS 443-1598 or commercial 301-443-1598. Once connected, the recorded voice will direct you through the order processing procedure, on a step-by-step basis. Correcting mistakes and verification of data is provided in our directions. An example of the order process, including the directions provided to you and a sample response is provided below for your information.

Note: (1) The pound sign (#) activates the System to mark each separate part of your order. It must be pressed in order to proceed to the next step.

(2) The asterisk (*) will erase your entry back to the last # sign.

Step	PECOS says	You key in (sample responses provided)
	"This is the Public Health Service, Perry Point, Maryland. Our audio Response Data Entry System is ready to accept your order. Please do not send a confirming written order. Your entry into the touch phone constitutes your order. If, at any time during data entry you become aware that you made an error, you may correct your last entry by entering an * in lieu of a # sign. This will erase your entry back to the preceding # sign."	
Step 1	"Please begin by entering your 4-digit identification code followed by the # sign."	8 1 0 0 # (enter the ID number assigned by Perry Point)
Step 2	"Thank you. Please enter your 8-digit customer number followed by the # sign."	0 4 4 3 1 4 3 6 # (enter your assigned customer number)
Step 3	"Thank you. To assist us in the event it is necessary to contact you, please enter your area code and telephone number, followed by the # sign. If you are on FTS, substitute the numbers 387 for the area code."	3 0 1 4 4 3 4 1 3 6 #
Step 4	"Thank you. Please enter your appropriation number followed by the # sign."	7 5 5 0 1 4 8 # (self explanatory)
Step 5	"Thank you. Activities of the Department of Health and Human Services, please enter your CAN number followed by the # sign. If you are not funded by the Department of Health and Human Services, enter 46 followed by the # sign."	4 6 #
Step 6	"Thank you. Please enter your purchase order number followed by the # sign."	2 4 6 8 0 #

Step	PECOS says	You key in (sample responses provided)
Step 7	"Thank you. We are now ready to accept your order. Please enter the 13-digit National Stock Number followed by the # sign and the quantity for that item followed by the # sign. Do not enter a second line item until you hear "Line Item Accepted". Then continue in this fashion with all of your items and when your order is completed, enter the # sign twice."	7 5 1 0 0 0 0 0 0 1 0 3 1 # 5 # Enter the next line item AFTER THE RECORDED VOICE SAYS "Line Item Accepted". 6 5 3 0 0 0 7 7 0 6 4 2 5 # 5 # "Line Item Accepted" #. (This represents ordering 5 Soft Touch 2 Tone Dialers and 5 Bag Hot Water-Ice. Note: AFTER HEARING THE RECORDED VOICE SAY "LINE ITEM ACCEPTED" following the last item of your order, an additional # sign is necessary.
Step 8	"Thank you. In order to permit you to provide us with special instructions, please enter the codes for the special instructions that were provided in our Flyer 83-1. If more than one special instruction is provided, follow each instruction with the # sign. When the special instructions are complete, signify same by entering the # sign twice. In a later step, you will be given the opportunity to request items using an additional CAN number."	5 2 5 # Enter second special Instruction after the recorded voice says "Message Code Accepted". Code 527 #. "Message Code Accepted." #. Note: AFTER HEARING THE RECORDED VOICE SAY "MESSAGE CODE ACCEPTED", following the last special instruction, an additional # sign is necessary.
Step 9	YOUR ORDER FOR THIS CAN NUMBER HAS NOW BEEN ENTERED INTO OUR COMPUTER FOR PROCESSING. In the event that you want your data entries repeated, please enter 99 followed by a # sign and the computer will repeat the above data as it was entered. To correct any errors, follow the instructions in Flyer No. 83-1. If you do not want the order repeated, enter 46 followed by the # sign.	35 # (Page 8 shows an example of having your entry repeated). PLEASE NOTE THAT if you are disconncected or hang up prior to hearing the message that the computer has accepted your order, YOUR ENTIRE ORDER IS AUTOMATICALLY CANCELLED and you must redial and "RE-ENTER your entire order".

Step	PECOS says	You key in (sample responses provided)
Step 10	If you wish to order additional material using another CAN No. enter 99 and the # sign. If not, press the # sign.	# (Indicates no additional CAN No. is required)

Note: If you enter 99, you will automatically go back to Step 5.

If you stay on the line, a special message will follow which provides instructions or sales information which may be of interest to you or other staff members. You will be disconnected from the System simply by hanging up the receiver.

Example of having order verified:

	The Recorded Voice says	You key in (sample responses provided)
Step 9		9 9 #
(Step 1)	8 1 0 0	Note: your ID number will not be verified
(Step 2)	0 4 4 3 1 4 3 6	#
(Step 3)	3 8 7 4 4 3 4 1 3 6	* 3 8 7 4 4 3 14 3 6 # (original entry incorrect, corrected entry provided)
(Step 4)	7 5 3 0 1 4 8	#
(Step 5	4 6	#
(Step 6)	2 4 6 8 0	* 1 4 6 8 0 #
(Step 7)	7 5 1 0 0 0 0 0 0 1 0 3 1	#
(Step 7)	5	#
	6 5 3 0 0 0 7 7 0 6 4 2 5	#
	5 0	* 5 #
	5 2 5	#
	5 2 7	#

ATTENTION: After each response, you must enter either a # sign which indicates the entry is correct or an * if the entry is in error. When you enter an * this erases the entry and you must reenter the correct data, followed by the # sign.

Note: this entry will not be verified to you.

REQUEST FOR REQUISITIONER IDENTIFICATION (ID) NUMBER

(Complete one form for each person authorized to place orders electronically with the HRSA Supply Service Center, Perry Point, Maryland)

_____ Authorized Person

_____ Office Address

_____

_____ (Zip)

_____ Telephone No. (Give Area Code or indicate FTS)

The person is authorized to submit orders on behalf of the following activity(ies):

(Activity-Hospital, Clinic, etc.) If more than one please list all:	(Address)	(Customer No.)*

_____ Approving Official

_____ Date

---

*Customer No. is the 8-digit number assigned by Perry Point and can be found on any old shipping document from Perry Point.

RETURN THIS FORM TO:

HRSA SUPPLY SERVICE CENTER
PERRY POINT, MARYLAND 21902

DRUG RECEIPT AND ASSIGNMENT LOG

Clinical Center _____

List each drug type (C1, C2, A1, A2, R) on separate forms.

Circle drug type listed on this form: C1 C2 A1 A2 R

Receipt		Assignment			Prescribed by:	
Date	Bottle #	Date	Name of Participant	SHEP ID	Name	Code

Signature of person completing this page: _____ Code

SHEP PARTICIPANT DRUG DISPENSING RECORD

Clinical Center _____

1. Participant's name: _____

2. SHEP ID: [ ][ ] - [ ][ ][ ][ ] - [ ][ ] 3. Acrostic: [ ][ ][ ][ ][ ][ ]

Date	Drug (C1,C2, A1,A2,R*)	Bottle #	Prescription # (if applicable)	Number of Bottles	Prescribed by: Name and Code	Dispensed by: Name and Code

*Note if R is dose 1 or dose 2

CHAPTER 9

AUXILIARY STUDY FORMS

9.1 SHEP ECG Coding Form - SH10

Twelve-lead ECGs and two-minute rhythm strips will be done on all SHEP participants at Baseline Visit 1, Year 2, and the Final Annual Visit (may be Year 4 or Year 5), as described in Appendix C of this manual. ECGs and rhythm strips done at Baseline Visit 1 for participants who are subsequently not randomized should not be sent for coding. All other ECGs should be held at the Clinical Centers until a participant is randomized; at that time, an SH10 should be filled out to initiate the routing and coding process.

At the SHEP Clinic, the participant's ID number and acrostic should be entered into Items 1 and 2 of the SH10. The date the ECG was recorded at the Clinical Center should be entered in Item 3, and the appropriate visit checked in Item 4. The person responsible for obtaining that particular ECG (i.e., placing the leads and running the machine) should record his or her ID code number in Item 5. On the day that the hardcopies are sent to the Coordinating Center, that date should be entered into Item 6. No other items should be filled out by the Clinical Center personnel.

The Clinic should retain a photocopy of the ECG and rhythm strip (or duplicate strips) for the participant's folder, as well as the last NCR copy (goldenrod) of the SH10. The original ECG and rhythm strip should be cut apart and both labelled as per Appendix C instructions. The remaining parts of the SH10 and the original ECG and rhythm strip should be clipped securely together (not stapled) and sent to the Coordinating Center with the next regular mailing of SHEP forms.

The data on this form will not be entered onto the Clinical Center data system.

SHEP ECG CODING FORM

1. SHEP ID: [ ][ ] - [ ][ ][ ][ ] - [ ][ ] 2. Acrostic: [ ][ ][ ][ ][ ][ ]

3. Date ECG recorded at Clinical Center: [ ][ ] Month [ ][ ] Day [ ][ ] Year

4. Type of visit: 1 ☐ Baseline Visit 1
   2 ☐ Second Annual
   3 ☐ Final Annual

5. ECG Technician Code: [ ][ ]

6. Date sent to Coordinating Center: [ ][ ] Month [ ][ ] Day [ ][ ] Year

7. Date Coordinating Center sends to ECG Reading Center: [ ][ ] Month [ ][ ] Day [ ][ ] Year

8. Date of coding: [ ][ ] Month [ ][ ] Day [ ][ ] Year

Twelve-lead ECG:

Q and QS Patterns (1X)			S - T Junction and Segment Depression (4X)			T Wave Items (5X)			ST Segment Elevation (9.2)			R	A-V Conduction Defect	Ventricular Conduction Defect	Arrhythmias (8X)						Ectopic Codes				
1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	3 X	(6X)	(7X)	1 X	2 X	3 X	4 X	5 X	6 X	SVPB	VPB	RN BG	M F	T-R

Miscellaneous Items				Heart Rate (per minute)			+ or −	QRS Axis			Max. R Height (mms)			Max. S Depth (mms)			+ or −	T Hgt. (mms)	R Hgt. (mms)	Tech prob 98	Terminal P V1		CLEAR 1.0
91	93	95	U								Lead I II III		Lead V_4 V_5 V_6	Lead I II III		Lead V_1 V_2 V_3		V5	AVL		Duration	Depth (mms)	

Two-minute rhythm strip:

↳ Specify: _____

Heart Rate (per minute)			QT Duration (m. sec.)				Coupling Interval (m. sec.)				R-R (m.m.)				Ectopic Codes			
															VPB	RN BG	M F	

White - Coordinating Center
Yellow - ECG Center
Pink - Coordinating Center
Goldenrod - Clinic

9.2 Local Laboratory Results - SH11

This form is to be filled out by the SHEP clinician whenever a blood test, urine test or other test is done at the local level. The following local tests are required:

- Hematology, at BL2 and all annual visits
- Urine dipstick analysis, at BL1 and all annual visits

For participants with a history of kidney disease, or proteinuria or hematuria on dipstick urinalysis at Baseline Visit 1, a local serum creatinine is allowed at clinic discretion for exclusion purposes.

Other analyses may be done at the discretion of the clinician, such as re-checks on serum potassium. The serum potassiums required at visits following a start or increase in Step 1 medications are not to be done locally, but sent to the Central Laboratory.

As with most other SHEP forms, the first items entered onto the form are the participant's SHEP ID (Item 1) and acrostic (Item 2), and the date and sequence number of the corresponding clinic visit (Items 3 and 4). If the visit is solely for a serum potassium recheck, and if interim clinic visit documentation is not required, the sequence number of the previous clinic visit should be used. The date that the results are entered onto the form should be entered in Item 5; this may not necessarily be the date that test results are received, particularly if results of multiple tests are received at different times.

Various types of tests are listed: blood tests (Item 6), hematology (Item 7), urine dipstick (Item 8) and other (Item 9). The urine dipstick results listed are those given by the Ames Multistix. Any of these procedures that are not done and therefore not applicable to a particular SH11, should be checked "Not done" and no results recorded. For example, if only a serum potassium was done, those results should be recorded in the boxes provided for serum potassium (Item 6b). The box in front of serum potassium (Item 6a) should be checked, and the "Not done" boxes for Item 7 (hematology), Item 8 (urine dipstick) and Item 9 (other) should be checked.

Comments that the clinician feels are appropriate on any tests, or action required as a result of a test, should be recorded in Item 10 (Comments). The person completing the form should then sign their name and enter their ID code in Item 11.

This form should not be completed for SHEP Central Laboratory results (Chem-Screen Profile, Lipid Analyses, and potassium results after an increase in Step 1 medications).

LOCAL LABORATORY RESULTS

This form is to be filled out by the clinician whenever a blood sample, urine sample, or other test is done for local analysis.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date of clinic visit: ☐☐ ☐☐ ☐☐ 4. Sequence #: ☐☐
Month Day Year

5. Date form is filled out ☐☐ ☐☐ ☐☐
(within 24 hours of receiving lab results): Month Day Year

6. Blood results: 1 ☐ Not done

a. 1 ☐ Potassium b. ☐.☐ mEq/l

c. 1 ☐ Uric acid d. ☐☐.☐ mg/dl

e. 1 ☐ Creatinine f. ☐.☐☐ mg/dl

g. 1 ☐ Glucose h. ☐☐☐☐ mg/dl

i. 1 ☐ Sodium j. ☐☐☐ mEq/l

k. 1 ☐ Cholesterol l. ☐☐☐☐ mg/dl

m. 1 ☐ BUN n. ☐☐☐ mg/dl

o. 1 ☐ SGOT p. ☐☐☐☐ mu/ml

q. 1 ☐ Calcium r. ☐☐.☐ mg/dl

s. 1 ☐ HDL t. ☐☐☐ mg/dl

u. 1 ☐ Triglycerides v. ☐☐☐ mg/dl

w. 1 ☐ Other (specify)_____

7. Hematology results: 1 ☐ Not done

a. WBC (thousands) ☐☐ . ☐

b. Hematocrit (%) ☐☐ . ☐

c. Hemoglobin ☐☐ . ☐ g/100 ml

d. Other (specify) _____

8. Dipstick Urinalysis Results: 1 ☐ Not done

a. Protein:
1 ☐ Negative
2 ☐ Trace
3 ☐ 1+
4 ☐ 2+
5 ☐ 3+
6 ☐ 4+
7 ☐ DK

b. Glucose:
1 ☐ Negative
2 ☐ 1/10%
3 ☐ ¼%
4 ☐ ½%
5 ☐ 1%
6 ☐ 2+%
7 ☐ DK

c. pH:
1 ☐ pH 5
2 ☐ pH 6
3 ☐ pH 6.5
4 ☐ pH 7
5 ☐ pH 7.5
6 ☐ pH 8
7 ☐ pH 8.5
8 ☐ DK

d. Blood:
1 ☐ Negative
2 ☐ Non-hemolyzed trace
3 ☐ Hemolyzed trace
4 ☐ 1+
5 ☐ 2+
6 ☐ 3+
7 ☐ DK

e. Bilirubin:
1 ☐ Negative
2 ☐ 1+
3 ☐ 2+
4 ☐ 3+
5 ☐ DK

f. Ketones:
1 ☐ Negative
2 ☐ Trace
3 ☐ Small
4 ☐ Moderate
5 ☐ Large
6 ☐ DK

g. Urobilinogen:
1 ☐ Negative
2 ☐ 1 Ehrlich unit/dl
3 ☐ 2 Ehrlich units/dl
4 ☐ 4 Ehrlich units/dl
5 ☐ 8 Ehrlich units/dl
6 ☐ 12 Ehrlich units/dl
7 ☐ DK

} Normal range

9. Other tests: 1 ☐ None

_____

_____

10. Comments: _____

_____

11. Person completing form: _____ ☐☐
Signature Code

9.3 Receipt of Central Laboratory Alert Level - SH13

The Central Laboratory will alert the Clinical Center by telephone if any values on the laboratory tests are in what is considered to be an "alert" range (specified in Section 4.3.2 of this manual). Potassium and uric acid are the only tests for which the SHEP protocol specifies alert values and actions, so the clinic may receive some calls that do not, at least by our protocol, require action by the SHEP clinician. They may, however, be of some interest for general medical management of the participant. This form allows the documentation of those alerts.

The SHEP ID and acrostic (Items 1 and 2) should be entered first. The date and sequence number of the applicable clinic visit (Items 3 and 4), should also be completed. This should be the clinic visit for which the blood sample was drawn. Item 5 (Date test result received) is the date of the telephone call from the Central Laboratory. Item 6 (Date result received by clinician) may be filled out later, but should be the date that the alert report was reviewed by a SHEP clinician.

The result (Item 7) should be filled in while still in telephone contact with the laboratory, should be repeated as written by the receiver, and confirmed by the laboratory person who is calling.

Since only potassium and uric acid values are of immediate interest according to the protocol, and may require action by the SHEP clinician, these are listed separately. If an alert value is received for either potassium or uric acid, the box in front of that test should be checked, and the value entered in the boxes to the right. Any other out-of-range value received from the Central Laboratory should be considered as "Other" and described (test name and result) in the space provided.

More than one alert level may be received in one telephone call and may be listed on the same form. More than one alert value may be described under "Other."

The person at the Clinical Center who received the results should, upon completion of the call, sign the form in Item 8 and enter their ID code.

When the SHEP clinician reviews the result, he or she should complete Item 6 (date result received by clinician), sign the form in Item 9 and enter his or her ID code.

RECEIPT OF ALERT LEVEL FROM CENTRAL LABORATORY

To be completed upon receipt of abnormal laboratory test result from the Central Laboratory.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐

2. Acrostic: ☐☐☐☐☐☐

3. Date of clinic visit: ☐☐ ☐☐ ☐☐
   Month Day Year

4. Sequence #: ☐☐

5. Date test result received: ☐☐ ☐☐ ☐☐
   Month Day Year

6. Date result received by clinician: ☐☐ ☐☐ ☐☐
   Month Day Year

7. Result (check all that apply)

   a. 1 ☐ Potassium → b. ☐ . ☐ mEq/l

   c. 1 ☐ Uric acid → d. ☐☐ . ☐ mg/dl

   e. 1 ☐ Other → Describe: _____

   _____

   _____

8. Signature of person receiving result: _____ ☐☐
   Code

9. Signature of clinician reviewing result: _____ ☐☐
   Code

9.4 CT Scan Coding Form - SH14

This form is similar in function to the SH10 (SHEP ECG Coding Form), and is used whenever a CT scan is obtained from existing medical records or done by a SHEP consulting neurologist.

Items 1 through 5 only should be filled out by Clinical Center personnel. The SHEP ID and acrostic (Items 1 and 2) should be entered first. Item 3 (Date this form initiated), is simply the date that these items are entered onto the form. The date that the CT scan was taken should be filled into Item 4a. The source of the CT scan refers to whether or not the CT scan had been (1) already requested by a non-SHEP physician or neurologist and was available in the medical record or (2) unavailable and, therefore, requested by SHEP neurologist or SHEP physician. The submission of a CT scan is motivated by the ascertainment of a possible SHEP neurologic event; medical records for these events are submitted with a Final Report (SH22 or SH24). The date of that final report should be entered into Item 5.

The CT scan and the SH14, plus the final report and other records, should be prepared for submission to the Coordinating Center as per Section 9.6 or 9.8 of this manual.

The Clinic should keep the goldenrod copy of the first page of the SH14, as instructed below Item 5, for the participant's record.

SHEP CT SCAN CODING FORM FOR STROKE

1. SHEP ID: [ ] - [ ] - [ ] 2. Acrostic: [ ]

3. Date this form initiated: [ ] [ ] [ ] Month Day Year

4. a. Date of CT scan: [ ] [ ] [ ] Month Day Year

   b. Source of CT scan: Available with participant's medical record ☐ 1
   SHEP ☐ 2

5. a. Date of Final Report (SH21 or SH23, Item 3) to which this CT scan applies: [ ] [ ] [ ] Month Day Year

   b. Date of onset of event/date of death: [ ] [ ] [ ] Month Day Year

Clinic: Keep goldenrod copy of this page only.

---

6. a. Date Coordinating Center sends to CT Scan Reading Center: [ ] [ ] [ ] Month Day Year

   b. Coder number: [ ]

---

7. Date of coding: [ ] [ ] [ ] Month Day Year

8. a. This is a: CT Scan ☐ 1
   MRI ☐ 2
   Other (specify_____) ☐ 3

   b. Technical adequacy of this study: Adequate ☐ 1
   Inadequate ☐ 2
   Unknown ☐ 3

9. Is CT scan normal? Normal ☐ 1 → STOP
   Abnormal ☐ 2

10. Number of lesions related to this event: [ ] → If none, skip to Item 27.

DESCRIPTION OF LESIONS: Put the most important lesion in Column 1, next in Column 2, etc.

		1	2	3	4	5	6
11.	Side:	☐	☐	☐	☐	☐	☐
	Codes: 1 Mid, 2 Left, 3 Right, 4 Both						
12.	Pathology (circle all applicable):						
	No longer seen	01	01	01	01	01	01
	Superficial infarct	02	02	02	02	02	02
	Deep, small infarct (<2 cm)	03	03	03	03	03	03
	Deep, large infarct	04	04	04	04	04	04
	Super and deep infarct	05	05	05	05	05	05
	Intracerebral hemorrhage (ICH)	06	06	06	06	06	06
	Subarachnoid hemorrhage (SAH)	07	07	07	07	07	07
	AVM	08	08	08	08	08	08
	Aneurysm	09	09	09	09	09	09
	Other (specify_____)	10	10	10	10	10	10
13.	Anatomy (circle all applicable):						
	Frontal lobe	01	01	01	01	01	01
	Parietal lobe	02	02	02	02	02	02
	Temporal lobe	03	03	03	03	03	03
	Occipital lobe	04	04	04	04	04	04
	Operculum	05	05	05	05	05	05
	Insula	06	06	06	06	06	06
	Caudate	07	07	07	07	07	07
	Putamen	08	08	08	08	08	08
	Thalamus	09	09	09	09	09	09
	Anterior capsule	10	10	10	10	10	10
	Genu	11	11	11	11	11	11
	Posterior capsule	12	12	12	12	12	12
	Corona radiata	13	13	13	13	13	13
	Centrum semiovale	14	14	14	14	14	14
	Corpus callosum	15	15	15	15	15	15
	Midbrain	16	16	16	16	16	16
	Pons	17	17	17	17	17	17
	Medulla	18	18	18	18	18	18
	Cerebellum	19	19	19	19	19	19
	Ventricular space	20	20	20	20	20	20
	Subarachnoid space	21	21	21	21	21	21
	Subdural space	22	22	22	22	22	22
	Epidural space	23	23	23	23	23	23
14.	Section thickness (mm):	☐☐.☐	☐☐.☐	☐☐.☐	☐☐.☐	☐☐.☐	☐☐.☐
15.	Number of sections lesion is visible in:	☐	☐	☐	☐	☐	☐
16.	Largest diameter (mm):	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
17.	Diameter (mm) at right angles to diameter in Item 16:	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐

Explanation of Codes for Items 18-25:

Density (18):

1 Low
2 High
3 Both (mixed)
4 Isodense

Size change from previous CT (20):

0 None
1 Initial
2 Smaller
3 Larger
4 Not applicable/no previous CT

Enhancement, type (24):

1 Gyral/deep
2 Ring
3 Other
4 None

Size scale (19):

0 Absent
1 <1 cm
2 <½ lobe
3 <1 lobe
4 >1 lobe

Edema/Mass/Enhancement (21-23):

0 Absent
1 Mild
2 Moderate
3 Marked
4 Not applicable

Clin Relevance (25):

0 Lesions consistent with time from onset to CT
1 Not consistent
2 Unkown

	1	2	3	4	5	6
18. Density	☐	☐	☐	☐	☐	☐
19. Size, scale	☐	☐	☐	☐	☐	☐
20. Size, change from previous CT	☐	☐	☐	☐	☐	☐
21. Edema	☐	☐	☐	☐	☐	☐
22. Mass effect	☐	☐	☐	☐	☐	☐
23. Enhancement	☐	☐	☐	☐	☐	☐
24. Enhancement, type	☐	☐	☐	☐	☐	☐
25. Clin relevance	☐	☐	☐	☐	☐	☐

SKIP ITEM 26 IF PATHOLOGY (ITEM 12) DOES NOT INCLUDE HEMORRHAGE.

Explanation of codes for Item 26:

For SAH:

0 None
1 Diffuse and less than 1 mm
2 Localized clot or greater than 1 mm
3 Clots

For ICH:

0 None
1 Intraventricular extension
2 Cisternal
3 Both

	1	2	3	4	5	6
26. Hemorrhage:	☐	☐	☐	☐	☐	☐

CT SCAN ABNORMALITIES

27. Cortical atrophy?

None ☐ 1
Minimal ☐ 2
Moderate ☐ 3
Marked ☐ 4
Unknown ☐ 5

28. Hydrocephalus?

None ☐ 1
Minimal ☐ 2
Moderate ☐ 3
Marked ☐ 4
Unknown ☐ 5

29. Periventricular hypodensity (by CT):

Not present ☐ 1
Visible ☐ 2
Not applicable ☐ 3

30. Bright plaques (T 2 image MRI):

Not present ☐ 1
Visible ☐ 2
Not applicable ☐ 3

31. Comments or additional description:

32. CT Coder Signature: _____

STOP

Coordinating Center Use Only

33. Coding result:

Agrees with other coder ☐ 1
Needs adjudication ☐ 2

Adjudicator's Use Only

34. Result of adjudication:

Use this coder's form ☐ 1
Use alternate coder's form ☐ 2

35. Comments:

36. Signature of adjudicator: _____

9.5 Initial Notification of Morbid Event - SH20

Morbid events may be ascertained during a SHEP clinic visit, follow-up for a missed visit, or other notification by the participant's family, a friend, or personal physician, and through the use of the HCFA tapes. These morbid events include possible strokes, acute myocardial infarction, left ventricular failure, transient ischemic attacks, other hospitalizations, and intermediate or skilled nursing home admissions. "Other hospitalizations" does not include emergency room visits or outpatient surgeries.

Upon ascertaining that one of the above morbid events has possibly occurred, an SH20 (Initial Notification of Morbid Event) should be completed and mailed to Terri Henry at the Coordinating Center within 48 hours, with the appropriate batch sheet (see Appendix F).

The participant's SHEP ID and acrostic should be entered into Items 1 and 2, checking to be sure that they match the participant's SH06. The date the form is completed should be entered into Item 3. The date of onset of the morbid event (Item 4) will have been reported by the participant, or should be ascertained as closely as possible by clinic personnel at the time of notification of the event. Please do not use any "99s" in this date. Give your best estimate for the event date. If you are not sure of the exact day use "15."

Some judgment is required in Item 5 regarding the possible nature of the event. These events are defined in Chapter 5 of this manual. Multiple events may be indicated.

If the event includes a possible stroke, box 5a should be checked; a SHEP Neurological Evaluation of Stroke (SH27) and a CT scan (if not already done) should be obtained as soon as possible.

If the event includes transient ischemic attack, box 5d should be checked; a SHEP Neurological Evaluation for TIA (SH28) should be obtained as soon as possible.

If the event includes an MI, left ventricular failure, hospitalization for other reason, or admission to a skilled or intermediate care nursing home (Item 5b, 5c, 5e, 5f), the boxes in front of those items should be checked. For other hospitalizations and admissions to skilled or intermediate care nursing homes, a reason should be provided.

Item 6 asks whether the participant has been hospitalized or admitted to a skilled or intermediate care nursing home for this event; if so, fill in the name, address and telephone number of the hospital or nursing home, and the date of admission. (If the address and telephone number are not known at the time of notification, they may be looked up later.) As stated previously, emergency room visits and outpatient surgeries do not count as hospitalizations. If the participant has had a possible stroke, TIA, MI or LVF and was only seen in the emergency room, then "No" should be checked here--in this case, check "Yes" to Item 7 (Non-SHEP physician visit). If a blanket authorization to obtain medical and hospital records has not been signed, the participant should be asked to sign an authorization at this time. If the participant is not able to provide authorization, a family member may be asked to do so.

Item 7, regarding visits to a non-SHEP physician, may be reported by the participant at a SHEP clinic visit, but otherwise may be difficult to determine if the clinic is notified of the event by someone other than the participant. If notified by a family member or friend, some probing may be done to obtain some information about any physician visits in the several weeks prior to the event. If it can be determined that the participant was seen by his or her personal physician in the several weeks prior to the event, authorization should be obtained (as described above) to obtain the medical records. (If the participant was hospitalized, or a private MD visit did not pertain to the possible event, these records are not usually necessary.)

The person completing the form should then sign the form and enter their ID code in Item 8.

It should be noted that complete hospitalization or nursing home records should be obtained in the case of possible stroke, acute myocardial infarction, left ventricular failure, and TIA. For events including only a hospitalization for any other reason, and/or an admission to a skilled or intermediate care nursing home, only the discharge summary or admission record need be obtained.

INITIAL NOTIFICATION OF MORBID EVENT

SPECIAL INSTRUCTIONS

- This form should be completed and a copy mailed to the Coordinating Center within 48 hours after the SHEP staff learns that a randomized participant has had a possible stroke, MI, TIA, left ventricular failure, other hospitalization or intermediate or skilled nursing home admission during a routine SHEP clinic visit or through other notification.
- A Final Report of Morbid Event (SH21) should be completed within 6 weeks and sent to the Coordinating Center with appropriate attached materials.
- If the participant dies during the acute phase of this same event, complete Forms SH22 and SH23 for fatal events, instead of the SH20 and SH21.

1. SHEP ID: [ ] - [ ] - [ ]

2. Acrostic: [ ]

3. Date this form completed:
   [ ] [ ] [ ]
   Month Day Year

4. Date of onset of morbid event:
   [ ] [ ] [ ]
   Month Day Year

5. Nature of possible morbid event (check all that apply):
   a. 1 □ Stroke - obtain SHEP Neurological Exam for Stroke (SH27) and CT Scan (if not already available) as soon as possible
   b. 1 □ Acute myocardial infarction
   c. 1 □ Left ventricular failure
   d. 1 □ Transient ischemic attack - obtain SHEP Neurological Exam for TIA (SH28) as soon as possible
   e. 1 □ Other hospitalization → Reason: _____
   f. 1 □ Admission to intermediate or skilled nursing home

6. Was the participant hospitalized or admitted to an intermediate or skilled care nursing home? Yes □ 1 No □ 2 Unknown □ 3

   Institution _____
   Address _____
   City _____ State ____ Zip ____
   Telephone number _____
   Date of admission _____

   Obtain complete hospital or nursing home record for stroke, MI, LVF and TIA. For other hospitalizations, obtain discharge summary or admission record only.

7. Was the participant seen by a non-SHEP physician? Yes □ 1 No □ 2 Unknown □ 3

   Name _____
   Address _____
   City _____ State ____ Zip ____
   Telephone number _____
   Date(s) _____

   Obtain medical records.

8. Person completing this form: _____ [ ]
   Signature Code

9.6 Final Report of Morbid Event - SH21

This form should be completed and sent to the Coordinating Center, along with the appropriate documents, within six weeks of the Initial Report (SH20) of a possible stroke, acute MI, left ventricular failure, transient ischemic attack, other hospitalization or admission to a skilled or intermediate care nursing home. "Other hospitalization" does not include emergency room visits or outpatient surgeries.

As with the SH20, the SHEP ID, acrostic, date form completed, and the date of onset of the event (Items 1-4) should be completed. Check to be sure that the ID and acrostic match what is on the participant's SH06. If the date of onset of symptoms cannot be determined, the date of hospital or nursing home admission (if applicable) or date of detection may be used here. Item 5, whether or not the participant was hospitalized or admitted to a nursing home, and date of admission and discharge, should be filled in next; the dates may be obtained from the records themselves or, if the records were not obtained, from the participant or his/her family, friends, or physician, or other resource. If the event is a possible MI, LVF, stroke or TIA and the participant was only seen in the emergency room, then 5a should be checked "no" and 5b and 5c should be skipped.

The records that will be attached should be checked in Item 6. These may include hospital records, a SHEP Neurological Evaluation for Stroke (SH27), a CT scan, SHEP Neurological Evaluation for TIA (SH28), emergency room records, ambulance records, nursing home records, records form the participant's private physician or other source of care, and interviews with the participant, his or her physician, or next-of-kin (an SH24). Records will fit into one of three categories:

"Does Not Exist" - applies to items that are known not to be applicable, (e.g., a CT scan for a possible LVF) or that are not known to exist

"Enclosed" - applies to documents that are attached to the SH21 and will be sent to the Coordinating Center

"Not enclosed" - applies to documents that are known to exist, but are not enclosed (e.g., if no authorization is available to obtain records, or Clinical Center still trying to obtain records)

If the records exist but are "Not Enclosed," a "Reason" is expected. If the event is a possible stroke, and a CT scan is "Not Enclosed" or "Does Not Exist," the Coordinating Center's endpoint monitor, Terri Henry, will be calling for verification. Every effort should be made to get a CT scan on every participant who has had a possible stroke (a written report of CT scan results is not acceptable). Similarly, for possible MIs, photocopies of ECGs (not just written reports) and enzyme results will be expected if a hospitalization or emergency room visit occurred.

The person completing the form should then sign the form (Item 7) and enter their ID code. The Principal Investigator should review the form and the documents that are to be attached for completeness and accuracy, and sign the form.

The SH21 and the attached documents should be clipped together, and put in an envelope that will accommodate them without folding. The participant's ID and acrostic and "SH21" should then be entered onto the front of the envelope, and the packet should be sent to the Coordinating Center with the next regular SHEP mailing.

FINAL REPORT OF MORBID EVENT

SPECIAL INSTRUCTIONS

This form, together with attached documents and other forms, should be completed and forwarded to the Coordinating Center no later than six weeks after submitting Form SH20.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date this form completed: ☐☐ Month ☐☐ Day ☐☐ Year

4. Date of onset of morbid event: ☐☐ Month ☐☐ Day ☐☐ Year

5. a. Was participant hospitalized or admitted to a skilled or intermediate care nursing home? Yes ☐ 1 No ☐ 2 Unknown ☐ 3

   b. Date of admission (if hospitalized): ☐☐ Month ☐☐ Day ☐☐ Year

   c. Date of discharge (if applicable): ☐☐ Month ☐☐ Day ☐☐ Year

6. The following records are enclosed:

	Does Not Exist	Enclosed	Not Enclosed →	Reason
a. Hospital records				
(1) Discharge summary	☐ 1	☐ 2	☐ 3	
(2) Discharge diagnosis	☐ 1	☐ 2	☐ 3	
(3) ECGs	☐ 1	☐ 2	☐ 3	
(4) Laboratory reports	☐ 1	☐ 2	☐ 3	
(5) Non-SHEP CT scan	☐ 1	☐ 2	☐ 3	
(6) X-ray or angiography result	☐ 1	☐ 2	☐ 3	
(7) Surgical pathology results	☐ 1	☐ 2	☐ 3	
b. SHEP Neurologic Exam for Stroke (SH27)	☐ 1	☐ 2	☐ 3	
c. SHEP CT scan	☐ 1	☐ 2	☐ 3	
d. SHEP Neurologic Exam for TIA (SH28)	☐ 1	☐ 2	☐ 3	
e. Emergency room records	☐ 1	☐ 2	☐ 3	
f. Ambulance records	☐ 1	☐ 2	☐ 3	
g. Nursing home records	☐ 1	☐ 2	☐ 3	
h. Records from usual source of care	☐ 1	☐ 2	☐ 3	
i. Interviews (SH24)				
(1) Participant	☐ 1	☐ 2	☐ 3	
(2) Participant's physician	☐ 1	☐ 2	☐ 3	
(3) Next-of kin	☐ 1	☐ 2	☐ 3	

7. Signature of person completing this form: _____ Signature ☐☐ Code

8. Signature of PI, who has reviewed this form and attached records for completeness and accuracy: _____ Signature

9.7 Initial Notification of Death - SH22

This form should be completed within 48 hours after the SHEP Staff learns of any randomized participant's death, and should be mailed to Mrs. Donna Spross at the Coordinating Center within 48 hours of completion, with the appropriate batch sheet (see Appendix F).

Items 1 though 4 are similar to Items 1 through 4 on the morbid event reporting forms: the participant's SHEP ID and acrostic, the date the form was completed, and the date of death. Check to be sure that the ID and acrostic match the participant's SH06. Item 5 is the date that the SHEP Staff learned of the death.

The place of death (Item 6) requires entry of the city, county, proper state abbreviation (see attached list) and zip code (if known). This information is useful in obtaining the death certificate, as well as in locating other information on the circumstances surrounding the death (e.g., Items 7 and 8). (If the place of death is a foreign country, do not fill in abbreviation or zip code.)

Item 7, regarding hospitalization after onset of the fatal event, should be filled in at the time of notification. Within 48 hours, if it is not able to be determined that the participant definitely was or was not taken to a hospital, then "Unknown" should be checked and the form submitted to the Coordinating Center within the 48-hour period. Please note the wording "taken to a hospital." This includes any visit to the hospital including emergency room visits.

Item 8, regarding visits to a non-SHEP clinician, should be handled similarly. If, within 48 hours of notification, it cannot be determined if the participant did or did not visit a non-SHEP physician, "Unknown" should be checked, and the form submitted to the Coordinating Center within the 48-hour period.

If a blanket authorization has not been signed by the participant, it may be necessary to obtain permission from the participant's next-of-kin to obtain the death certificate and the pertinent medical records.

The person completing the form should sign and enter their ID code in Item 9.

TWO-LETTER STATE ABBREVIATIONS

Alabama	AL	Kentucky	KY	Ohio	OH
Alaska	AK	Louisiana	LA	Oklahoma	OK
Arizona	AZ	Maine	ME	Oregon	OR
Arkansas	AR	Maryland	MD	Pennsylvania	PA
California	CA	Massachusetts	MA	Puerto Rico	PR
Colorado	CO	Michigan	MI	Rhode Island	RI
Connecticut	CT	Minnesota	MN	South Carolina	SC
Delaware	DE	Mississippi	MS	South Dakota	SD
District of Columbia	DC	Missouri	MO	Tennessee	TN
Florida	FL	Montana	MT	Texas	TX
Georgia	GA	Nebraska	NB	Utah	UT
Guam	GU	Nevada	NV	Vermont	VT
Hawaii	HI	New Hampshire	NH	Virginia	VA
Idaho	ID	New Jersey	NJ	Virgin Islands	VI
Illinois	IL	New Mexico	NM	Washington	WA
Indiana	IN	New York	NY	West Virginia	WV
Iowa	IA	North Carolina	NC	Wisconsin	WI
Kansas	KS	North Dakota	ND	Wyoming	WY

INITIAL NOTIFICATION OF DEATH

SPECIAL INSTRUCTIONS

- This form should be completed within 48 hours after the SHEP staff learns of any randomized participant's death.
- A copy of this form should be mailed to the Coordinating Center within 48 hours after completion.
- The Final Report of Death Form (SH23) should be completed within 6 weeks and sent to the Coordinating Center with appropriate materials attached.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date this form completed: ☐☐ Month ☐☐ Day ☐☐ Year

4. Date of death: ☐☐ Month ☐☐ Day ☐☐ Year

5. Date SHEP staff learned of death: ☐☐ Month ☐☐ Day ☐☐ Year

6. Place of death: _____ / _____ City County ☐☐ State ☐☐☐☐☐ Zip

7. After the onset of the fatal event, was the participant taken to a hospital? Yes ☐ 1 No ☐ 2 Unknown ☐ 3

   Hospital _____

   Address _____

   City _____ State____ Zip _____

   Telephone number _____

   Date of admission _____

   Obtain hospital records.

8. After the onset of the fatal event, was the participant seen by a clinician? Yes ☐ 1 No ☐ 2 Unknown ☐ 3

   Name _____

   Address _____

   City _____ State____ Zip _____

   Telephone number _____

   Date(s)_____

   Obtain medical records.

9. Signature of person completing this form: _____ Signature ☐☐ Code

9.8 Final Report of Death - SH23

This form is to be completed and forwarded to the Coordinating Center no later than six weeks after the SHEP staff learns of participant's death. Copies of the appropriate documents should accompany the form, as described below.

The first four items are the same as on the Initial Notification (SH22)--SHEP ID and acrostic (check to be sure that the ID and acrostic match the participant's SH06), date form completed, and date of death. The date of death, if not reported correctly on the SH22, should be updated here. Do not automatically copy this information from the SH22.

If known, the time of death should be entered in Item 5. Do not use military time; a box for a.m. or p.m. is provided. If unknown, fill in the boxes with 9s.

If a death certificate is attached, this should be indicated as "Yes" in Item 6. It is anticipated that, in most cases, the death certificate will be available eventually, but not always in the six-weeks allowed. If a death certificate is not available by that time, the form should be submitted with this item marked "No," and an explanation provided in Item 9. If the death certificate is subsequently available, it may be submitted with an SH67 ("Correction to Previously Transmitted Data") to correct Item 6 to "Yes."

It should be indicated in Item 7 whether or not an autopsy was performed. If it is not known whether an autopsy was definitely performed ("Yes") or definitely not performed ("No"), "DK" should be marked. (The death certificate will indicate if an autopsy was performed.) If an autopsy was performed, indicate if a copy of the report is attached ("Copy of report attached") or not ("Copy not attached"). If an autopsy was performed and a copy of the report is not attached, an explanation should be provided in Item 9.

Records that will accompany this form should be indicated in Item 8, which is similar to Item 6 on the Final Report of Morbid Event (SH21):

"Does Not Exist" - applies to items that are known not to be applicable, or that are not known to exist

"Enclosed" - applies to documents that are attached to the SH23 and will be sent to the Coordinating Center

"Not enclosed" - applies to documents that are known to exist, but are not enclosed (e.g., if no authorization is available to obtain records, or Clinical Center is still trying to obtain records)

Any "Not Enclosed" requires an explanation in Item 9, "Comments." In Item 8h ("Interviews"), the number of each type of interview (with witness to death, next of kin, or participant's physician) should be entered into the appropriate spaces.

When the documentation is complete, and all obtainable records have been gathered, or when six weeks have passed, the person responsible for this form should sign it and enter their ID code in Item 10. The Principal Investigator should review the documents for completeness and accuracy, and sign at Item 11.

The SH23 and the other documents should be clipped together, and put in an envelope that will accommodate them without folding. The participant's ID and acrostic and "SH23" should then be entered onto the front of the envelope, and the packet should be sent to the Coordinating Center with the next regular mailing of SHEP forms.

FINAL REPORT OF DEATH

SPECIAL INSTRUCTIONS

- This form is to be completed and forwarded to the Coordinating Center no later than 6 weeks after staff learns of participant's death.
- Copies of the appropriate documents should accompany this form.
- Each of the documents should be carefully reviewed for completeness prior to being forwarded to the Coordinating Center.
- The participant's SHEP ID and acrostic should be entered onto the top of each accompanying document.

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date this form completed: ☐☐ Month ☐☐ Day ☐☐ Year

4. Date of death: ☐☐ Month ☐☐ Day ☐☐ Year

5. Time of death, if known: ☐☐ Hour : ☐☐ Minute ☐ a.m. ☐ p.m.

6. Is a copy of the death certificate enclosed? 1 ☐ Yes 2 ☐ No → Explain in Comments, Section 9.

7. Was an autopsy performed? a. 1 ☐ Yes → b. 1 ☐ Copy of report attached; 2 ☐ Copy not attached (explain in Comments, Section 9); 2 ☐ No; 3 ☐ DK

8. The following records are enclosed:

	Does Not Exist	Enclosed	Not Enclosed →	Explain in Comments, Section 9.
a. Hospital records				
(1) Discharge summary	☐ 1	☐ 2	☐ 3	
(2) Discharge diagnosis	☐ 1	☐ 2	☐ 3	
(3) ECGs	☐ 1	☐ 2	☐ 3	
(4) Laboratory reports	☐ 1	☐ 2	☐ 3	
(5) Non-SHEP CT scan	☐ 1	☐ 2	☐ 3	
(6) X-ray or angiography results	☐ 1	☐ 2	☐ 3	
(7) Surgical pathology results	☐ 1	☐ 2	☐ 3	
b. SHEP Neurologic Exam for Stroke (SH27)	☐ 1	☐ 2	☐ 3	
c. SHEP CT scan	☐ 1	☐ 2	☐ 3	
d. SHEP Neurologic Exam for TIA (SH28)	☐ 1	☐ 2	☐ 3	
e. Emergency room records	☐ 1	☐ 2	☐ 3	

		Does Not Exist	Enclosed	Not Enclosed →	Explain in Comments, Section 9.
f.	Ambulance records	☐ 1	☐ 2	☐ 3	
g.	Nursing home records	☐ 1	☐ 2	☐ 3	
h.	Records from usual source of care	☐ 1	☐ 2	☐ 3	
i.	Interviews				
	(1) Witness to death (SH26)	☐ 1	☐ 2	☐ 3	
	(a) Number ___				
	(2) Next-of-kin (SH26)	☐ 1	☐ 2	☐ 3	
	(a) Number ___				
	(3) Participant's clinician (SH25)	☐ 1	☐ 2	☐ 3	
	(a) Number ___				

Note: Interviews with the witness to death, next of kin or participant's clinician should be sought for every out-of-hospital death. For deaths occurring in the hospital, these interviews are optional, and indicated whenever the Principal Investigator believes the additional information would contribute usefully to assigning the cause of death.

9. Comments: _____

_____

_____

_____

10. Signature of person completing this form: _____ ☐☐
Signature Code

11. Signature of PI, who has reviewed this form and attached records for completeness and accuracy: _____
Signature of PI

9.9 Interview with Participant, Next of Kin, or Personal Clinician for Morbid Event - SH24

If the Principal Investigator feels that the information available on a possible morbid event is not adequate, particularly if the participant was not hospitalized or more details are needed (or available) on recent medical history, interviews may be sought with the participant, his or her family, or personal physician. This interview form may also provide a written documentation of pertinent details that are revealed in conversations and discussions during a search of or for medical records. It may also be useful during a clinic visit to have a place to document comments offered by the participant in response to certain questions that are apparently "yes/no" questions. For example, at every clinic visit the participant is asked about several general symptoms for stroke (see SH08, Items 20-25). These questions may be answered "yes," and prompt comments from the participant that would be useful to the Endpoint and Toxicity Subcommittee in coding a possible stroke, but would not necessarily be recorded elsewhere.

A separate SH24 should be filled out for each of these interviews. The person being interviewed should be aware of the fact that their comments will be recorded, and give their verbal permission.

Since there are so many different types of morbid events in the SHEP, no specific questions are provided. Space is provided for relevant comments from the person being interviewed (Item 6) and from the interviewer (Item 7). During the interview, documents may be provided that are not listed on the SH21 (e.g., a letter or a note), and these should be listed in Item 8 ("Nature of documents attached, if any").

The participant's SHEP ID and acrostic should be entered into Items 1 and 2, the date of the interview entered into Item 3, and the date of the onset of morbid event into Item 4. Item 5 identifies the person being interviewed: name, relationship to participant (write "self" or "participant" if the participant is being interviewed), address and telephone number. These items may be filled out prior to the interview for scheduled interviews, or after the interview (for unscheduled interviews). It may be useful, for scheduled interviews, to record the name of the participant in the space provided for reference by the interviewer.

INTERVIEW WITH PARTICIPANT, NEXT OF KIN, OR PERSONAL CLINICIAN FOR MORBID EVENT

SPECIAL INSTRUCTIONS

This form offers an opportunity to record any relevant findings from interviews regarding a randomized participant who had had a morbid event.

Fill out a separate form for each interview and attach any relevant documents.

Participant's Name: _____

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date of this interview: ☐☐ ☐☐ ☐☐
   Month Day Year

4. Date of onset of morbid event: ☐☐ ☐☐ ☐☐
   Month Day Year

5. a. Name of person interviewed: _____
   b. Relationship to participant: _____
   c. Address: _____
      City _____ State _____ Zip _____
   d. Telephone number: _____

6. Relevant comments from person interviewed: _____

7. Relevant comments from interviewer: _____

8. Nature of documents attached, if any: _____

9. Signature of interviewer: _____ ☐☐
   Signature Code

9.10 Interview with Participant's Physician In the Case of a Death - SH25

These interviews should be accomplished for all out-of-hospital deaths and for certain in-hospital deaths if the Principal Investigator feels that the interview is likely to contribute useful information for assigning cause of death. More than one physician may be interviewed. The form may be prepared as described below and mailed to the participant's physician with a return envelope, if this is more convenient to the SHEP staff and the physician from whom information is being sought.

Prior to the interview, the participant's name, SHEP ID and acrostic should be entered onto the form, as well as the identification of the physician interviewed (name, address, telephone number). The date of the interview and the date form completed will probably, but not necessarily, be the same day (e.g., interviews may be interrupted, or the physician may need to access records that are not available at the interview site).

The remaining Items (6 through 13) are the interview items, and include:

6. Date of last contact with participant
7. Information on terminal or life-threatening diseases
8. Visits in the two weeks prior to death
9. Co-morbid conditions
10. Recent signs and symptoms
11. Other circumstances surrounding the death
12. Recent ECGs
13. Who pronounced the patient dead

At the conclusion of the interview, the SHEP clinician should then sign the form (Item 14) and enter his or her ID code.

INTERVIEW WITH PARTICIPANT'S PHYSICIAN IN THE CASE OF A DEATH

SPECIAL INSTRUCTIONS

- This form should be completed within 6 weeks of the out-of-hospital death of a randomized participant and also for certain in-hospital deaths if the interview is likely to contribute information useful for assigning cause of death.
- The interview should be carried out with the participant's personal physician (or other regular source of medical care).
- More than one form may be filled out if more than one physician was involved in the terminal care that was provided.

Participant's Name: _____

1. SHEP ID: ☐☐ - ☐☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date this form completed: ☐☐ Month ☐☐ Day ☐☐ Year

4. Date physician interviewed: ☐☐ Month ☐☐ Day ☐☐ Year

5. Physician Interviewed:
   Name _____
   Address _____
   City _____ State _____ Zip _____
   Telephone _____

6. Date of physician's last contact with participant: ☐☐ Month ☐☐ Day ☐☐ Year

7. To your knowledge, was the participant suffering from a terminal or life threatening disease prior to his/her death? ☐ 1 Yes → Please indicate nature and duration of medical conditions: _____ _____ ☐ 2 No ☐ 3 DK

8. Did you see the participant during the two weeks prior to his/her death? ☐ 1 Yes → Please summarize any contacts with the participant during the two weeks prior to his/her death: ☐ 2 No

Date	Reason for Contact	Diagnosis	Treatment

(Please list additional entries on separate page.)

9. According to your records, did the participant ever have, or were you treating the participant for:

				If Yes is checked:			
					Was he/she currently being treated for this condition		
	Yes	No	Unknown	Give the length of time in months the patient had this condition	Yes	No	Date of last treatment
Angina Pectoris							
Myocardial Infarction							
Other Clinical Coronary Disease							
Rheumatic Heart Disease							
Myocardiopathy							
Diabetes Mellitus							
Hypertension							
Stroke or Cerebrovascular Disease							
Cancer							
Obesity							
Headaches							
Inability to sleep							
Other major Illnesses (Please list below.)							

10. Please indicate which of the symptoms or signs listed below were present just prior to the participant's death: (Please list any other symptoms or signs which were present but which are not listed below.)

Symptoms	Yes	No	Unknown	How many hours prior to death?
Chest pain, chest discomfort				
Pressure on chest				
Shortness of breath				
Coughing				
Fainting or passing out				
Dizziness				
Palpitations, tachycardia				
Marked or increased fatigue, tiredness or weakness				
Headaches				
Sweating				
Paralysis				
Loss of speech				
Others - List				

Signs:	Yes	No	Unknown	How many hours prior to death?
Shock				
Congestive Heart failure				
Major arrhythmia (describe)				
Others - List				

11. Please give a brief narrative of the circumstances surrounding the death of the patient:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

12. Was an ECG taken just prior to the patient's death? ☐ 1 Yes ☐ 2 No ☐ 3 Don't know

If "YES," we would appreciate having a copy of this tracing for our follow-up. If the physician interviewed does not have responsibility for this ECG, please indicate below whom we may contact to obtain a copy.

Person or Institution: _____

Address: _____

_____

13. Did the physician interviewed pronounce the patient dead? ☐ 1 Yes ☐ 2 No

If "NO," who did? Name: _____

Address: _____

Telephone Number: _____

14. SHEP Clinician conducting the interview: _____ ☐☐

Signature Code

9.11 Interview with Witness to Death or Next of Kin - SH26

These interviews, as with the SH25s, should be accomplished for all out-of-hospital deaths and for certain in-hospital deaths as described in Section 9.10. They should be carried out by a SHEP clinician. More than one SH26 may be completed if several relevant interviews are carried out. These interviews may not be carried out by mail, but may be carried out by telephone.

Prior to the interview(s), the participant's name, SHEP ID and acrostic should be entered onto the form. The date of the interview(s) (Items 3 and 11) and the respondent information (Items 4 and 12) may also be entered. If the relationship of the respondent to the participant is not known prior to the interview, it should be ascertained during the interview.

Part A (with witness to death, or the last person to see participant alive), includes the following items:

5. If the repondent was with the participant when he/she died
6. When the participant was last seen alive by the respondent
7. Place of death
8. What the participant was doing at the time of death
9. Events leading to death
10. Changes in medical condition just prior to death

Part B (with person who had frequent contact in two weeks prior to death) may be carried out with the Part A respondent if appropriate, and includes information on the following:

13. Changes in medical condition of the participant in the several weeks prior to death (covers a longer period of time than Item 10)

14. Visits to physician

Part C applies to all interviews, and asks about specific symptoms around the time of death (for Part A) and during the several weeks prior to death (for Part B). The specific symptoms may require some clarification or explanation for the respondent. For any positive answers, comments should be recorded in Item 16, and should, if possible include time course (i.e., how long the participant had or complained of the symptoms, and whether they got progressively worse over that time). All respondents should be asked whether anyone else would have additional information about the death (Item 17).

The SHEP clinician performing the interview(s) should then sign the form and enter his/her ID code (Item 18).

INTERVIEW WITH WITNESS TO DEATH OR NEXT OF KIN

SPECIAL INSTRUCTIONS

These interviews should be carried out by a SHEP clinician within six weeks of the out-of-hospital death of a randomized participant, and also for certain in-hospital deaths if the interview is likely to contribute information useful for assigning cause of death. Part A of this form should be filled out by interviewing a person who witnessed the death, or if there was no witness, the person who last saw the participant alive. Part B, which pertains to the onset of the terminal condition, should be filled out by interviewing the next of kin (or other person who had frequent contact with this participant in the two weeks interval preceding death). The interviews can usually be carried out by telephone, and should follow the specified sequence. More than one Form SH26 may be filled out if several relevant interviews were carried out.

Name: _____

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

PART A - Interview with witness to death, or last person to see participant alive.

3. Date of interview: ☐☐ (Month) ☐☐ (Day) ☐☐ (Year)

4. _____ (Name of Respondent) _____ (Relationship)

_____ (Address) _____ (City/State/Zip) _____ (Telephone Number)

5. Was the respondent with the participant when he/she died? 1 ☐ Yes → 2 ☐ No 3 ☐ DK

Date of death: ☐☐ (Month) ☐☐ (Day) ☐☐ (Year)

Time of death (or discovery): ☐☐ (Hour) : ☐☐ (Minute) ☐ a.m. ☐ p.m.

6. Participant was last seen alive at: ☐☐ (Month) ☐☐ (Day) ☐☐ (Year) at ☐☐ (Hour) : ☐☐ (Minute) ☐ a.m. ☐ p.m.

7. Where did the death occur? _____

_____

8. What was the participant doing at the time of death? _____

_____

9. In the words of the respondent, describe the events leading up to death (attach extra pages if needed):

_____

_____

_____

_____

_____

_____

10. Describe any changes in the participant's medical condition or treatment in the period immediately before death: _____

_____

_____

(GO TO SECTION C.)

PART B.	Interview with a person who had frequent contact with the participant in the two weeks preceding death (may be the same person interviewed in PART A.

11. Date of interview: ☐☐ ☐☐ ☐☐
Month Day Year

12. _____
Name of Respondent Relationship

_____
Address City/State/Zip Telephone Number

13. Describe any changes in the participant's medical condition or treatment during the several weeks prior to death:

_____

_____

_____

14. Was the participant seen by a physician?
1 ☐ Yes → Name: _____
2 ☐ No
3 ☐ DK
Address: _____
City/State/Zip: _____
Telephone Number: _____

PART C. Ask of all respondents, and check all that apply.

15. Were any of the following symptoms present (ask about each item):

		Around Time of Death (Part A)			During Several Weeks Leading Up to Death (Part B)		
		Yes	No	DK	Yes	No	DK
a.	Chest pain or discomfort or pressure	☐	☐	☐	☐	☐	☐
b.	Shortness of breath	☐	☐	☐	☐	☐	☐
c.	Coughing	☐	☐	☐	☐	☐	☐
d.	Fainting or passing out	☐	☐	☐	☐	☐	☐
e.	Dizziness	☐	☐	☐	☐	☐	☐
f.	Headaches	☐	☐	☐	☐	☐	☐
g.	Paralysis	☐	☐	☐	☐	☐	☐
h.	Difficulty speaking	☐	☐	☐	☐	☐	☐
i.	Visual loss	☐	☐	☐	☐	☐	☐
j.	Change in color or appearance	☐	☐	☐	☐	☐	☐
k.	Nausea or vomiting	☐	☐	☐	☐	☐	☐
l.	Sweating	☐	☐	☐	☐	☐	☐
m.	Fever	☐	☐	☐	☐	☐	☐
n.	Fast or irregular heart beat	☐	☐	☐	☐	☐	☐

16. Amplify on positives in Item 15, including time course: _____

_____

_____

_____

_____

17. Would any other persons have additional information about the death?

☐ Yes → Name: _____

☐ No

Address: _____

Telephone Number: _____

Name: _____

Address: _____

Telephone Number: _____

18. SHEP Clinician performing interviews: _____ ☐☐

Signature Code

9.12 SHEP Neurological Evaluation for Stroke - SH27

For any participant in whom a stroke is suspected, the SHEP neurologist should perform a neurologic examination using the SH27. This form collects information on history, hospital record and/or interviews (Items 4-16), onset (Items 17-26), the examination itself (Items 27-43), the neurologist's diagnosis (Items 44-46), and the neurologist's final assessment (Items 47-61).

Several of the items on the questionnaire (33a-f, 35b-k, 36b-g, 37b-e, 41b-e) provide a response that the abnormality observed is not related to the current event. This is indicated by "Not Related," which should be checked if an abnormality is present and it is not related to the current event. This should be done in addition to indicating the abnormality itself.

This form should be completed and submitted to the Coordinating Center with a final report of a possible stroke.

NOTE: All SHEP personnel, including SHEP neurologists, should have a two-digit ID code. This code should be entered in Item 61 of this form.

SHEP NEUROLOGICAL EVALUATION FOR STROKE

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date of Evaluation: ☐☐ Month ☐☐ Day ☐☐ Year

HISTORY, HOSPITAL RECORD, INTERVIEW

4. Handedness:

1 ☐ Left 2 ☐ Right 3 ☐ Ambidextrous or switched 4 ☐ Unknown

5. Previous or simultaneous myocardial infarction:

1 ☐ Yes, most recent more than 6 months ago
2 ☐ Yes, indeterminate age (e.g., ECG only)
3 ☐ Yes, less than 6 months ago
4 ☐ No
5 ☐ Unknown

6. Date of most recent myocardial infarction: ☐☐ Month ☐☐ Day ☐☐ Year

7. Evidence of valvular heart disease:

1 ☐ Yes 2 ☐ No 3 ☐ Unknown
↓
Which valves? _____

		Yes	No	Unknown
8.	Has the patient been diagnosed or treated for:			
a.	Atrial fibrillation	☐ 1	☐ 2	☐ 3
b.	Other arrhythmias	☐ 1	☐ 2	☐ 3
c.	Angina	☐ 1	☐ 2	☐ 3
d.	Congestive failure	☐ 1	☐ 2	☐ 3
e.	Claudication in the lower limbs	☐ 1	☐ 2	☐ 3
f.	Echocardiogram or cardiac CT shows mural thrombus or source of emboli	☐ 1	☐ 2	☐ 3
g.	Systemic emboli	☐ 1	☐ 2	☐ 3
h.	Other source for emboli	☐ 1	☐ 2	☐ 3

9. Has the patient ever been diagnosed or treated for diabetes?

1 ☐ Yes, no treatment or diet only
2 ☐ Yes, oral agents
3 ☐ Yes, insulin
4 ☐ No
5 ☐ Unknown

10. Has the patient ever been diagnosed or treated for cancer?

1 ☐ Yes 2 ☐ No 3 ☐ Unknown
↓
Type of cancer: _____

11. Is there evidence for intracranial infectious disease, brain tumor, trauma or metabolic cause (such as uremic coma) for the neurologic symptoms or signs?

1 □ Yes 2 □ No

↓

Explain: _____

12. Evidence for past history of migraines?

1 □ Yes 2 □ No 3 □ Unknown

13. Evidence for past history of seizures?

1 □ Yes 2 □ No 3 □ Unknown

14. Date and time (hour) of onset of these neurologic signs or symptoms?

Month	Day	Year	at	Hour
□□	□□	□□		□□

1 □ am
2 □ pm

15. a. Has the patient ever had a TIA?

1 □ Yes 2 □ No 3 □ Unknown

↓ ↓

GO TO 16

b. How long ago?
1 □ 1-7 days ago
2 □ 8-30 days ago
3 □ 1-6 months ago
4 □ Over 6 months ago
5 □ Unknown

c. Number of TIAs? 1 □ One 2 □ 2-5 3 □ 6-50 4 □ >50 5 □ Unknown

d. Vascular territory of past TIAs:

1 □ Right carotid
2 □ Left carotid
3 □ Vertebral-basilar
4 □ Multiple territories
5 □ Unknown

e. Prior TIA in same territory as present neurologic signs and symptoms?

1 □ Yes 2 □ No 3 □ Unknown

16. a. Has the patient ever had a stroke before this event?

1 □ Yes 2 □ No 3 □ Unknown

↓ ↓

GO TO 17

b. How long ago?
1 □ 1-7 days ago
2 □ 8-30 days ago
3 □ 1-6 months ago
4 □ Over 6 months ago
5 □ Unknown

c. Number of strokes? 1 □ One 2 □ 2-5 3 □ >5 4 □ Unknown

d. Types of strokes (check all that apply):

1 □ Ischemic
1 □ Intracerebral hemorrhage (ICH)
1 □ Subarachnoid hemorrhage (SAH)
1 □ Unknown

e. Vascular territory:

1 □ Right carotid
2 □ Left carotid
3 □ Vertebral-basilar
4 □ Multiple territories
5 □ SAH
6 □ Unknown

ONSET

17. Deficit present on awakening?

1 □ Yes 2 □ No 3 □ Unknown

18. At the time of onset, was there:

		Yes	No	Unknown
a.	Severe headache	□ 1	□ 2	□ 3
b.	Vomiting	□ 1	□ 2	□ 3
c.	Seizures	□ 1	□ 2	□ 3
d.	Focal deficit	□ 1	□ 2	□ 3
e.	Decreased consciousness	□ 1	□ 2	□ 3
f.	Coma	□ 1	□ 2	□ 3

19. Sudden onset with maximum deficit within 10 minutes? 1 □ Yes 2 □ No 3 □ Unknown

20. Worsening was steplike? 1 □ Yes 2 □ No 3 □ Unknown

21. Worsening was gradual? 1 □ Yes 2 □ No 3 □ Unknown

22. Deficit reached maximum within one week of onset? 1 □ Yes 2 □ No 3 □ Unknown

23. Improvement occurred even temporarily within the first 24 hours after onset? 1 □ Yes 2 □ No 3 □ Unknown

24. Was documented hypotension a possible precipitator of this event? 1 □ Yes 2 □ No 3 □ Unknown

25. Were anticoagulants (heparin, coumadin) being used at the time of the event? 1 □ Yes 2 □ No 3 □ Unknown

26. Were antiplatelet drugs being used at the time of the event? 1 □ Yes 2 □ No 3 □ Unknown

EXAMINATION □ Not Done

27. Verbal response (aphasics are untestable):

1 □ Oriented and converses
2 □ Disoriented
3 □ Inappropriate words
4 □ Incomprehensible sounds
5 □ None
6 □ Untestable

28. Eye opening:

1 □ Spontaneous
2 □ To speech
3 □ To pain
4 □ None
5 □ Untestable

29. Motor response:

1 ☐ Obeys
2 ☐ Localizes
3 ☐ Withdraws
4 ☐ Abnormal flexion
5 ☐ Abnormal extension
6 ☐ None
7 ☐ Untestable

30. Degree of alertness:

1 ☐ Alert 2 ☐ Lethargic or drowsy 3 ☐ Stupor 4 ☐ Coma

31. a. Remainder of neurologic exam:

1 ☐ Normal ↓ GO TO 32
2 ☐ Abnormal, focal
3 ☐ Abnormal, multifocal
4 ☐ Unknown ↓ GO TO 32

b. Related to current event? 1 ☐ Yes 2 ☐ No 3 ☐ Unknown

32. a. Weakness:

1 ☐ Normal ↓ GO TO 33
2 ☐ Left hemiparesis
3 ☐ Right hemiparesis
4 ☐ Bilateral hemiparesis
5 ☐ Unknown ↓ GO TO 33

b. Related to current event? 1 ☐ Yes 2 ☐ No 3 ☐ Unknown

33. Weakness scale--Fill in the proper codes in the boxes provided, and check "Not related" if an indicated abnormality is not due to present event. For tongue and face, use only codes 0, 1, 2, 6.

0=Normal	2=Against resistance	4=Without gravity	6=Untestable
1=Slight weakness	3=Against gravity	5=No movement	

		Left		Right	
a.	Tongue	☐	1 ☐ Not related	☐	1 ☐ Not related
b.	Face	☐	1 ☐ Not related	☐	1 ☐ Not related
c.	Shoulder	☐	1 ☐ Not related	☐	1 ☐ Not related
d.	Hand	☐	1 ☐ Not related	☐	1 ☐ Not related
e.	Hip	☐	1 ☐ Not related	☐	1 ☐ Not related
f.	Foot	☐	1 ☐ Not related	☐	1 ☐ Not related

34. a. Ataxia:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both

↓

GO TO 35

b. Related to present event? 1 □ Yes 2 □ No 3 □ Unknown

35. a. Extraocular movements:

1 □ Normal 2 □ Abnormal 3 □ Untestable

↓ ↓

GO TO 36 GO TO 36

Check if not related to present event:

b. Horizontal gaze palsy:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

c. Vertical gaze palsy:

1 □ Absent 2 □ Up 3 □ Down 4 □ Both 5 □ Unknown 1 □ Not Related

d. Internuc opthalmoplegia:

1 □ Absent 2 □ Present 3 □ Unknown 1 □ Not Related

e. CN III palsy:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

f. CN VI palsy:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

g. Skew deviation:

1 □ Absent 2 □ Present 3 □ Unknown 1 □ Not Related

h. Vertical nystagmus:

1 □ Absent 2 □ Present 3 □ Unknown 1 □ Not Related

i. Horizontal nystagmus:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

j. Fixed pupils:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

k. Subhyaloid hemorrhage:

1 □ Absent 2 □ Left 3 □ Right 4 □ Both 5 □ Unknown 1 □ Not Related

36. a. Sensory deficits (pin test)

1 □ None 2 □ Left 3 □ Right 4 □ Both 5 □ Untestable

↓ ↓

GO TO 37 GO TO 37

Fill in the proper codes in the boxes provided, and check "Not related" if an indicated abnormality is not due to present event.

0=Normal	1=Partial	2=Severe	3=Untestable

		Left		Right	
b.	Face	☐	1 ☐ Not related	☐	1 ☐ Not related
c.	Shoulder	☐	1 ☐ Not related	☐	1 ☐ Not related
d.	Hand	☐	1 ☐ Not related	☐	1 ☐ Not related
e.	Hip	☐	1 ☐ Not related	☐	1 ☐ Not related
f.	Foot	☐	1 ☐ Not related	☐	1 ☐ Not related
g.	Trunk	☐	1 ☐ Not related	☐	1 ☐ Not related

37. a. Visual fields:

1 ☐ Normal → GO TO 38

2 ☐ Abnormal

3 ☐ Untestable → GO TO 38

Check if not related to present event:

b. Monocular:
1 ☐ Absent 2 ☐ Left 3 ☐ Right 4 ☐ Both 5 ☐ Unknown 1 ☐ Not Related

c. Quadrantanopia:
1 ☐ Absent 2 ☐ Left 3 ☐ Right 4 ☐ Both 5 ☐ Unknown 1 ☐ Not Related

d. Hemianopia:
1 ☐ Absent 2 ☐ Left 3 ☐ Right 4 ☐ Both 5 ☐ Unknown 1 ☐ Not Related

e. Hemineglect:
1 ☐ Absent 2 ☐ Left 3 ☐ Right 4 ☐ Both 5 ☐ Unknown 1 ☐ Not Related

38. a. Language:

1 ☐ Normal → GO TO 39
2 ☐ Broca
3 ☐ Wernicke
4 ☐ Global
5 ☐ Anomic
6 ☐ Other
7 ☐ Unknown → GO TO 39

b. Related to present event? 1 ☐ Yes 2 ☐ No 3 ☐ Unknown

39. a. Dysarthria:

1 □ Absent → GO TO 40

2 □ Present

3 □ Unknown → GO TO 40

b. Related to present event? 1 □ Yes 2 □ No 3 □ Unknown

40. a. Nuchal rigidity?

1 □ No → GO TO 41

2 □ Slight

3 □ Severe

4 □ Unknown → GO TO 41

b. Related to present event? 1 □ Yes 2 □ No 3 □ Unknown

41. a. Cervical bruit:

1 □ Absent → GO TO 42

2 □ Present

3 □ Unknown → GO TO 42

			Check if not related to present event
b.	Left Carotid	1 □ Absent 2 □ Present 3 □ Unknown	1 □ Not related
c.	Right Carotid	1 □ Absent 2 □ Present 3 □ Unknown	1 □ Not related
d.	Left Subclavian	1 □ Absent 2 □ Present 3 □ Unknown	1 □ Not related
e.	Right Subclavian	1 □ Absent 2 □ Present 3 □ Unknown	1 □ Not related

42. Peripheral pulses in the foot and ankle:

1 □ Present 2 □ Diminished or absent 3 □ Unknown

43. a. Other hemispheral signs (apraxia, neglect):

1 □ None → GO TO 44

2 □ Present

3 □ Untestable → GO TO 44

b. Related to this event? 1 □ Yes 2 □ No 3 □ Unknown

DIAGNOSIS

44. Primary diagnosis (check one):

1 □ Not a stroke (skip to 47)
2 □ Subarachnoid hemorrhage
3 □ Intraparenchymal hemorrhage
4 □ Lacunar infarction
5 □ Embolic infarction
6 □ Atherosclerotic infarction
7 □ Other, unknown infarction
8 □ Unknown type stroke

45. Cerebral site codes:

	Left	Right		
Cerebral hemisphere (not futher specified)	01	02	Midline (third ventricular callosum)	33
Frontal lobe	03	04	Intracranial (not further specified)	34
Parietal lobe	05	06	Brain stem	35
Insular-operculum	07	08	Midbrain	36
Occipital lobe	09	10	Pons	37
Temporal lobe	11	12	Medulla	38
Putamen	13	14	Subarachnoid space	39
Thalamus	15	16	Intraventricular space	40
Internal capsule	17	18		
Cerebellum	19	20		
Fronto-parietal lobe	21	22		
Parieto-occipital lobe	23	24		
Temporo-parietal lobe	25	26		
Temporo-occipital lobe	27	28		
Fronto-temporo-parietal lobe	29	30		
Basal ganglia and capsule	31	32		

a. Two-digit code for primary cerebral site: ☐☐

b. Other cerebral sites: ☐☐ ☐☐ ☐☐ ☐☐

c. Are more than five cerebral sites indicated? 1 ☐ Yes 2 ☐ No

46. Vascular territory codes:

	Left	Right
Common carotid	01	02
External carotid	03	04
Internal carotid	05	06
At bifurcation	07	08
Distal extracranial	09	10
Intracranial	11	12
Junction of posterior communicating	13	14
Other	15	16
Anterior cerebral	17	18
Junction of anterior communicating	19	20
Other	21	22
Middle cerebral	23	24
Penetrating or lentriculostriate	25	26
Stem	27	28
Upper branch	29	30
Lower branch	31	32
Posterior communicating	33	34
Posterior cerebral	35	36
Penetrating	37	38
Stem	39	40
Calcarine branch	41	42
Superior cerebellar	43	44
Posterior inferior cerebellar	45	46
Vertebral	47	48
Subclavian	49	50

Anterior communicating	51
Basilar	52
Penetrating	53
Full	54
Upper branch	55
Lower branch	56
Innominate	57
Unknown	58

a. Two-digit code for primary vascular territory: ☐☐

b. Two-digit codes for other vascular territories: ☐☐ ☐☐ ☐☐ ☐☐

c. Are more than five vascular territories indicated? 1 □ Yes 2 □ No

FINAL ASSESSMENT

Taking into account all of the available information, is there evidence of:

		Yes	No	Unknown
47.	A deficit that lasted more than 24 hours or until death intervenes?	1 ☐	2 ☐	3 ☐
48.	Rapid onset?	1 ☐	2 ☐	3 ☐
49.	Loss of consciousness?	1 ☐	2 ☐	3 ☐
50.	Focal brain deficit due to this event?	1 ☐	2 ☐ ↓ GO TO 51	3 ☐ ↓
	a. Lacunar in type?	1 ☐	2 ☐ ↓ GO TO 50b	3 ☐ ↓
	(1) pure motor hemiparesis	1 ☐	2 ☐	3 ☐
	(2) pure sensory	1 ☐	2 ☐	3 ☐
	(3) dysarthria clumsy hand	1 ☐	2 ☐	3 ☐
	(4) ataxic hemiparesis	1 ☐	2 ☐	3 ☐
	b. sensory motor only?	1 ☐	2 ☐	3 ☐
	c. hemichorea?	1 ☐	2 ☐	3 ☐
	d. aphasia only?	1 ☐	2 ☐	3 ☐
	e. visual field defect only?	1 ☐	2 ☐	3 ☐
	f. other hemisphere deficit? Specify: _____ _____	1 ☐	2 ☐	3 ☐
	g. bilateral brainstem-cerebellar?	1 ☐	2 ☐	3 ☐
	h. unilateral brainstem-cerebellar (not under 50a)?	1 ☐	2 ☐	3 ☐
	i. other? Specify: _____ _____	1 ☐	2 ☐	3 ☐

		Yes	No	Unknown	Not Done
51.	LP evidence of hemorrhage?	1 ☐	2 ☐	3 ☐	4 ☐
52.	CT scan evidence of a lesion compatible with this event?	1 ☐	2 ☐ ↓	3 ☐ ↓	4 ☐ ↓
			GO TO 53		
	a. deep lacunar infarction <2 cm	1 ☐	2 ☐	3 ☐	
	b. cortical infarction <1/2 lobe	1 ☐	2 ☐	3 ☐	
	c. larger infarction	1 ☐	2 ☐	3 ☐	
	d. mottled hemorrhagic infarction	1 ☐	2 ☐	3 ☐	
	e. subarachnoid hemorrhage	1 ☐	2 ☐	3 ☐	
	f. intraparenchymal hemorrhage	1 ☐	2 ☐	3 ☐	
	g. watershed area infarction	1 ☐	2 ☐	3 ☐	
	h. more than 1 infarction, old or new	1 ☐	2 ☐	3 ☐	
53.	a. EEG abnormal?	1 ☐	2 ☐ ↓	3 ☐ ↓	4 ☐ ↓
			GO TO 54		
	b. EEG shows focal slowing compatible with stroke?	1 ☐	2 ☐	3 ☐	
54.	Noninvasive testing shows evidence of severe stenosis or occlusion of relevant carotid?	1 ☐	2 ☐	3 ☐	4 ☐
55.	Angiographic (including DSA) evidence of a cause or source of event?	1 ☐	2 ☐ ↓	3 ☐ ↓	4 ☐ ↓
			GO TO 56		
	a. AVM	1 ☐	2 ☐	3 ☐	
	b. Aneurysm	1 ☐	2 ☐	3 ☐	
	c. Mass effect	1 ☐	2 ☐	3 ☐	
	d. Source for embolus-- ulcerated plaque or free clot	1 ☐	2 ☐	3 ☐	

		Yes	No	Unknown	Not Done
e.	Stenosis ≥70% or occlusion:				
	(1) Relevant extracranial artery	1 ☐	2 ☐	3 ☐	
	(2) Relevant major cerebral stem or basilar	1 ☐	2 ☐	3 ☐	
	(3) Relevant branch occlusion	1 ☐	2 ☐	3 ☐	
f.	Arteritis	1 ☐	2 ☐	3 ☐	
g.	Dissection of the arterial wall	1 ☐	2 ☐	3 ☐	
h.	Other Specify: _____	1 ☐	2 ☐	3 ☐	
56.	Surgical evidence of stroke?	1 ☐	2 ☐	3 ☐	4 ☐
57.	For deaths, autopsy evidence of stroke?	1 ☐	2 ☐	3 ☐	4 ☐

If neither of 56 or 57 is "Yes,", go to 59.

58. Evidence is for:

a.	Subarachnoid hemorrhage	1 ☐	2 ☐	3 ☐
b.	Intraparenchymal hemorrhage	1 ☐	2 ☐	3 ☐
c.	Ischemic stroke	1 ☐	2 ☐ ↓ GO TO 59	3 ☐ ↓
	(1) Lacune	1 ☐	2 ☐	3 ☐
	(2) Embolic	1 ☐	2 ☐	3 ☐
	(3) Atherosclerotic	1 ☐	2 ☐	3 ☐
	(4) Other	1 ☐	2 ☐	3 ☐

59. Death occurred within 24 hours of event? 1 ☐ 2 ☐ 3 ☐

60. Comments:

61. SHEP Neurologist: _____ ☐☐
Signature Code

9.13 SHEP Neurological Evaluation for TIA - SH28

For any participant in whom a TIA is suspected, the SHEP neurologist should perform a neurological evaluation using the SH28. This form collects information on history, evidence for other conditions, symptoms, and the neurologist's judgment on whether TIAs have occurred.

This form should be completed and submitted to the Coordinating Center with a final report of a possible TIA.

NOTE: All SHEP personnel, including SHEP neurologists, should have a two-digit ID code. This code should be entered in Item 32 of this form.

SHEP NEUROLOGICAL EVALUATION FOR TIA

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date of Evaluation: ☐☐ Month ☐☐ Day ☐☐ Year

		Yes	No	Unknown
4.	One event or events:			
	a. lasting less than 24 hours?	☐ 1	☐ 2	☐ 3
	b. lasting more than 30 seconds?	☐ 1	☐ 2	☐ 3
	c. maximal deficit was attained in less than 5 minutes?	☐ 1	☐ 2	☐ 3
5.	History of proceeding head trauma?	☐ 1	☐ 2	☐ 3
6.	History of clonic jerking?	☐ 1	☐ 2	☐ 3
7.	History of conjugate eye deviation?	☐ 1	☐ 2	☐ 3
8.	History of scintillating scotoma?	☐ 1	☐ 2	☐ 3
9.	History of headache with nausea and vomiting?	☐ 1	☐ 2	☐ 3
10.	Other evidence for seizures?	☐ 1	☐ 2	☐ 3
11.	Other evidence for hypoglycemia?	☐ 1	☐ 2	☐ 3
12.	Other evidence for migraine?	☐ 1	☐ 2	☐ 3
13.	Other evidence for drug intoxication?	☐ 1	☐ 2	☐ 3
14.	Other evidence for orthostatic hypotension?	☐ 1	☐ 2	☐ 3
15.	Other evidence for brain tumor?	☐ 1	☐ 2	☐ 3
16.	Other evidence for generalized cerebral ischemia?	☐ 1	☐ 2	☐ 3

SYMPTOMS DURING THE ATTACK

		Yes	No	Unknown
17.	Visual loss:			
	a. left eye?	☐ 1	☐ 2	☐ 3
	b. right eye?	☐ 1	☐ 2	☐ 3
	c. left visual field?	☐ 1	☐ 2	☐ 3
	d. right visual field?	☐ 1	☐ 2	☐ 3
	e. both simultaneously?	☐ 1	☐ 2	☐ 3

		Left			Right		
		Yes	No	Unknown	Yes	No	Unknown
18.	Weakness or paralysis or clumsiness of:						
	a. face	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	b. arm	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	c. leg	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
19.	Loss of feeling:						
	a. face	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	b. arm	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	c. leg	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
20.	Numbness paresthesias:						
	a. face	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	b. arm	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3
	c. leg	☐ 1	☐ 2	☐ 3	☐ 1	☐ 2	☐ 3

		Yes	No	Unknown
21.	Dysarthria	☐ 1	☐ 2	☐ 3
22.	Aphasia	☐ 1	☐ 2	☐ 3
23.	Ataxia	☐ 1	☐ 2	☐ 3
24.	Loss of balance	☐ 1	☐ 2	☐ 3
25.	Vertigo	☐ 1	☐ 2	☐ 3
26.	Diplopia	☐ 1	☐ 2	☐ 3
27.	Dysphagia	☐ 1	☐ 2	☐ 3
28.	Attacks are sterotyped	☐ 1	☐ 2	☐ 3

29. Number of attacks:
- One ☐ 1
- 2-5 ☐ 2
- 6-10 ☐ 3
- >10 ☐ 4

30. Description of the event(s): _____

_____

_____

_____

_____

31. a. In your opinion, do these attacks represent TIAs?
- Probably yes ☐ 1
- Possibly ☐ 2
- Probably not ☐ 3

	b. If "Probably yes," location:	Yes	No	Unknown
(1)	Left carotid?	☐ 1	☐ 2	☐ 3
(2)	Right carotid?	☐ 1	☐ 2	☐ 3
(3)	Vertebrobasilar?	☐ 1	☐ 2	☐ 3
(2)	Multifocal?	☐ 1	☐ 2	☐ 3

32. SHEP Neurologist: _____ ☐☐
Signature Code

9.14 SHEP Behavioral Evaluation Package

The SHEP behavioral evaluation consists of the following:

- SHEP SHORTCARE Form (includes CES/D) - SH30
- Diagnostic Criteria for Dementia - SH31
- Diagnostic Criteria for Depression - SH32
- Activities of Daily Life - SH33
- Social Network Questionnaire - SH34
- Behavioral Evaluation--Part II - SH35
- SHORTCARE Scoring Sheet - SH36

Refer to the SHEP Behavioral Evaluation Manual for Details.

9.15 Compliance Evaluation - SH40

This form is required at the first required clinic visit after SHEP medications are started or increased, and at semi-annual visits. (The visit checklist on the SH08 should be used as a guide to which procedures are required at SHEP visits; these items are included on the SH09, SHEP Annual Visit Form.) If SHEP medications were not prescribed at the last visit, the compliance evaluation should be skipped. Also, if the pill count cannot be completed at the scheduled clinic visit, no additional attempt should be made to obtain pill count information (e.g., do not ask the participant to count the pills and call the Clinic).

Prior to the clinic visit, Items 1-4 should be filled out as previously described, and the proper drugs circled in Items 9 and 12. At the one-month visit (the first visit after a participant is on SHEP medications), a short explanation should be provided as to why these questions are being asked. At other visits a brief introduction similar to the one provided, should be used. The statements that are provided are guidelines only; interviewers should use phraseology that they are comfortable with, yet should not appear at any time to be either anticipating a missed dose or incorrect answer, or chastising the participant should he or she report any. The participant should not perceive this as a "test," but only as a part of a complete follow-up visit.

Questions 5 through 8 inquire about the SHEP medications in general, regardless of dose or step currently being prescribed.

If the participant responds "No" to Item 5 (missed doses in last 7 days), skip to Item 9. If the participant seems confused, or cannot remember, it is permissible to help him/her by saying something like, "Well, what about yesterday?" and name the day, working backward until a week is covered or the participant responds with a "Yes" or "No." If the participant responds with a "Yes," Items 6, 7 and 8 must be asked. In Item 6, the participant is asked to report which days he/she missed. Again, if the participant cannot remember, probing may be used as described above. Also, the participant may remember that only one or two days were missed, but not the specific days. If the participant responds with a range (e.g., "one or two," etc.) try to pin the answer down to one answer or the other with a statement something like, "Well, would you say that it is probably one or probably two?"

Item 7 asks for reasons why the participant has missed taking their SHEP medications. Use the open-ended questions, and do not mention any of the specific categories listed. If the participant gives an answer and stops, ask, "Is that all?" or "Are there any other reasons?" to determine if that was the only reason or if there are others. If a reason is given that does not fit into the categories listed, it should be specified as "Other" and written in the space provided.

Item 8 asks about what the participant did when he/she missed taking their medicine. As with Item 7, none of the specific answers should be mentioned to the participant, but if the participant reports one answer and stops, ask, "Is that all?" or "Did you do anything else?" to probe for other possible answers. If an answer is given that does not fit in with the specific answers, it should be counted as "Other" and listed in the space provided.

Questions 9-11 ask specifically about the Step 1 drug, which should be circled in Item 9 prior to the visit (for interviewer's ease of reference). These questions ask about the number of times per day, number of pills each time, and time of day that the medications are being taken. If an answer is given by the participant that is not specifically listed, it should be counted as "Other" and written in the space provided.

Items 12-14 are the same questions, but pertain to the Step 2 medications. If the participant is not on Step 2 medications, skip to 15.

A pill count is required whenever this form is administered, except when it is administered at a home visit or telephone visit. A worksheet is provided for this purpose (SH62). The participant should always bring their SHEP medications (whether bottles have been opened or not) to clinic visits, although a pill count will not always be required. Specific instructions for the pill count are included with instructions for the SH62. If no pill count is performed, check "No" in 15 and leave 15a and 15b blank. The results, if the pill counts are performed, should be entered into Items 15a and, if applicable, 15b.

If the participant reports missing doses, or if either pill count result is less than 80%, or if the participant is not taking the pills properly, instructions on how to take the medications should be reinforced.

COMPLIANCE EVALUATION

1. SHEP ID: ____ - ____ - ____ 2. Acrostic: ____

3. Date of clinic visit: ____ (Month) ____ (Day) ____ (Year) 4. Sequence number: ____

This form is required at the next scheduled visit after SHEP medications are started or increased, and at semi-annual visits. Do not administer if participant was not prescribed SHEP blinded medications at the last visit.

At the one-month visit: "We know that people sometimes miss a dose of their medicine for one reason or another, or they just forget. We are going to ask you a few questions at each clinic visit about taking your SHEP medicines. Your answers may help us to understand certain problems that can occur when people have to take medicines for a long period of time."

At other visits: "I am now going to ask you a few questions about taking your medicines since your last visit."

5. Have you missed taking your SHEP medicines anytime in the past 7 days? 1 □ Yes 2 □ No → Go to 9.

6. Which days did you miss? (Circle days mentioned.)

M T W Th F S S → Total days missed ____

7. Why did you miss taking the medicines? (Push for answers, but do not mention specific categories.)

		Mentioned	Not Mentioned
a.	Wasn't feeling well	1 □	2 □
b.	Medicine made participant ill (Specify) _____	1 □	2 □
c.	Just forgot	1 □	2 □
d.	Away from home/didn't have medicine	1 □	2 □
e.	Ran out of medicine	1 □	2 □
f.	Didn't want to take (Reason) _____	1 □	2 □
g.	Doctor (usual source of care) told me to stop	1 □	2 □
h.	Other (Specify) _____	1 □	2 □

8. What did you do when you missed taking your SHEP medicines? (Push for answers, but do not provide specific categories.)

		Mentioned	Not Mentioned
a.	Waited and doubled up the next dose	1 □	2 □
b.	Did nothing/took usual dose next time	1 □	2 □
c.	Reports missed dose(s) at next clinic visit	1 □	2 □
d.	Called SHEP clinic	1 □	2 □
e.	Recorded missed dose(s)	1 □	2 □
f.	Took it later	1 □	2 □
g.	Other (specify) _____		

If the participant is not currently being prescribed C1 or C2, skip to Item 12.

9. How many times a day do you take your C1/C2? (Circle correct Step I drug.)

Every other day	☐ 1
Once per day	☐ 2
Other _____ (Specify)	☐ 3

10. How many do you take each time?

One	☐ 1
Other _____ (Specify)	☐ 2

11. When do you take it?

Morning when getting up	☐ 1
Other _____ (Specify)	☐ 2

If participant is not currently being prescribed A1, A2 or R, skip to Item 15.

12. How many times a day to your take your A1/A2/R? (Circle correct Step II drug.)

Once per day	☐ 1
Twice per day	☐ 2
Other _____ (Specify)	☐ 3

13. How many do you take each time?

One	☐ 1
Other _____ (Specify)	☐ 2

14. When do you take it?

Morning when getting up	☐ 1
Morning when getting up, and late afternoon or bedtime	☐ 2
Other _____ (Specify)	☐ 3

Item 15 for interviewer only. Skip pill count for home and telephone visits.

15. Was a pill count done at this visit? Yes ☐ 1 No ☐ 2

a. Step 1 result: [, ,].[ ]

b. Step 2 result: [, ,].[ ]

If participant reports missing doses, or pill count result (if done) is less than 80% for either Step I or Step II, or participant is not taking drugs properly, reinforce instructions on how to take SHEP medications.

9.16 Side Effects Questionnaire (SH42)

This form is to be administered at the first required visit after any SHEP medication is started or increased, in response to a "Yes" response to Item 28b on the SH08 and at interim visits scheduled due to possible side effects. This form is never required for participants who have been off of SHEP blinded medications for more than six months.

As with other auxiliary forms, Item 1-4 (participant's SHEP ID and acrostic, date and sequence number of clinic visit) should be entered onto the form prior to the clinic visit, if the form will definitely be administered. If the form is only conditionally required at this visit (i.e., only on specific positive responses to the General Well-Being questions), these items may be left blank to avoid wasting the form if it is not used. In the latter situations, extra care must be taken to enter Items 1-4 as soon as possible after the form is completed.

The specific side effects should be asked exactly as listed. The first one should be prefaced with, "Since your last visit, have you had . . . ?" This phrase should be repeated few side effects to reinforce the time interval of interest.

Any "Yes" response to a specific side effect prompts a series of questions:

- New since last visit (Yes, No)
- Frequency (once only, less than weekly, 2-6 times weekly, daily, constantly)
- Severity (not troublesome, troublesome, intolerable)

The above should be according to the participant's responses. It may be convenient to provide the participant with a "flashcard" with the above responses printed relatively large, since the responses are the same for each side effect.

Also, for every "Yes" response to specific side effects, the SHEP clinician is asked to make a judgment if the condition is due to the SHEP medication (yes, possibly, no).

Completion of items on the side effects form which require physical assessment (listed below) will be optional (may be left blank). Referral to the Clinic physician for positive responses on these items will be at the discretion of the Clinic nurse.

SH09	SH42	Description
32f	6f	Acute skin rash
38f	12f	Acute arthritis
48f	22f	Arrhythmia
51f	25f	Bronchospasm
53f	27f	CHF
61f	35f	Stroke
62f	36f	Other relevant signs on PE

One of the right-hand column items is not a physical examination item, but has several extra questions that should be asked directly of the participant. This is Item 30, "Any changes in your sexual activities?" Several specific problems are listed:

- Loss of interest
- Decline in frequency

- Loss of enjoyment
- Functional impairment (includes physical problems such as inability to maintain an erection, premature ejaculation, or problem with lubrication)

Item 35, "Other relevant symptoms," may include problems reported by the participant on the General Well-being section of the SH08, but not otherwise listed on this form.

Upon completion of the form, the interviewer should return to the SH08, Item 29.

9.16.1 Guidelines for CHF and Arrhythmia

The diagnosis of possible CHF by Clinic staff is not always clear. The following historical items may indicate that the participant has CHF and should be referred to the SHEP physician:

1. 2-3 pillow orthopnea (needed 2-3 pillows in order to sleep at night without shortness of breath)
2. paroxysmal nocturnal dyspnea (getting up at night and sitting up or standing due to difficulty breathing lying down)
3. new onset of swollen ankles which doesn't get better at night when elevated
4. new onset or increased shortness of breath with exertion (such as walking, especially upstairs or uphill)

In assessing possible arrhythmias, items 1-3 below will be performed at Clinic visits routinely. Item 4 needs to be performed only if the participant indicates that he/she is currently or very recently (within the last 2 hours) having complaints that the heart is beating too slow, too fast, skipping beats or if he/she is having chest pains. It should also be performed if Items 1-3 show an arrhythmia. Determinations of bradycardia and tachycardia (Items 1 and 2) should not be made using standing pulses. These items may indicate that the participant has an arrhythmia and should be referred to the SHEP physician.

1. peripheral pulse less than 50 (bradycardia)
2. pulse greater than 100 (tachycardia)
3. four or more skipped beats per minute or totally irregular pulse
4. differences between the apical and peripheral pulse (listen to the heart and compare to peripheral pulse)

SIDE EFFECTS QUESTIONNAIRE

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐

2. Acrostic: ☐☐☐☐☐☐

3. Date of clinic visit to which this form applies: ☐☐ Month ☐☐ Day ☐☐ Year

4. Sequence number of clinic visit: ☐☐

This form is required at all clinic visits after a SHEP medication is started or increased; at all visits where the participant responds positively to any of the general side effects questions, and at all Annual visits.

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
5. Unusual coldness or numbness of the hands or feet?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
6. Unusual skin rash or bruising?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Is an acute skin rash present on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
7. Any feelings of unsteadiness or imbalance?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
8. Faintness or light headedness when you stand up quickly?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Is there an observable postural drop in blood pressure? Yes ☐ 1 No ☐ 2
9. Loss of consciousness or passing out	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
10. Falls?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
11. Fractures?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Hip? Yes ☐ 1 No ☐ 2 (g) Spine? Yes ☐ 1 No ☐ 2 (h) Forearm? Yes ☐ 1 No ☐ 2

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
12. Unusual pain in any joint?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐ →	(f) Are there physical signs of acute arthritis? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
13. Muscle weakness or cramping?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
14. Excessive thirst?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
15. Loss of appetite?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
16. Nausea or vomiting?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
17. Unusual indigestion?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
18. Change in bowel habits?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
19. Tarry black stools or red blood in the stools?	Yes ☐ 1 → No ☐ 2 →	☐	☐	☐	☐	
20. Heart beating unusually fast or skipping beats?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
21. Heart beating unusually slow?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	→ (f) Is an arrhythmia present on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
22. Episodes of chest pain or heaviness in the chest?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
23. Headaches so bad you had to stop what you were doing?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
24. Stuffy nose?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
25. Unusual shortness of breath or wheezing?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Is there evidence for bronchospasm on auscultation of the chest? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
26. Unusual tiredness or loss of pep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
27. Swelling of the ankles?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Is there evidence of CHF on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
28. Feeling so depressed (sad or blue) that it interfered with your work, recreation or sleep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
29. Any trouble with your memory or concentration?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
30. Nightmares?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
31. Any changes in your sexual activity?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	(f) Loss of interest Yes ☐ 1 No ☐ 2 (g) Decline in frequency? Yes ☐ 1 No ☐ 2 (h) Loss of enjoyment? Yes ☐ 1 No ☐ 2 (i) Functional impairment? Yes ☐ 1 No ☐ 2

Since your last visit, have you had:	(a)	New since last visit? (b) 1=Yes 2=No	Frequency: (c) 1=once only 2=<weekly 3=2-6 x weekly 4=daily 5=constantly	Severity: (d) 1=Not troublesome 2=Troublesome 3=Intolerable	In the opinion of the SHEP clinician, is this due to the use of SHEP medications? (e) 1=Yes 2=Possibly 3=No	
32. Trouble going to sleep, or waking early and having trouble getting back to sleep?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
33. Waking up in the night more frequently to urinate?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
34. More worry or anxiety than usual?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐	
35. Weakness or numbness on one side, or unexpected difficulties talking or thinking?	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐ → (f)	Is there evidence of a stroke on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3
36. Other relevant symptoms: Specify:_____	Yes ☐ 1 → No ☐ 2	☐	☐	☐	☐ → (f)	Are there other relevant signs on physical exam? Yes ☐ 1 Possibly ☐ 2 No ☐ 3 Specify: _____

RETURN TO SH41

9.17 Report of Study Drug Disclosure - SH49

There will be times during the study when the blind will need to be broken for a particular participant, for a variety of reasons. These are documented on the SH49, which is required in any case of breaking the blind.

The participant's SHEP ID and acrostic should be entered into Items 1 and 2. The date of disclosure should be entered into Item 3, and the date the form completed in Item 4 (these two dates may not necessarily be the same).

The reason for disclosure may be multiple and should be documented in Item 5. These include:

- adverse reaction
- diagnostic test and/or surgery where there was not time for tapering without unblinding
- other medical reason
- private physician request, no reason given
- patient curiosity
- other

The last three reasons (non-medical) are discouraged except in cases where the participant's cooperation in the study is likely to be sacrificed if disclosure is refused. In these cases, the requestor may withdraw the request if the participant is not really having a problem, and reassurance is given that the participant is being carefully monitored. This should be stressed to the person in each clinic who is responsible for the list of unblinded codes.

It should be noted in Item 6 who was told, and are therefore aware, of what actual SHEP medication is being prescribed.

Many cases of unblinding will not be emergencies. Therefore, the Chairman of the Steering Committee (Dr. Berge--(507) 284-5164) or a representative of the Coordinating Center (Dr. Davis--(713) 792-4480) should be consulted prior to the unblinding. Whether or not this was done should be indicated in Item 7.

Item 8 is provided for the comments that are required on other items, or other comments which may be appropriate.

The person filling out the form should sign and enter his/her ID code in Item 9.

REPORT OF STUDY DRUG DISCLOSURE

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date of disclosure: ☐☐ ☐☐ ☐☐
   Month Day Year

4. Date this form completed: ☐☐ ☐☐ ☐☐
   Month Day Year

5. Reason for disclosure (check all that apply):
   a. 1 ☐ Suspect adverse reaction to SHEP medications
   b. 1 ☐ Diagnostic test and/or surgery where there was not time to taper patient off medication without unblinding
   c. 1 ☐ Other medical reasons (specify in Comments, Item 8)
   d. 1 ☐ Private physician request, no reason given
   e. 1 ☐ Patient curiosity
   f. 1 ☐ Other (specify in Comments, Item 8)

6. The following persons know which SHEP medication is being taken by the participant (check all that apply):
   a. 1 ☐ Participant
   b. 1 ☐ SHEP personnel
   c. 1 ☐ Pharmacy
   d. 1 ☐ Participant's private physician
   e. 1 ☐ Other → Specify: _____

7. Was the Chairman of the Steering Committee, or the Coordinating Center, consulted prior to unblinding?
   1 ☐ Yes
   2 ☐ No → Explain in Comments, Item 8

8. Comments: _____

   _____

   _____

9. Signature of person completing form: _____ ☐☐
   Code

9.18 Report of Missed Quarterly or Annual Visit--SH51

An SH51 should be completed whenever a quarterly or annual visit does not take place in the prescribed visit window (+/- 6 weeks for annual, +/- 2 weeks for quarterlies), even if a visit occurs immediately after the closing of the visit window.

If a visit does take place in the window, whether in the clinic, or the telephone, or at the participant's home, then no SH51 is necessary. Sometimes you will be able to contact the participant by telephone, but will not be able to do a complete telephone visit. Please use your judgment in deciding whether to complete a visit form or an SH51 in these cases.

If there is no visit in the window, it is appropriate to have the participant come into the Clinic as soon as possible for an interim blood pressure check.

Items 1-3: SHEP ID, acrostic and today's date (date this form is completed.

Items 4a-b: Type of visit missed and earliest window date of missed visit. These items identify the missed visit. For the earliest window date of the missed visit, look on the participant's randomization verification report--copy the date from this report.

Item 5: Reason for missed visit. Only one reason should be checked (your data entry operator cannot indicate more than one reason).

Item 6: Date of last attempt to contact. Please do not use invalid dates here. We want to know when it was that you most recently attempted to at least ascertain vital status regardless of who you actually contacted or what information (if any) you obtained. The attempt did not have to be successful.

Item 7: Date last know alive. Please do not use invalid dates here. If you can only respond, for example, "sometime in September 1988," indicate 09-15-88. Use any source that you need to for this information, if you cannot talk to the participant.

Item 8: Is participant on (a) SHEP medications, (b) open-label therapy? These are relatively straightforward items.

Items 9a-f: Morbid event information. Some uncertainly is allowed here, due to the varying possible sources of information. We intend for these items to simply be reminders for the interviewer to get this information if possible.

Item 10: Primary source of information. Indicate one only.

Item 11: Please indicate any important comments in this item.

Item 12: Signature and ID code.

REPORT OF MISSED QUARTERLY OR ANNUAL VISIT

If visit is missing because participant is deceased, please complete SH22 instead of this form.

1. SHEP ID: [ ] - [ ] - [ ] 2. Acrostic: [ ]

3. Today's date: [ ] Month [ ] Day [ ] Year

4a. Type of visit missed:
- Quarterly ☐ 1
- Annual ☐ 2

4b. Earliest window date of missed visit (from randomization verification report): [ ] Month [ ] Day [ ] Year

5. Reason for missed visit (check one):
- Currently refuses to participate ☐ 1
- Medically unable to complete visit ☐ 2
- Scheduling problem ☐ 3
- Transportation problem ☐ 4
- Out of town temporarily ☐ 5
- Has moved to unknown address ☐ 6
- Otherwise unable to contact participant ☐ 7
- Other (specify)_____ ☐ 8
- Unknown ☐ 9

6. Date of last attempt to contact: [ ] Month [ ] Day [ ] Year

7. Date last known alive: [ ] Month [ ] Day [ ] Year

8. Is participant on:

	Yes	No	Unknown
a. SHEP medications?	☐ 1	☐ 2	☐ 3
b. Open-label therapy?	☐ 1	☐ 2	☐ 3

9. Has the participant had a new:

	Yes	Possibly	No	Unknown
a. Stroke?	☐ 1	☐ 2	☐ 3	☐ 4
b. TIA?	☐ 1	☐ 2	☐ 3	☐ 4
c. MI?	☐ 1	☐ 2	☐ 3	☐ 4
d. LVF?	☐ 1	☐ 2	☐ 3	☐ 4
e. Other hospitalization?	☐ 1	☐ 2	☐ 3	☐ 4
f. Nursing home admission?	☐ 1	☐ 2	☐ 3	☐ 4

10. Primary source of information:
- Participant ☐ 1
- Spouse ☐ 2
- Other relative ☐ 3
- Friend ☐ 4
- Neighbor ☐ 5
- Medical records ☐ 6
- None ☐ 7
- Other_____ ☐ 8

11. Comments:

12. Signature: _____ [ ] Code

9.19 Pill Count Worksheet - SH62

This form is a worksheet which may be used by the SHEP staff person in calculating compliance percentages for the SHEP when it is required. The form itself is relatively self-explanatory. The number of days since the last visit should not include the day of the last clinic visit, but should include the day of the visit at which the pill count is done. The compliance percentages should be transferred to the SH40, Item 15; the SH62 is not sent to the Coordinating Center.

Proper procedure in conducting the pill count is absolutely essential if useful information is to be obtained about adherence. If participants ask why they must return unused medications and empty bottles, they may be told the following:

- To confirm the accuracy of the previous prescription
- To check for deterioration of the unused medication
- To check the accuracy of the new prescription

Preservation of the usefulness of the pill count for assessing adherence requires:

- That the participant remain unaware that returned pills are counted, and
- That the participant not be confronted with pill count information as the basis for admonishing or encouraging him or her towards better compliance, and
- The assumption that the participant is taking his medications as prescribed unless he volunteers or acknowledges on self-report that he is not taking his medicine as prescribed.

If a participant asks if his pills are being counted, do not deny it. One might simply acknowledge that "I have noticed that there seem to be more pills left in the bottle than I expected" and then proceed to explore the reasons for non-compliance, or if appropriate, "It appears that you are taking most of your medicine as you should."

(a) The Procedure for Pill Counting

(1) Instruct each participant to bring unused medication in the original container and any empty pill containers back to the clinic at the next regularly scheduled treatment visit. Repeat this instruction every time a prescription is distributed.

(2) Do not count pills in front of the participant. The preferred strategy is to have all bottles and pills left with the receptionist when the participant arrives in the clinic. The receptionist (if unobserved) could then do the count or give them to someone else for that purpose. An alternative strategy to avoid being observed would be to leave the room to get the new medication and perform the count while out. Having counted the number of pills remaining in the bottle(s), this number is recorded on Form SH62.

(3) If the percentage taken is found to be less than 80%, it is an indication for the clinician to probe further for compliance information without revealing that pills have been counted. Non-compliance is not a reason for discontinuing SHEP medication, unless, in the judgment of the clinician, it seriously affects the participant's health.

(4) Unopened bottles of medication may be returned to the participant if he/she is to continue on the same medication.

(5) Opened bottles of medication may be returned to the participant only if all of the following conditions are met:

- no pill count is to be done at the next visit
- the participant is remaining on the same medications
- there are enough pills to last until the next visit

The purpose of these rules is to assure that the pill count calculations are not invalidated, while avoiding wasting study medications.

(6) New pills should be dispensed in unopened whole bottle amounts. Do not open a bottle and dispense only a fraction of the pills in the bottle.

(7) Bottles contain 100 tablets. For all medications except reserpine, this will cover 3 months at 1 tablet daily. For reserpine, this will cover 3 months for dose 1; at dose 2, two bottles will be required to cover a 3-month period.

(8) The following ground rules for participants should be stressed at each visit:

- Return all unused medications and empty bottles at each regularly scheduled treatment visit.
- Never throw away unused medication or empty bottles.

SHEP DRUG COMPLIANCE WORKSHEET

This form is a worksheet which may be used by the SHEP clinican to assist in calculating compliance with SHEP medication based on pill counts at treatment visits.

Note that compliance is calculated separately for Step I and Step II meds. Use of the worksheet is optional; its data is not to be forwarded to the Coordinating Center nor entered on the data system.

SHEP ID: _____ - _____ - _____ Acrostic: _____

Current Clinic Visit Date: _____ _____ _____ Sequence #: _____
Month Day Year

Last Visit Date: _____ _____ _____
Month Day Year

Prescription (circle): C1, dose ½ A1 Other: _____
C1 A2
C2 R, Dose 1
R, Dose 2

Last Visit Prescription		Step I (C1, C2)	Step II (A1, A2, R)
Pills per day		a. _____	a. _____
Step/Dose	Pills/Day		
C1, dose ½	½		
C1	1		
C2	1		
A1	1		
A2	1		
R, Dose 1	1		
R, Dose 2	2		
Days since last visit		b. _____	b. _____
Total pills to be taken (a x b)		c. _____	c. _____
Prescription Usage			
Number of bottles given at last visit		d. _____	d. _____
Number of pills given (d x 100)		e. _____	e. _____
Number of pills returned		f. _____	f. _____
Pills taken (e-f)		g. _____	g. _____
Compliance % (g/c x 100)		h. _____ ↓	h. _____ ↓

TRANSFER TO ITEM 15 ON SH40.

9.20 SHEP Interviewer/Observer Codes - SH66

The purpose of this form is to keep track of ID codes assigned to each staff member at each Clinical Center. Each person who is associated with the clinic will have a two-digit ID code. The Principal Investigator is code 01, and the Clinic Coordinator is 02. Other clinic personnel who were trained centrally to take blood pressures will be already listed as 03, 04 . . . . As additional staff are hired and trained, they should be assigned the subsequent ID numbers in order, and it should be noted whether they are certified to do blood pressure readings, behavioral evaluations, and/or ECGs. As these are completed or changed, copies should be sent to Mrs. Donna Spross at the Coordinating Center. Of course, multiple pages may be used (you may photocopy this form), with one set of codes being submitted to the Coordinating Center per Clinical Center area, regardless of the number of sites. Each Clinical Center has been supplied with legal-size copies of both pages.

These should be submitted prior to transmitting hard or electronic copies of any study forms to the Coordinating Center.

SHEP INTERVIEWER/OBSERVER CODES

SHEP CENTER #____ _____

Code	Name	Title	Date of ECG Certification	Date of Behav. Certification	Date of BP Certification	Date BP Recert.	Date BP Recert.	Date BP Recert.	Date BP Recert.	Date BP Recert.
01		PRINCIPAL INVESTIGATOR								
02		CLINIC COORDINATOR								
03										
04										
05										
06										
07										
08										
09										
10										
11										
12										
13										
14										
15										
16										
17										

SHEP INTERVIEWER/OBSERVER CODES

SHEP CENTER #____ _____ PAGE _____

Code	Name	Title	Date of ECG Certification	Date of Behav. Certification	Date of BP Certification	Date BP Recert.	Date BP Recert.	Date BP Recert.	Date BP Recert.	Date BP Recert.

9.21 Corrections to Transmitted Data - SH67

This form will be used to document and provide input for changes to be made to previously transmitted (electronic) data, or in the case of a transfer, to permanently change an ID number. One change is permitted per form.

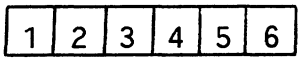
The participant's SHEP ID and acrostic are entered into Item 1, and the date ("today's date") in Item 2. The form number to which the change applies (a two-digit number 03, 04, 06-50, with few exceptions) should be entered in Item 3. In the case of a transfer, this number is always 06 (the ID is assigned at Baseline Visit 1, on the SH06). The date of the form to which the change should be made will be entered in Item 4.

Corrections may be a result of an error discovered by Clinical Center staff, Coordinating Center edit report, other Coordinating Center contact, or other special report, and this should be documented in Item 5.

A common correction is one to a mispunched SHEP ID number, which results in an apparent missing form on the computer masterfile, apparent "extra" forms for the other participants, or forms that are not acceptable to the masterfile. Item 6 is provided for this type of correction. This item should also be used in the case of a transfer to permanently change an ID (only the first two digits will change to the new center number). The "old" or "wrong" ID should be entered in Item 1, and the "new" or "correct" ID should be entered into Item 6. The reason for the ID change should be provided in "Explanation required." If an ID change is made, the person completing the form should skip to Item 10, sign the form and enter their ID code.

If a different change is required, Items 7, 8 and 9 are applicable. A form may be either deleted, replaced, or corrected. In the case of a deletion or replacement, Items 8 and 9 are not necessary. In the case of a replacement,* the date the form was re-transmitted to the Coordinating Center should be entered; in most cases, it will be the same day that the SH67 is transmitted.

A single item on a form may also be corrected. If this is the case, "Corrected" should be checked in Item 7, and the item number and description should be provided. In this case, Items 8 and 9 should be completed. The old data, as previously transmitted, should be provided in Item 8; six spaces are provided, although many items do not take up that much space. If the information takes up more than six spaces, fill in all six spaces, and write the remaining characters to the right of the boxes (the extra characters are not data entered). For example, if a Social Security number "123-45-6789" is being changed, write:



The new corrected data should be entered into Item 9, and six spaces are provided there also.

Your comments in the blank spaces on this form, regarding the reason for the change, are helpful.

When the form is completed, the person completing the form should sign and enter their ID code in Item 10.

---

*If a form is being "replaced," the entire "new" form must be entered into the data system, answering "Yes" to the final question, "Is this SH _ _ form a replacement for a previously transmitted form? 1=Yes."

CORRECTIONS TO TRANSMITTED DATA

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ Acrostic: ☐☐☐☐☐☐

2. Today's Date: ☐☐ ☐☐ ☐☐
   Month Day Year

3. Form Number: SH ☐☐

4. Date of the form to which this correction applies: ☐☐ ☐☐ ☐☐
   Month Day Year

5. Correction a result of:
   1 ☐ Clinical Center
   2 ☐ Coordinating Center
   3 ☐ Coordinating Center error edit report
   4 ☐ Other Report: _____

6. Is Participant ID changed with this correction? 1 ☐ Yes 2 ☐ No
   ↓
   New Participant ID: ☐☐ - ☐☐☐☐ - ☐☐
   ↓
   Explanation required: _____

If Participant ID is changed, SKIP to Item 10.

7. Is form being:

   1 ☐ Deleted

   2 ☐ Replaced → Date form retransmitted to Coordinating Center: ☐☐ ☐☐ ☐☐
   Month Day Year

   3 ☐ Corrected → Item number and description: _____

8. Old data as previously transmitted to Coordinating Center

   ☐☐☐☐☐☐

9. New data to be entered in Coordinating Center files.

   ☐☐☐☐☐☐

10. Person Completing Form: _____ ☐☐
    Code

APPENDIX A

INFORMED CONSENT GUIDELINES

A.1 Introduction

Every clinical trial depends for its success on the cooperative participation of its subjects. They must take their medication as prescribed, return for follow-up visits as indicated, and contact the SHEP Clinic if side effects develop. It is therefore imperative that we try to obtain truly informed voluntary consent. If the consent process is simply a mechanical ritual, the trial could be jeopardized not only on ethical grounds, but also by a high number of early drop outs, poor adherence to therapy, and allegations of coercion.

A.2 Basic Elements of Informed Consent

According to DHHS guidelines, informed consent is interpreted to mean:

> "the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion."

The guidelines also set forth eight essential ingredients of informed consent as follows:

(1) Participants must be advised that the study involves research. An explanation must be given regarding the purposes of the research, the expected duration of the subject's participation and a description of the procedures to be followed, including identification of anyexperimental procedures.

In the SHEP trial none of the procedures is novel or experimental. Chlorthalidone, atenolol and reserpine have been used to treat patients with high blood pressure. However, we must carefully explain that two kinds of medications (active and a placebo) are being prescribed in the study and that half the participants will be assigned by chance to each therapy group. It is essential that the participant understand that he or she will not necessarily be taking an active drug. It is just as likely that placebo tablets will be prescribed.

Health professionals are not in the habit of discussing with patients the pros and cons of placebo therapy, and there tends to be a feeling among physicians and patients that active treatment with some procedure or drug is always preferable to an inactive approach. Yet, a number of studies have shown that patients may be better off taking an inert placebo than an active medication, if their health status is carefully monitored in both cases.

In our situation we have a special reason for including a placebo group, and participants should be given some understanding of its purpose. This calls for an explanation of the scientific approach to the study--the need to control as many variables as possible. By emphasizing the importance of the placebo group, we explicitly call attention to the fact that this is primarily a study, rather than a therapeutic program specifically designed for the individual. Each

participant will be cared for in terms of his or her individual needs, but the scientific design of the study requires that certain conditions must be uniform.

We should carefully explain that this is a double-blind trial in which neither the participant nor the physician will know which medication the patient is taking.

To allay anxiety, it is important to note that not everyone connected with the trial will be "blinded" in the sense of the study. An appropriate person at each medical center will be able to identify the participant's medication in an emergency situation.

Furthermore, a panel of national experts will know which participants are taking which medication and what is happening to each therapy group. If active therapy proves to be significantly more beneficial than placebo tablets, the study will be stopped so that everyone can have an opportunity to take the active drugs; and if active treatment proves to be significantly harmful the study will also be stopped, at least for those who might be harmed. Experts who have access to all the data from the trial are in the best position to judge the effectiveness or harm of active treatment to the participants as a whole and special subgroups of them.

With respect to routine procedures, participants should be told that they are expected to take their medication on a daily basis over the course of the trial and visit the SHEP clinic at least every three months. To avoid misunderstanding, it should be made clear that the study is expected to last until August 1991.

(2) Anticipated benefits of the trial must be explained to patients.

Many participants appreciate the opportunity to be involved in relevant research and to contribute to medical knowledge. In the SHEP trial the knowledge we gain will be specifically applicable to participants in the study as well as elderly persons with ISH in general, and this is an added benefit of participation.

About one third of the elderly persons in the United States are on antihypertensive treatment. Although active antihypertensive therapy has been shown to reduce all cause mortality and fatal and nonfatal cardiovascular and cerebrovascular events in younger hypertensives, no adequate evaluation has been carried out to assess the effects on health (benefits and risks) of antihypertensive treatment in elderly subjects with ISH. It is therefore in the participant's best interest that a careful scientific study concerned with these issues be carried out.

All participants in the trial will be monitored closely. Furthermore, tests and medications associated with the study are provided at no cost to the participant. The participant will not be charged for the active or placebo tablets, periodic examinations relevant to the study, or laboratory tests and electrocardiograms required for the study. There is no way of knowing in advance whether a particular participant will personally benefit from active treatment during the course of the trial. That will depend on whether the drugs are effective and whether the participant is assigned to the active treatment group. We should be careful not to suggest that participants will benefit from active treatment simply by entering the trial. If we were convinced that the drugs were effective, we would not be conducting the trial. The study may show that participants on placebo therapy do as well or better than participants on active treatment.

(3) Attendant discomforts and risks "reasonably to be expected" must be described.

All drugs have side effects. What is important is their severity and frequency. In the SHEP there is very little likelihood that the subjects will be seriously harmed by participating. To reduce the risks, we have purposely excluded subjects for whom active therapy is contraindicated.

In spite of our precautions, however, adverse reactions will still occur. Some participants in the active treatment group will probably experience annoying discomforts from the drugs, such as drowsiness, tiredness, weakness, dry mouth, impotence, and nasal stuffiness. Depression, a slow pulse, a reduction in heart function or asthma may occur, but are rare. If they know such problems can occur, they will be less surprised if they do occur, and we hope they will be less inclined to withdraw from the study. It should be made clear that participants will be monitored very closely, particularly when they begin taking study medication, so that any problems that arise can be immediately treated. Participants who have an exaggerated response to the medication will be taken off the study medication or have their dosage reduced, whichever is appropriate.

To avoid the implication that side effects and problems are only linked to the active drug, we should indicate that participants on placebo therapy may also experienced discomforts and difficulties similar to those attributable to the active drug. Since placebo participants may think they are taking active drugs, they may experience and report more drug related difficulties than otherwise.

(4) Appropriate alternative procedures that might be advantageous for the subject must be disclosed.

This mandate is often overlooked in written consent forms. It means that the participant should be told what options exist if he or she elects not to participate in the trial. They may elect to be treated for their ISH by their own private physician, but it should be stressed that safety precautions have been set up to ensure that if blood pressure is at very high levels, active treatment will be initiated by a SHEP physician.

(5) The extent, if any, to which confidentiality of records identifying the participant will be maintained must be described.

Confidentiality of all participant information is assured in all participating centers. No unauthorized personnel should have access to participant records or results of interviews or tests. Additionally, all record storage rooms should be appropriately secured, and should contain necessary locked files or other storage equipment.

It may be useful to explain that in studies of this nature, numerical and alphabetic codes are assigned by which central study files may be linked to individual participants. The Clinical Centers retain forms which permit such linkage. These Participant Identification Forms contain participant identifiers and study codes. If, in the future, it is necessary for participant safety reasons to contact individual participants, these locally maintained forms will allow such contacts. Participants are not identified by name in any of the forms submitted for central coding or in any reports or publications.

(6) Prospective subjects must be advised of the availability or non-availability of medical treatment or compensation for physical injuries incurred as a result of participation in the study, and, if available, what they consist of, or where further information may be obtained.

It may be useful to distinguish between providing study treatment and follow-up free of charge, and financial compensation for injuries incurred. The Federal Government is prohibited by law from commiting funds that have not yet been appropriated by Congress, and no funds have been allocated for compensating injured subjects in trials such as the SHEP. The only recourse for such participants is to seek compensation through the courts or through negotiation with the Clinical Center involved.

Reimbursing the cost of medical treatment for a research-induced injury is a separate issue. Every effort will be made by the Project Office and the cooperating centers to reimburse injured subjects for their medical expenses if the participants are required to pay such costs out of their own pockets. Any such problems will be dealt with on a case by case basis.

Policies regarding compensation and reimbursement vary from institution to institution, so we cannot recommend a standard approach for all participating centers. However, on the basis of our observations to date in other clinical trials using the active study medications, we offer several suggestions. Staff members should stress the fact that the chance of serious injury in the SHEP is extremely small but the government requires that compensation be discussed with

participants if there is any risk at all. Legal terms and concepts should be translated into layman's language, and the ideas should be made relevant to the SHEP, not simply to research in general. Comments regarding compensation should be as brief as possible. Where every contingency is described, these statements tend to be lengthy and out of balance with the rest of the consent form. They give the impression that injuries are likely to occur, even though we say elsewhere that the probability of serious side effects is minimal.

(7) Persons responsible for the study must offer an explanation of whom to contact for answers to pertinent questions about the research and research participant's rights, and whom to contact in the event of a research related injury to the participant.

We suggest that one or more people associated with the trial be available to answer relevant questions while participants are contemplating participation.

Prospective subjects should be handed the names of these people on a card when they are first approached. If no names are provided, they may ask questions of persons not knowledgeable about the study and be given evasive answers or misinformation.

Once enrolled in the study, we recommend that participants receive written information regarding whom to contact at any time about possible side effects during therapy or rights as a volunteer in the study.

(8) Participants must be told that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which he or she is otherwise entitled.

We obviously would like our participants to remain in the study as long as possible, but they have the right to withdraw at any time. We must communicate this option to participants without luring them into the trial on a probationary "look and see" basis. Hesitant participants should be evaluated very carefully to screen out those who are likely to withdraw early.

The right to withdraw from a trial is meaningless if such behavior invokes penalties. This is the reason for the phrase, "without penalty or loss of benefits," and that idea should be explained to participants. If they drop out of the trial, the fact of dropping out will not jeopardize their regular care, and we welcome them back into the study at any time they wish to return.

A.3 The Process of Obtaining Consent

The eight requirements of informed consent in the DHHS guidelines refer primarily to categories of information that enable participants to make rational decisions regarding participation in clinical trials. Except for the stipulation that participant inquiries should be answered, these basic elements do not refer to the process of obtaining informed consent.

Various studies indicate that the circumstances under which consent is obtained in clinical trials can have a profound influence on the participant's interpretation of information communicated during the consent discussion and on the freedom of participants to make their own decisions.

Given the data at hand, we are recommending the following guidelines to ensure that the consent we obtain will be as informed and voluntary as possible:

(1) Participants should be fully informed about the study and have adequate time to evaluate the pros and cons of participation.

Although it is not permitted at all SHEP Clinical Centers, the Informed Consent for Baseline Visit 1 and Baseline Visit 2 may be sent home with the participant after the Initial Contact, so that he or she may more carefully review it. (It should be returned to the Baseline Visit 1 unsigned.) Time has been set aside at Baseline Visit 2 for orientation to the SHEP for eligible participants, at which time the pros and cons of participation will be discussed.

(2) Participants should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (for example, persons who might be needed to provide transportation).

Close associates of the participant may raise questions and considerations that the participant is likely to overlook, and questions that concern the family are better answered sooner than later. Furthermore, there is evidence to suggest that family support for studies of this kind increases the probability of participant cooperation during the course of the research.

(3) To be eligible for participation in the SHEP, participants must have the capacity to give their own informed consent.

If a participant is incapable of understanding what is expected of him or her as a subject in the study, it is not permissible to obtain informed consent from a guardian. The study requires daily responsibilities that cannot be easliy assumed by other persons.

(4) The setting in which consent is obtained should be as private as possible so participants can freely ask questions without embarrassment. If extraneous parties can hear the conversation, participants may be reluctant to ask appropriate questions.

(5) To avoid pressuring the participant, only one person associated with the study should be present when the participant reviews the consent forms. If a second witness is required, he or she should be as unobstrusive and non-committal as the situation permits.

(6) The participant should be given a copy of the informed consent forms after they are signed and witnessed.

Even though participants are free to withdraw from the study at anytime, the consent form spells out our obligations to the participant and the participant's obligations to the study while he or she is a subject.

(7) Participants should be encouraged to keep the consent forms because they contain useful information about the study which they can review from time to time.

A.4 Reducing the Vulnerability of Participants

A participant's trust in his or her physician is not a substitute for truly informed voluntary consent. Where dependency is particularly evident, we must be especially careful to give participants all the freedom they need to say "no" if this is their inclination.

Where the person responsible for obtaining the participant's consent is also the person in charge of that participant's regular medical care, participants must be told in no uncertain terms that they will be treated with the same degree of interest and concern regardless of whether they participate in the study.

In approaching the issue of informed consent, we should keep in mind its two essential components -- information and voluntary choice. When we share with participants important facts about the SHEP trial, we treat them as potential partners in our research and enable them to rationally evaluate their capacity and willingness to participate. By fully disclosing information about the study, we are expressing respect for our participants and reducing their vulnerability to coercions.

_____
(INSTITUTION)

CONSENT TO PARTICIPATE IN THE INITIAL CONTACT PROCEDURES OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

I AGREE TO TAKE PART IN THE INITIAL CONTACT OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM. IF INVITED, I AGREE TO RETURN FOR A FOLLOW-UP IN THE CLINIC.

THE FOLLOWING WILL BE DONE AT THE INITIAL CONTACT VISIT:

1. MY BLOOD PRESSURE WILL BE MEASURED THREE TIMES. BLOOD PRESSURE MEASUREMENT IS NOT PAINFUL AND THERE ARE NO RISKS INVOLVED.
2. A FEW QUESTIONS ABOUT MY MEDICAL HISTORY WILL BE ASKED. IF I AM INVITED TO RETURN FOR THE FOLLOW-UP VISIT TO THE CLINIC, I WILL BE GIVEN A MEDICAL HISTORY QUESTIONNAIRE, A DEMOGRAPHIC INFORMATION AND MEDICATION HISTORY QUESTIONNAIRE, AND AN INFORMATION SHEET TO TAKE HOME AND FILL OUT.

THE INITIAL CONTACT WILL TAKE ABOUT 15 MINUTES. THE PURPOSE OF THE INITIAL CONTACT IS TO DETERMINE IF I AM ELIGIBLE TO TAKE PART IN THE OTHER PARTS OF THE STUDY. THIS EXAMINATION AND ANY OTHER PARTS OF THE STUDY FOR WHICH I AM ELIGIBLE WILL BE PROVIDED AT NO COST AT ALL TO ME.

ANY INFORMATION OBTAINED AS PART OF THIS STUDY WILL BE CONSIDERED CONFIDENTIAL AND USED ONLY FOR RESEARCH PURPOSES. MY IDENTITY WILL BE KEPT CONFIDENTIAL WITHIN THE LIMITS OF THE LAW.

I UNDERSTAND THAT _____ HAS MADE NO PROVISION FOR MONETARY COMPENSATION TO ME IN THE EVENT OF PHYSICAL INJURY RESULTING FROM THE RESEARCH PROCEDURES. SHOULD PHYSICAL INJURY OCCUR, MEDICAL TREATMENT IS AVAILABLE, BUT TREATMENT IS NOT PROVIDED FREE OF CHARGE.

I UNDERSTAND THAT MY PARTICIPATION IN THESE PROCEDURES IS ENTIRELY VOLUNTARY AND WILL NOT AFFECT ANY MEDICAL CARE TO WHICH I AM ENTITLED. FURTHER, I AM FREE TO REFUSE TO TAKE PART OR WITHDRAW AT ANY TIME. I HAVE BEEN GIVEN A COPY OF THIS FORM.

_____ HAS DISCUSSED THIS INFORMATION WITH ME AND IF I HAVE ANY MORE QUESTIONS ABOUT THE STUDY OR THESE PROCEDURES I CAN CALL _____.
(TELEPHONE NUMBER)

SIGNATURE: _____

WITNESS: _____

DATE: _____

CONSENT TO DISCONTINUE ANTIHYPERTENSIVE MEDICINE(S)
IN ORDER TO BECOME ELGIBLE AS A RESEARCH PARTICIPANT
IN THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP)

HAVING TAKEN PART IN THE INITIAL CONTACT EXAMINATION OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM, I UNDERSTAND THAT I AM NOT ELIGIBLE TO PARTICIPATE IN THE SHEP AT THIS TIME BECAUSE OF MY CURRENT USE OF ANTIHYPERTENSIVE MEDICINE(S). I AGREE TO DISCONTINUE USE OF MY MEDICINE(S) AND TO BE EVALUATED AGAIN OVER AN EIGHT-WEEK PERIOD AFTER DISCONTINUING MY MEDICINE(S) TO DETERMINE IF I AM THEN ELIGIBLE FOR PARTICIPATION IN THE STUDY.

1. MY BLOOD PRESSURE WILL BE MEASURED THREE TIMES AT EACH RE-EVALUATION VISIT. BLOOD PRESSURE MEASUREMENT IS NOT PAINFUL AND THERE ARE NO RISKS INVOLVED.

2. MY MEDICAL HISTORY WILL BE REVIEWED.

3. I UNDERSTAND THAT MY PHYSICIAN DR. _____, WILL BE CONTACTED, IF I SO CHOOSE, WITHIN ONE WEEK FOR CONSENT TO DISCONTINUE MEDICINE(S).

4. DURING THE TIME THAT I AM STOPPING MY MEDICINE(S) AND BEING RE-EVALUATED, I UNDERSTAND THAT MY HEALTH WILL BE CLOSELY AND CAREFULLY MONITORED BY THE SHEP MEDICAL PERSONNEL TO BE CERTAIN THERE ARE NO SERIOUS ILL EFFECTS OF DISCONTINUING THE MEDICINE(S). EXPERIENCE HAS SHOWN THAT FOLLOWING DISCONTINUATION OF ANTI-HYPERTENSIVE MEDICATION, BLOOD PRESSURE MAY RISE VERY SLOWLY, IF AT ALL. MEDICAL EVALUATION SHOULD BE SOUGHT IF SHORTNESS OF BREATH, SWELLING, OR CHEST PAIN OCCUR.

EACH RE-EVALUATION VISIT WILL TAKE ABOUT 15 MINUTES. THE PURPOSE OF THESE VISITS IS TO DETERMINE IF I AM ELIGIBLE TO TAKE PART IN THE STUDY. IF IT IS DETERMINED THAT I AM ELIGIBLE, THE STUDY WILL BE PROVIDED AT NO COST AT ALL TO ME.

I WILL BE GIVEN THE RESULTS OF MY BLOOD PRESSURE READINGS AND, IF I SO REQUEST, THE RESULTS MAY ALSO BE REPORTED TO MY DOCTOR.

ANY INFORMATION OBTAINED AS PART OF THIS STUDY WILL BE CONSIDERED CONFIDENTIAL AND USED ONLY FOR RESEARCH PURPOSES. MY IDENTITY WILL BE KEPT CONFIDENTIAL WITHIN THE LIMITS OF THE LAW.

I UNDERSTAND THAT THE INVESTIGATOR IS WILLING TO ANSWER ANY INQUIRIES I MAY HAVE CONCERNING THE PROCEDURES HEREIN DESCRIBED. ALL THE INQUIRIES I HAVE AT THIS TIME HAVE BEEN ANSWERED. I UNDERSTAND THAT I MAY ASK ADDITIONAL QUESTIONS AT ANY TIME.

Participant Initials_____

I UNDERSTAND THAT I AM FREE TO WITHDRAW MY CONSENT AND TO DISCONTINUE PARTICIPATION IN THE PROJECT AT ANY TIME WITHOUT JEOPARDIZING ANY RIGHTS TO MEDICAL CARE TO WHICH I MAY BE ENTITLED. I ALSO UNDERSTAND THAT I MAY ASK A QUESTION OR STATE A CONCERN TO ANY OF THE SHEP STAFF AT ANY TIME.

I UNDERSTAND THAT _____ HAS MADE NO PROVISION FOR MONETARY COMPENSATION TO ME IN THE EVENT OF PHYSICAL INJURY RESULTING FROM THE RESEARCH PROCEDURES. SHOULD PHYSICAL INJURY OCCUR, MEDICAL TREATMENT IS AVAILABLE, BUT TREATMENT IS NOT PROVIDED FREE OF CHARGE.

I HAVE READ THE FOREGOING STATEMENT, UNDERSTAND IT, AND ANY QUESTIONS WHICH HAVE OCCURRED TO ME HAVE BEEN ANSWERED TO MY SATISFACTION.

_____ HAS DISCUSSED THIS INFORMATION WITH ME AND IF I HAVE ANY MORE QUESTIONS ABOUT THE STUDY OR THESE PROCEDURES I CAN CALL _____.
(TELEPHONE NUMBER)

_____	_____
INVESTIGATOR	PARTICIPANT
_____	_____
WITNESS	DATE

_____
(INSTITUTION)

CONSENT TO PARTICIPATE IN THE BASELINE VISITS 1 AND 2 OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

I AGREE TO TAKE PART IN THE PROCEDURES TO BE DONE AT BASELINE VISITS 1 AND 2 OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM. THE RESULTS OF THESE CLINIC VISITS WILL DETERMINE IF I AM ELIGIBLE TO PARTICIPATE IN THE ACTUAL STUDY.

AT BASELINE VISIT 1, THE FOLLOWING WILL TAKE PLACE:

1. MY BLOOD PRESSURE WILL BE MEASURED THREE TIMES. BLOOD PRESSURE MEASUREMENT IS NOT PAINFUL AND THERE ARE NO RISKS INVOLVED.

2. I WILL BE GIVEN AN ECG (ELECTROCARDIOGRAM) WHILE I AM LYING DOWN, RESTING. THIS PROCEDURE IS NOT PAINFUL AND THERE ARE NO RISKS INVOLVED.

3. THE MEDICAL HISTORY QUESTIONNAIRE AND DEMOGRAPHIC INFORMATION AND MEDICATION HISTORY QUESTIONNAIRE I FILLED OUT WILL BE REVIEWED WITH ME.

4. I WILL BE GIVEN A GENERAL PHYSICAL EXAMINATION.

5. SAMPLES OF MY URINE MAY BE COLLECTED FOR TESTS. THERE ARE NO RISKS INVOLVED IN THIS PROCEDURE.

6. I MAY HAVE BLOOD DRAWN FROM MY ARM WITH A NEEDLE, FOR TESTS. I UNDERSTAND THAT THE NEEDLE FEELS LIKE A PIN PRICK; OCCASIONALLY BRUISING OR, VERY RARELY, INFECTION MAY RESULT.

BASELINE VISIT 1 WILL TAKE ABOUT 3 HOURS.

BASELINE VISIT 2 WILL TAKE PLACE ABOUT 2 WEEKS AFTER THE FIRST BASELINE VISIT AND WILL TAKE ABOUT 3 HOURS.

AT BASELINE VISIT 2, THE FOLLOWING WILL TAKE PLACE:

1. MY BLOOD PRESSURE WILL BE MEASURED THREE TIMES, EXACTLY AS BEFORE.

2. I WILL BE GIVEN A SHORT PSYCHOLOGICAL TEST AND ASKED TO ANSWER QUESTIONS ABOUT MY EMOTIONAL WELL-BEING.

Participant Initials_____

3. I WILL BE ASKED ABOUT HOW I HAVE BEEN FEELING, AND ABOUT SPECIFIC HEALTH PROBLEMS THAT I MIGHT BE HAVING.

4. IF I QUALIFY AND AGREE TO PARTICIPATE, I WILL BE GIVEN THE REMAINDER OF A SERIES OF PSYCHOLOGICAL TESTS. THIS PART OF THE EXAM TAKES ABOUT 40 MINUTES. THE PURPOSE OF THESE TESTS IS TO GET A COMPLETE PICTURE OF MY HEALTH, AND TO ASSESS THE POSSIBLE EFFECTS OF MEDICATIONS ON IT.

5. IF I QUALIFY AND AGREE TO PARTICIPATE, I WILL HAVE BLOOD DRAWN FROM MY ARM WITH A NEEDLE. I UNDERSTAND THAT THE NEEDLE FEELS LIKE A PIN PRICK; OCCASIONALLY BRUISING OR, VERY RARELY, INFECTION MAY RESULT.

I UNDERSTAND THAT MY PARTICIPATION IN THESE PROCEDURES IS ENTIRELY VOLUNTARY AND WILL NOT AFFECT ANY MEDICAL CARE TO WHICH I AM ENTITLED. FURTHER, I AM FREE TO REFUSE TO TAKE PART OR WITHDRAW AT ANY TIME. I HAVE BEEN GIVEN A COPY OF THIS FORM.

I UNDERSTAND THAT MY SOCIAL SECURITY OR MEDICARE NUMBER MAY BE USED TO PERIODICALLY ASCERTAIN MY VITAL STATUS, EVEN IF I DO NOT QUALIFY FOR THE TRIAL.

I WILL BE GIVEN THE RESULTS OF MY BLOOD PRESSURE READINGS AT ALL CLINIC VISITS AND, IF I GIVE MY PERMISSION, THESE RESULTS MAY ALSO BE REPORTED TO MY DOCTOR.

I UNDERSTAND THAT THIS AND ALL INFORMATION OBTAINED AS PART OF THE STUDY, WILL BE CONSIDERED CONFIDENTIAL AND ONLY USED FOR RESEARCH PURPOSES. MY IDENTITY WILL BE KEPT CONFIDENTIAL WITHIN THE LIMITS OF THE LAW.

I UNDERSTAND THAT _____ HAS MADE NO PROVISION FOR MONETARY COMPENSATION TO ME IN THE EVENT OF PHYSICAL INJURY RESULTING FROM THE RESEARCH PROCEDURES. SHOULD PHYSICAL INJURY OCCUR, MEDICAL TREATMENT IS AVAILABLE, BUT TREATMENT IS NOT PROVIDED FREE OF CHARGE.

_____ HAS DISCUSSED THIS INFORMATION WITH ME AND IF I HAVE ANY FURTHER QUESTIONS ABOUT THE STUDY OR THESE PROCEDURES, I CAN CALL _____.
(TELEPHONE NUMBER)

SIGNATURE: _____

WITNESS: _____

DATE: _____

_____

(INSTITUTION)

CONSENT TO PARTICIPATE AS A RESEARCH SUBJECT IN THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM

I AGREE TO PARTICIPATE IN A STUDY OF SYSTOLIC HYPERTENSION IN THE ELDERLY WHICH IS SCHEDULED TO CONCLUDE IN 1991. I HAVE BEEN FOUND TO HAVE ISOLATED SYSTOLIC HYPERTENSION, WHICH IS A FORM OF HIGH BLOOD PRESSURE, AND I UNDERSTAND THAT PERSONS WITH HIGH BLOOD PRESSURE ARE MORE LIKELY TO SUFFER FROM HEART ATTACK, STROKE, KIDNEY FAILURE AND EARLY DEATH THAN THOSE WHO HAVE NORMAL BLOOD PRESSURE.

DOCTORS DO NOT AGREE ABOUT WHETHER THE FORM OF HIGH BLOOD PRESSURE I HAVE SHOULD BE TREATED IN PERSONS WHO ARE AT LEAST 60 YEARS OLD. THE PURPOSE OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM IS TO EVALUATE WHETHER TREATMENT FOR THIS FORM OF HIGH BLOOD PRESSURE REDUCES THE CHANCE OF STROKE IN PERSONS AT LEAST 60 YEARS OF AGE.

STUDIES HAVE SHOWN THAT IT IS HELPFUL TO TREAT OTHER FORMS OF HIGH BLOOD PRESSURE IN MIDDLE-AGED PERSONS, AND IT IS POSSIBLE THAT SUCH TREATMENT CAN BENEFIT ME DIRECTLY. THIS STUDY PROVIDES ME WITH AN OPPORTUNITY TO PARTICIPATE IN RELEVANT RESEARCH AND TO CONTRIBUTE TO MEDICAL KNOWLEDGE. THE INFORMATION GATHERED IN THIS STUDY WILL BE VERY IMPORTANT FOR DOCTORS IN DECIDING WHETHER TO TREAT PERSONS MY AGE WITH ISOLATED SYSTOLIC HYPERTENSION.

THE TYPE OF DRUG I WILL BE TAKING IS SELECTED BY CHANCE RATHER THAN BY THE CLINIC DOCTOR, AND I HAVE A 1 IN 2 CHANCE OF RECEIVING AN INACTIVE PILL, CALLED A PLACEBO. NEITHER THE CLINIC DOCTOR NOR I WILL KNOW WHAT DRUG I AM TAKING, ALTHOUGH IN CASE OF AN EMERGENCY IT CAN BE REVEALED.

I WILL BE TAKING PILLS ONCE A DAY, AND THE DRUGS CAN CAUSE SIDE EFFECTS WHICH ARE RARELY SERIOUS BUT CAN BE BOTHERSOME. I COULD EXPERIENCE SUCH SIDE EFFECTS AS: DROWSINESS, TIREDNESS, WEAKNESS, DRY MOUTH, IMPOTENCE, AND NASAL STUFFINESS. RARELY, DEPRESSION, A SLOW PULSE, A REDUCTION IN HEART FUNCTION OR ASTHMA MAY OCCUR. IF THIS HAPPENS, MY TREATMENT MAY BE CHANGED.

I ALSO UNDERSTAND THAT SAFETY PRECAUTIONS HAVE BEEN SET UP TO ENSURE THAT IF MY BLOOD PRESSURE IS TOO HIGH OR TOO LOW, MY TREATMENT MAY BE CHANGED.

Participant's Initials _____

DURING THE STUDY, I AGREE TO VISIT THE CLINIC AT LEAST EVERY THREE MONTHS FOR FOLLOW-UP EXAMS AND PRESCRIPTION REFILLS. AT ALL VISITS, THE FOLLOWING WILL TAKE PLACE:

1. MY BLOOD PRESSURE WILL BE MEASURED THREE TIMES.

2. MY PULSE AND WEIGHT WILL BE MEASURED.

3. I WILL BE ASKED QUESTIONS ABOUT ANY SIDE EFFECTS I MAY HAVE.

4. I WILL BE GIVEN A BRIEF PHYSICAL EXAMINATION, IF NECESSARY.

AT CERTAIN FOLLOW-UP VISITS THE FOLLOWING MAY BE DONE:

1. BLOOD MAY BE DRAWN FROM MY ARM WITH A NEEDLE FOR TESTING. I UNDERSTAND THAT THE NEEDLE FEELS LIKE A PINPRICK; OCCASIONALLY BRUISING OR, VERY RARELY, INFECTION MAY RESULT.

2. SOME OF THE PSYCHOLOGICAL TESTS MAY BE REPEATED.

ALL OF THESE PROCEDURES TOGETHER SHOULD TAKE ABOUT ONE HOUR.

AT THE END OF EACH YEAR, I WILL RECEIVE A MORE COMPLETE EXAMINATION, TO INCLUDE THE FOLLOWING:

1. I WILL BE GIVEN A GENERAL PHYSICAL EXAM BY THE DOCTOR.

2. I WILL BE ASKED MORE QUESTIONS ABOUT BY MEDICAL HISTORY.

3. BLOOD WILL BE DRAWN AND URINE COLLECTED.

4. AT SELECTED ANNUAL VISITS, I WILL BE GIVEN AN ECG (ELECTROCARDIOGRAM) WHILE I AM RESTING.

5. I WILL BE GIVEN THE SAME SERIES OF PSYCHOLOGICAL TESTS I RECEIVED IN BASELINE VISIT 2.

THE ANNUAL EXAM SHOULD TAKE ABOUT 3 HOURS TO COMPLETE.

I UNDERSTAND THAT THIS AND ALL INFORMATION OBTAINED AS PART OF THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM WILL BE CONSIDERED CONFIDENTIAL AND ONLY USED FOR RESEARCH PURPOSES. MY IDENTITY WILL BE KEPT CONFIDENTIAL WITHIN THE LIMITS OF THE LAW.

Participant's Initials _____

FOR THIS STUDY TO BE A SUCCESS, IT IS IMPORTANT THAT I REMAIN IN COMMUNICATION WITH THE STUDY AND IF I LOSE TOUCH WITH THE CLINIC, THEY WILL TRY TO FIND ME TO ASK ABOUT MY HEALTH. FOR THIS REASON, I AGREE TO TELL THE CLINIC WHEN I MOVE AND ALSO TO PROVIDE NAMES, ADDRESSES AND PHONE NUMBERS OF RELATIVES WHO WILL KNOW MY STATE OF HEALTH.

I UNDERSTAND THAT MY SOCIAL SECURITY OR MEDICARE NUMBER WILL BE USED TO HELP THE SHEP CLINIC KNOW IF I AM IN THE HOSPITAL. I ALSO UNDERSTAND THAT THIS IS NO WAY WILL AFFECT MY MEDICARE COVERAGE.

I AGREE TO TRY MY BEST TO KEEP APPOINTMENTS AT THE CLINIC AND TO LET THE CLINIC KNOW IF I NEED TO CHANGE APPOINTMENTS OR WHEN I HAVE ANY PROBLEMS FOLLOWING THE INSTRUCTION OF THE CLINIC STAFF.

I UNDERSTAND THAT _____ HAS MADE NO PROVISIONS FOR MONETARY COMPENSATION TO ME IN THE EVENT OF PHYSICAL INJURY RESULTING FROM THE RESEARCH PROCEDURES. SHOULD PHYSICAL INJURY OCCUR, MEDICAL TREATMENT IS AVAILABLE, BUT TREATMENT IS NOT PROVIDED FREE OF CHARGE.

MY PARTICIPATION IN THE STUDY IS ENTIRELY VOLUNTARY AND WILL NOT AFFECT ANY MEDICAL CARE TO WHICH I AM ENTITLED. I ALSO UNDERSTAND THAT TREATMENT FOR MY ISOLATED SYSTOLIC HYPERTENSION IS AVAILABLE FROM MY OWN USUAL SOURCE OF CARE, IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY. FURTHER, I AM FREE TO REFUSE TO TAKE PART OR WITHDRAW AT ANY TIME. I HAVE BEEN GIVEN A COPY OF THIS FORM.

_____ HAS DISCUSSED THIS INFORMATION WITH ME AND IF I HAVE ANY QUESTIONS ABOUT THE STUDY, I CAN CALL _____.
(TELEPHONE NUMBER)

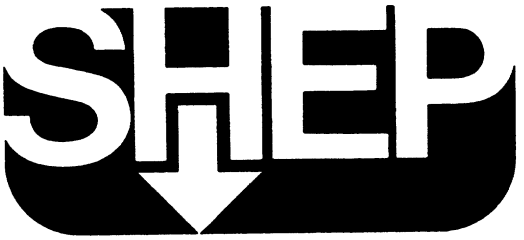
SIGNATURE: _____

WITNESS: _____

DATE: _____

APPENDIX B

SHEP ORIENTATION MANUAL



Systolic Hypertension in the Elderly Program

ORIENTATION BOOKLET

REVISED JULY 1985

THIS BOOKLET BELONGS TO:

NAME: _____

ADDRESS: _____

CITY: _____

PHONE NO.: _____

MY SHEP CLINIC ADDRESS AND PHONE:

_____

_____

_____

_____

REVISED JULY 1985

TABLE OF CONTENTS

TABLE OF CONTENTS

(Continued)

TABLE OF CONTENTS

(Continued)

ACKNOWLEDGMENTS

The members of the SHEP Pilot Study Medical Care and Quality Control Committee had primary responsibility for developing this booklet, on behalf of the entire SHEP Pilot Study Research Group. It was reviewed and revised for the SHEP Main Trial by representatives from the SHEP Operations Working Group.

WELCOME--AND WHAT NEXT?

The Systolic Hypertension in the Elderly Program--SHEP--welcomes you as a participant in a major national research project. It is important for you to understand what the SHEP is all about and that is the reason for this booklet--to answer your questions about what has been planned for you during the months ahead and to provide you with information about why we are conducting this study.

BACKGROUND

What Is Isolated Systolic Hypertension?

When we take your blood pressure, we get two numbers that are usually recorded this way: 120/80. The first, or the larger number, is called the systolic pressure. The second, or the smaller number, is called the diastolic pressure. A slight rise in blood pressure, both systolic and diastolic, tends to occur as we grow older. It occurs in all people: white and black; men and women. An increase in the systolic pressure appears more frequently in the years after age 60.

You have been selected to participate in the SHEP because you are at least 60 years old, your systolic blood pressure has averaged 160 or higher and your diastolic blood pressure has averaged below 90 over the last several times we took it. For example, your blood pressure reading may look something like this: 172/78. You have isolated systolic hypertension. Your systolic pressure is higher than the normal range but your diastolic pressure is within the normal range. It is still usually called hypertension (high blood pressure), but it is different than

the usual form which is high for both the systolic and diastolic pressures.

We are not sure what causes most types of high blood pressure. Isolated systolic hypertension is thought to be mainly the end result of "hardening" of the large arteries which carry the blood from your heart to various parts of your body. These arteries can become thickened and somewhat stiff. When this condition exists in the arteries, your heart must work harder to pump blood throughout your system, and your systolic blood pressure rises to higher than normal levels.

What Effect Does Isolated Systolic Hypertension Have On Your Health?

Several research studies have confirmed that usual high blood pressure may be a cause of heart attacks, strokes, and kidney disease.

For many years it was thought that the complications of hypertension were primarily caused by the elevation of the diastolic blood pressure alone. However, there is now good reason to think that an elevated systolic pressure may be a cause of certain types of health problems. It is also possible that an elevated systolic blood pressure may contribute to mental or emotional changes in the elderly.

Studies of diastolic hypertension have shown that serious health problems can often be prevented if the high blood pressure is reduced with drug treatment, or with certain lifestyle changes such as diet and exercise.

Does all of this mean that treatment of isolated systolic hypertension is also helpful? The answer is--we don't know.

Why the SHEP Is Being Done

As a result of advances in medical care and individuals' efforts to improve their own health, more people are living to an older age. This means that more of us live long enough to get isolated systolic hypertension. Although major strides have been made in the treatment of hypertension, a number of questions remain about treatment of the older adult who has isolated sytolic hypertension. The purpose of the SHEP, therefore, is to investigate the effects of treating this condition which occurs principally in persons who are at least 60 years of age.

Revised July 1985

Where is the Study Being Done, Who Sponsors It, and Who Is Involved?

The SHEP is being conducted in seventeen locations:

New York, New York	Honolulu, Hawaii
Atlanta, Georgia	Lexington, Kentucky
Portland, Oregon	Baltimore, Maryland
Miami Beach, Florida	Minneapolis, Minnesota
Chicago, Illinois	Pittsburgh, Pennsylvania
San Francisco, California	Memphis, Tennessee
New Brunswick, New Jersey	St. Louis, Missouri
Birmingham, Alabama	New Haven, Connecticut
Davis, California	

Revised July 1985

Each SHEP clinic is directed by a medical scientist with extensive experience in health care and heart disease research. The clinics are staffed by qualified people who have been especially trained and certified to assist you during the course of the study. Each clinic will have about 300 SHEP participants like yourself.

The Coordinating Center of the SHEP is located in Houston, Texas and helps to plan, organize and guide the progress of the study, to gather the information necessary to evaluate the results, and to serve as a communication link among all of the clinics and laboratories. It also has a highly competent professional and support staff which provides support to the seventeen clinics in various ways.

The SHEP is sponsored by two of the National Institutes of Health: The National Heart, Lung, and Blood Institute and the National Institute on Aging. These institutes provide financial and staff support, and have placed a very high priority on this particular clinical research study.

As you can see, you are part of a large National Research Study and your continued participation in the SHEP will help to answer some important unanswered questions about the treatment of isolated systolic hypertension in older adults. It is no exaggeration to say that your contributions are likely to benefit millions of people, now and in the future, who have this common condition.

THE SHEP PLAN

The SHEP Study Design and Treatment Plan

All good research studies have a specific design and plan called a protocol that is followed by all clinic staff for every participant. The research protocol insures that believable results will be obtained from each of your visits to the clinic and that you will receive safe care and treatment. For example: Your blood pressure will be measured four times at every treatment visit; twice while you are seated and twice while you are standing. These procedures and all others that take place at your clinic visits have a reason and provide us with information about the effects of treating isolated systolic hypertension. The following is a summary of some points about the SHEP study design and treatment plan that we think are important for you to know.

Revised July 1985

Screening and Eligibility

You have already been through several visits where your blood pressure was taken several times, an electrocardiogram was obtained, a blood sample may have been taken, and many questions were asked about your health and personal history. These visits were scheduled to see if you were qualified to participate in the SHEP. This is called the screening or eligibility phase.

Treatment Assignment

Now that you have been found to be eligible, you have been assigned to a certain medication treatment plan. The medicines selected for the SHEP are well known for their current use in the treatment of high blood pressure and were chosen for their safety, effectiveness and tolerance in most adults. None of the medications are experimental. The names chosen for the SHEP medications are very simple: C1, C2, A1, A2, and R. These are given to you at no cost.

Your medication will either be an active pill or a placebo (an inactive pill that is often called a "sugar" pill). There is one chance in two that you will be assigned to a placebo. You will not know if you are taking an active medicine or placebo nor will the clinic staff know. Only the Coordinating Center knows to what treatment you have been assigned. However, the staff in both places are responsible for carefully monitoring your safety. This type of research design is known as a double-blind, placebo-controlled trial.

If you experience a medical emergency that requires your personal physician or a hospital to know what drug you are taking, the information is available 24 hours a day from designated local persons outside the SHEP clinic. This may be a university pharmacist or another physician in your city. These people may break a medication code, but only when it is clinically necessary.

The double-blind, placebo-controlled study is being done because it is the very best way to get accurate and believable results from a research study. When neither you or your clinician knows what drug you are taking, there is less chance for bias that might interfere with the treatment plan or the collection of the information. Placebo control allows us to compare the results of those who are receiving active medications with those who are not to see if treatment makes a difference. And this is the whole point of the study. If you have any questions about this approach, be sure to ask the staff.

Clinic Visits

Once you have been assigned to a treatment plan, a goal is set for reducing your systolic pressure. You will then be asked to come in for regular check-ups.

How often

You will be seen at least every three months, depending on your progress. Of course, if you have any unusual problems between visits, you can call the clinic for an additional appointment. You will be given an identification card that tells how to reach clinic staff during most hours of the day or night. Please carry this card with you at all times.

Appointments

We will make every effort to schedule your appointments at times that are convenient for you and, if necessary, to assist with transportation problems.

You will be reminded of your appointment ahead of time, by telephone or postcard, and if you miss an appointment you will be called to reschedule it.

An appointment card will be given to you which contains your next appointment date and time. We ask you to call us in advance if you are unable to keep the appointment.

Medicine

A supply of medicine will be given to you at your clinic visits that should last until your next appointment. You will receive clear instructions about taking the SHEP medicines. Please follow the directions faithfully. Your SHEP clinic staff are just a phone call away if you have any questions or concerns about taking the medicine.

You will be asked to bring the SHEP medicine bottle with you to each visit, even if it is empty. This is very important; we must have your used bottle before we can issue you a new supply of medicine. In a research study like this, all medications must be accounted for.

Tests and Procedures

Your blood pressure will be taken at every visit. This is to see how your blood pressure is responding to the medication treatment. You will be given a copy of your blood pressure reading if you wish.

In addition to taking your blood pressure, blood samples will be taken at some visits to make sure that all of your blood values remain within a normal range. Urine tests and electrocardiograms will also be done on occasion, and at the end of each year you will receive another complete physical examination.

All SHEP participants will be asked a series of questions about their mental and emotional health at some time during the study. Along with your medication treatment, this is an important part of the study because it is uncertain whether isolated systolic hypertension or its treatment cause changes in the mental and emotional health of older adults. We are interested in this part of your well-being as well as your physical health.

All of these tests and procedures are carried out so that we can monitor your health and safety throughout the study. It is unlikely that you will develop any problems that are a result of the SHEP treatment plan.

Revised July 1985

Expectations--Yours and ours

The above information should help you to understand what is planned for you in the next few years. We encourage you to share this information with your family or friends, and to ask more specific questions whenever you feel the need. By taking part in a cooperative research effort you are making a valuable contribution to medical knowledge.

We plan no surprises for you, and now that you have qualified and agreed to participate in the SHEP, we want you to understand clearly what we expect from you and what you can expect from us.

Here is what we expect from you -

1. Be informed. Read this booklet carefully and make good use of orientation sessions which will be conducted for you by the SHEP clinic staff. Ask questions, and be open and frank in discussing problems.
2. Be committed. As a responsible participant, participate fully in the SHEP study. That means coming to all scheduled visits or calling if you must reschedule for any reasons. It also means taking your medications exactly as you were instructed.

3. Keep us informed. We need to know if you develop other health problems, take other new medicines, go into the hospital for any reason, or change your address or telephone number.

Here is what you can expect from us -

1. Cooperative, friendly and qualified clinic staff to assist you during the study.
2. Continuous review of your medical condition during the study.
3. Certain medicines, tests and physical check-ups, provided at no cost.
4. A personal discussion and information session about the SHEP study before you begin.
5. An identification card to carry with you at all times with telephone numbers of your SHEP clinic staff.
6. Communication with your private health care provider when appropriate.
7. Results of the SHEP study when they become available.

YOUR HEALTH -- YOUR CHOICE

Many of the activities of your daily life can have a profound influence on your personal health and well-being. Since you have agreed to participate in the SHEP study, it is clear that you are interested in maintaining and improving your health. This section discusses the changes you can make in your daily life that will help you to feel better and live longer. These changes are divided into two sections: 1) those which influence blood pressure, and 2) those which do not affect blood pressure, but which do improve health.

Activities and behaviors which can assist in lowering blood pressure

Reduce the salt in your diet

The average American consumes about one to two teaspoonsful of salt daily. This is far more than we need. Large amounts of ordinary table salt may cause your body to retain extra water. This extra fluid in the blood can lead to an increase in blood pressure.

Salt is composed of two basic elements bound together: sodium and chloride. A certain amount of sodium is necessary to good health, but too much can lead to a rise in blood pressure. Other substances which contain sodium have a similar effect. Common substances which contain sodium, and should be used sparingly, include:

Table salt (sodium chloride)

Monosodium glutamate (MSG or Accent)

Baking soda (sodium bicarbonate, Alka-Seltzer)

Baking powder

Most people think that the majority of their salt comes from the shaker on the table. While this is the most obvious source, a great deal of sodium sneaks into our bodies without our general awareness. If you are trying to cut down on salt, first remove your salt shaker from the table, and second, stay away from the common food sources that have a very high salt content.

Revised July 1985

The followng "Rules of Thumb" for remembering the amount of sodium and salt in foods have been contributed by the SHEP clinic in Portland, Oregon.

1. Most raw or fresh foods are low in sodium.
2. Salting foods at the table and during cooking can add large amounts of sodium to the food.
3. Many "processed" or commercially prepared foods--canned, frozen, or packaged--are high in salt and sodium (soups, macaroni and cheese, chili, vegetables, ravioli, luncheon meats, sausages, hot dogs, TV dinners, frozen prepared entrees). Some of them have their sodium content per serving listed on their box or label.
4. Many "snack" foods are high in salt and sodium (salted peanuts, pretzels, potato chips, corn chips).

5. Many items that we add to foods for extra flavor are high in salt and sodium .... these include: sauces, gravies, seasoned salts (garlic, onion, celery salt) and condiments (catsup, mustard, horseradish, steak sauce, worchestershire sauce, teriyaki and soy sauce).
6. A few other foods such as pickles and other pickled or salt-cured products are very high in salt and sodium (olives, sauerkraut, ham, bacon).
7. Most cheeses contain large amounts of salt and sodium.

You should alse be aware that some of the medicines you buy in a drugstore or supermarket contain large amounts of sodium. For example: antacids such as Alka-Seltzer, Sal Hepatica and Bromo-Seltzer and laxatives such as Metamucil and Fleets Enema. These medicines should only be used when absolutely necessary and rarely every day. See your health provider about other natural ways to solve indigestion or constipation problems.

Getting along with less salt

Most people feel that foods taste bland and tasteless when they cut back on salt. There are at least three solutions to this difficulty:

1) Choose fresh vegetables and soups rather canned - their flavor is better and the salt content far lower.
2) Use more spices and herbs to add flavor.
3) Bear with it awhile. Research shows that high salt eaters who are placed on very low salt diets for about two weeks, then given all the salt they desire, choose to use less than half the salt they were using before going on the low salt diet. In other words, by staying with a low salt diet for a time, your desire for salt will gradually change, and you will actually want less salt.

Get more potassium in your diet

Potassium is an essential mineral ingredient of our diets. Medications that lower blood pressure sometimes produce a lowered level of body potassium. While you are in this study, it is especially important for you to eat foods which replace the potassium that may be lost. Bananas, oranges, tomatoes, milk and cauliflower, for example, are a few of the many foods which contain high levels of potassium. Your blood level of potassium will be checked on occasion to be certain that it is high enough. If it is too low, a potassium supplement may be prescribed by a SHEP physician to raise it.

Lose weight if you are too heavy

Each extra pound of weight adds miles of small blood vessels to your vascular system. The larger the system becomes, the harder the heart must pump and the higher the pressure must be to get blood through all those vessels.

Revised July 1985

The amount of food we eat and the weight that the food produces are a product of our entire lifestyle. As a consequence, simple diets seldom lead to long-term weight reduction. Long-term weight loss requires the changing of habits acquired over a lifetime. For this reason, if you are seriously interested in losing weight, try one or more of the following approaches:

1) Join a weight loss organization such as Weight Watchers, Overeaters Anonymous or Tops.
2) Enlist your entire family and your friends in the effort to lose weight. Ask them to help you in your efforts by preparing low calorie, tasty foods and by not offering snacks and seconds.
3) Lose weight slowly and sensibly. A pound a week is a good rate of weight loss. Don't be discouraged by plateaus or a slight increase.
4) Keep a chart of your progress publicly posted so family and friends can follow your progress. This increases your sense of commitment.
5) Exercise regularly.

Exercise

Regular exercise is a unique health activity. It benefits both physical and psychological well-being. It assists in weight loss, improves mental outlook, increases energy level and improves sleeping. Like losing weight, becoming involved in a regular exercise program can be difficult because it involves a serious commitment and changing long-term habits. After people start exercising, they often have trouble understanding why they didn't do it years ago. But getting going is not always easy. To begin exercising, follow these simple suggestions:

1) Never exercise to the point of exhaustion.
2) Check with your doctor before beginning your program to determine how much exercise you can safely do.
3) Build up gradually. People in their seventies and eighties have run marathons, but it takes a long time to build up that kind of endurance.

Revised July 1985

4) Pick an exercise that you enjoy, and preferably one that is non-competitive. Competition tends to make people exercise too hard, which can be dangerous, and less beneficial to health. Activities often recommended include a brisk daily walk, swimming, bicycling, hiking or jogging.

5) Exercise at least three days a week on a regular basis. Less frequent exercise is more likely to produce aches and pains than to improve your health.

6) Involve your friends and family. Do it together and help each other to work through the times when you may be less inclined to get out there and do it. Many Senior Centers have exercise classes.

7) Increase the amount of physical activity involved in your usual daily habits--for example, walk rather than drive to a nearby neighbor or store.

Other Activities Which Promote Good Health

Quit smoking

Many people think that quitting may be the most difficult task of a lifetime. In fact, statistics show that it's easier than some other healthy changes in lifestyle; people are more successful at quitting, for example, then at dealing with the problem of overweight. And, there is little a smoker can do that can more significantly improve health than quitting smoking. Smoking reduces your ability to exercise, damages the lungs and heart and, of course, causes cancer. Quitting can be aided by making other changes in lifestyle: Follow the hints suggested above for diet and exercise. Also, try one or more of the many smoking cessation programs offered by groups such as the American Cancer Society, the Lung Association and other organizations.

Relaxation

Relaxation exercises have been shown to produce significant improvements in mental and physical well-being. Such exercises may contribute to lowered blood pressure, to increased energy, to improve sleep, to greater endurance, and to fewer physical symptoms or illness. There are many effective techniques ranging from formally taught meditation programs (yoga, TM, shavasan, etc.) to simple, self-taught programs such as that described by Dr. Herbert Benson in his book The Relaxation Response. Literally hundreds of different approaches to relaxation are available in classes or books. Like exercise, to be effective, they must be performed regularly and properly.

Reduce the fat in your diet

Foods that are high in fat contribute to weight problems. Reducing fat in your diet may or may not make you feel physically better (some claim it gives them much more energy), but it can make it much easier for you to lose weight and it may reduce the risk of future cardiovascular problems. Fatty meats, pastries, butter, high-fat dairy products such as most cheeses and cream are the principal sources of fat in the American diet.

Eat more fiber

Some people claim that fiber in the diet reduces the risk of bowel cancer. Whether or not that is true, it is certainly clear that two or three tablespoons of bran a day mixed into your normal food can prevent the common problem of chronic constipation. Laxatives can be harmful over the long run, and in the majority of cases are simply unnecessary. They also cost a great deal more than bran.

Contrary to popular belief, vegetables are not a good source of fiber. Whole grains such as rice, oatmeal and whole wheat flour are the best source of fiber. If your diet does not include many whole grains, a few tablespoons of bran in a casserole can remedy the situation nicely.

Drink more water

Water is one of the more important body nutrients. Water helps to regulate and maintain the complicated internal environment of your body. The amount of water in the body is lower in older people. Also, some medications that lower blood pressure cause you to lose body water.

Therefore we encourage you to drink 4-6 glasses of water daily. Drinking lots of water can also help to relieve constipation and urinary problems - two very common complaints of older adults.

These activities are not all easy. But if you take one at a time (don't expect to do it all at once), you will slowly find yourself feeling better and better both physically and mentally. Doctors and medicines don't cure problems as efficiently or effectively as your own efforts and choices. Making even little changes in your lifestyle can prevent problems before they begin.

APPENDIX C

SHEP ECG PROCEDURES

C.1 Introduction

Resting electrocardiograms (ECGs) and two-minute rhythm strips are being collected in the SHEP at the following times:

- Baseline and 2-minute rhythm strip ECGs for each subject at the Baseline Visit 1--to determine ECG status of each subject before treatment is initiated and to exclude ECG-ineligible subjects.
- Year 2 and Final Annual ECG and 2-minute rhythm strip ECGs on every randomized participant--to determine ECG status in regard to myocardial ischemia, left ventricular hypertrophy, and arrhythmias for each subject.

ECGs for randomized participants will be read and coded according to the Minnesota Code at the SHEP ECG reading center in Minneapolis. Each ECG will be read independently by three technician readers and unresolved disagreements will be adjudicated by the ECG supervisor and/or an electrocardiographer at the reading center. All readings will be made without knowledge of the treatment group, clinical or laboratory findings for the subject. The final adjudicated readings will be returned to the Coordinating Center. At periodic intervals, a subsample of ECGs will be resubmitted to the ECG center for blind reading in order to monitor the ECG center performance.

C.2 Electrocardiogram Procedures

C.2.1 Recording the 12-lead electrocardiogram and 2-minute rhythm strip

The ECG machine that is used to take these electrocardiograms should meet the AHA recommendations (cf. Report to Committee on Optimal Electrocardiography, as reported in the March '78 issue of the American Journal of Cardiology).

A stop watch may be used to assure that a full minute of tracing is obtained for the 12-lead ECG (or by time adjustment for automatic machines). A series of 1 mv calibration pulses should be recorded at the beginning of the ECG recording followed by 5-second tracings of leads I, II, III, aVR, aVL, aVF and V1-V6. Tracings must be recorded at a paper speed of 25 mm per second. Leads which must be recorded at 1/2 standard should be preceded by a half standard cal pulse, and the words "1/2 STD." must be written on the top of the lead (do not write across any part of the beats).

A stop watch may also be used in recording the two-minute rhythm strip. The rhythm strip is recorded from lead II, and is recorded after the 12-lead ECG. A series of 1 mv calibration pulses should be recorded at the beginning of the strip. The strip is recorded at a paper speed of 25 mm per second. There must be 120 inches (2 minutes) acceptable quality recording of lead II rhythm strip. If a single channel ECG machine is used, fold the ECG 2-minute strip according to the example in Figure C-1.

Centers using 3-channel ECG machines with manual override should use the override for the 2-minute strip. The machine setting is placed on leads I, II, III so that 120 inches of all 3 leads is produced. Fold

the leads according to the example in Figure C-2. If the tracings are produced on 8½ x 11 paper, the tracing does not need to be folded. Tracings produced on wider paper should be folded at 6-inch intervals.

Centers using 3-channel machines without manual override must produce 120 inches of lead II also. Allow the machine to switch through the series of leads until 2-minutes of lead II is produced.

The standard 12-lead ECG and the two-minute rhythm strip should then be cut apart. Both should be labeled with the participant's ID and acrostic, close to the calibration pulses. Do not include any other information in the tracings. Fold the series according to the example in Figures C-1 or C-2.

Both the 12-lead and 2-minute strip are labeled and sent to the SHEP Coordinating Center.

C.2.2 Electrode Position Measuring and Marking

Because an essential for the trial is comparability of baseline ECG data with subsequent records, a uniform procedure for electrode placement and skin preparation is required. The method and procedure for standardizing electrode locations are outlined below:

The participant, stripped to the waist, is instructed to lie on the recording bed with shoulders straight and arms relaxed at the sides. The individual is asked to avoid movements which may cause errors in marking the electrode locations, but encouraged to converse with the technician and attending physician. Prior experience with electrocardiograms is discussed, as is the purpose of the ECG recording. The participant should be told this is a research ECG to be

used for statistical analysis later in the trial. However, it can also be used by the clinic physician for general diagnostic purposes, and a copy can be sent to the individual's private physician.

A good felt tip pen is used to mark the twelve electrode positions. It is extremely important that care be taken to accurately locate and mark the chest electrode positions. Therefore, the procedure given below must be meticulously followed.

(1) Electrode V2

- Locate the sternal angle and second left rib between the index and middle fingers of your right hand.
- Count down to the fourth rib and identify the fourth intercostal space below it.
- Locate V2 in the fourth intercostal space at the left of the sternal border.

(2) Electrode V1

- Locate electrode V1 in the fourth intercostal space at the right sternal border. This should be at the same level as V2 and immediately to the right of the sternum.

(3) Anterior 5th Interspace Marker (E Point)

- Identify the fifth rib and fifth intercostal space below V2 in the manner previously described. Follow this space to the midsternal line and mark this point. This is the "E" point.

(4) Electrode V6

- Locate the V6 electrode at the same level of the E point in the mid-axillary line. This is the location of the V6 electrode. This identifies the horizontal level of V4-V6 electrodes.
- Using a metric tape, measure the horizontal distance in cm from the E point to V6. The mid-point distance is the V4 electrode location.
- Now using a flexible ruler measure the distance between V4 and V6. The V5 electrode is placed midway between V4 and V6.
- In a similar manner measure the distance between V2 and V4. The mid-point is the location of the V3 electrode.

(5) Limb Leads

- Locate electrode LL on the left leg.
- Locate electrode RL on the right leg.
- Locate electrode LA on the left wrist (inside).
- Locate electrode RA on the right wrist (inside).

C.2.3 Skin Preparation

The following procedure for preparation of the skin before applying electrodes must be followed:

(1) With the participant's consent, remove any excess hair from each electrode site on the chest using an electric shaver or safety razor.

(2) At each electrode location, in turn, the outer horny layer of the epidermis is removed by gentle dermal abrasion with a piece of 6-0 (220) sandpaper or abrasive pad available especially for this purpose. Only three passes (in the form of an asterisk) at each site using light pressure are required.

If the skin preparation has removed the felt pen marking at any of the electrode sites, these should be accurately re-established by carefully repeating the procedure described in Section C.2.2. It is important that the electrode sites be marked accurately using the exact technique described previously.

C.2.4 Application of Electrodes

A small amount of electrode jelly is placed on the skin at each prepared site. It is most important that the electrode jelly not be smeared over a wider area than necessary in order to avoid low impedance pathways between electrodes and production of marked distortion of the ECG wave forms. (Pre-gelled disposable pads may be used.)

The ECG Reading Center advises that for large-breasted women, no difference in ECG quality can be detected regardless of whether the leads are placed over or under the breast. Therefore, the technician should use whichever method is simplest for him or her, while still following the correct spacing of electrodes described in Section C.2.2. There is no need to support the breast in any way.

The limb lead plate electrodes are placed in the appropriate locations. The patient cable is now attached to the appropriate electrodes with the subject in the supine position, hands at the sides, with care not to entangle or pull any of the leads. Calibration pulses

followed by the six limb leads are recorded first, followed by the six precordial leads as previously described and then the full two minutes using lead II. If the clinic wants a second "original" ECG, it should be recorded at this time.

C.2.5 Fault Detection Procedures

Should problems with noise or drift be encountered, electrodes should be replaced. The following is a guide for determining which electrodes may be faulty. The underlined electrodes are the predominant determinants of the appropriate lead and therefore are most likely to be the faulty electrodes for a given lead. After adjustment and/or replacement of suspect electrodes, all leads should be again recorded.

Lead Affected	Possible Faulty Electrode
I	RL, RA, LA
II	RL, RA, LL
III	RL, LA, LL
aVR	RL, RA, LL, LA
aVL	RL, LL, RA, LA
aVF	RL, LL, RA, LA
V1	RL, LL, RA, LA, V1
V2	RL, LL, RA, LA, V2
V3	RL, LL, RA, LA, V3
V4	RL, LL, RA, LA, V4
V5	RL, LL, RA, LA, V5
V6	RL, LL, RA, LA, V6

C.2.6 Self-Evaluation of Technical Performance

A reasonable estimate of the noise level and amount of baseline drift can be obtained by examining the ECG recording and an indication of technical performance level thereby obtained. Based on the requirements of the Minnesota Code, acceptable levels of noise and baseline drift have been established as indicated by grades 1-5 respectively of the self-evaluation of technical quality performance grade (Table C-1). The grade levels given in this table take into account measurement accuracy requirements and the ability of the readers to achieve the required accuracy in the presence of noise and drift as well as the significant improvement in technical quality expected from the conditions, equipment and the procedures specified for this study. Such an improvement will indeed result if the prescribed procedures for electrode position marking, electrode and skin preparation, electrode replacement and equipment use are carefully followed. Baseline drift problems, which are essentially caused by poor electrode-skin interface, should be particularly easy to remedy as should 60 cycle noise.

The ECG recordings should be examined for obvious errors such as wave form clipping, missing tracing or excessive noise and drift. The tracings should then be checked for right arm-left arm and other common lead misplacements. Once satisfied that the wave forms are basically correct and no obvious errors are present, the baselines (PR, ST, and TP segment) should be checked for the level of noise (Figure C-3). No 60 cycle noise should be present, and the baseline should be steady and free of transients. Converting the noise level to peak to peak values, and noting that recording sensitivity is 1 mv per

centimeter, the allowable noise level in terms of number of small paper deviations (1 small paper deviation = 1 mm) are obtained as indicated for each grade level in the self-evaluation Table C-1. These "eye ball" measurements serve as indications of the noise level performance grade. For instance, baseline fluctuations approaching 5 small paper deviations (5 mv peak to peak) are certainly indicative of unacceptable noise levels. The overall drift criteria may be checked and an indication of the overall drift grade level obtained by searching the record for the maximum and minimum baseline levels (as determined by the PR and TP segments) and measuring the vertical distance between them. This distance must be less than 10 small paper divisions (1 mv) to satisfy the minimum drift criteria.

An example of baseline measurement and beat to beat, overall drift and noise is indicated in Figure C-3.

(1) The baseline level of a waveform is determined by its P-R, S-T, and T-P segments.

(2) The overall drift (amplitude difference) in this example is 1.2 mV. Beat-to-beat drift is 0.6 mV. The noise level is 500 μV_{p-p}. The record is unacceptable in terms of noise, overall drift, and beat-to-beat drift.

The beat-to-beat drift level is determined by searching for the pair of successive QRS complexes having the largest amplitude differences vertical distance) between successive PR segments. Average values (numbers of small paper deviations) are given in Table C-1. Again, these figures are approximate and serve only to give a general indication of beat-to-beat drift grade level. Certainly, however, a difference of 4 small paper divisions (0.4 mv) or more indicates an unacceptable record.

C.2.7 Mounting and Labeling

The lead designations should be written clearly on the ECG record just above but not touching the recorded tracing. Care should be taken not to write over any peaks. In addition, each lead should be identified as follows: "Lead I," "Lead II," "Lead III," etc., in order to minimize the possibility of mounting errors. the original unmounted ECG record and two-minute rhythm strip (cut apart) should be prepared for shipment as per Section 9.1 of this manual. Labels have been provided by the Coordinating Center for use in putting the SHEP ID., acrostic and date of tracing on the ECG and two-minute strip. These self-stick labels should be affixed to the back of the beginning of the tracing for both the 12-lead ECG and two-minute strip. The participant's ID and acrostic and the date of the tracing should be entered in the spaces indicated; indicate the two-minute strip by writing "2 Min" in the corner of the label. If you wish to do so, the ECG technician code may be written on the label. Do not include any other information at any other place on the tracings. Double check that this participant is correctly identified.

C.3 Central ECG Reading

The SHEP ECG Reading Center mounts the original tracing and attaches a label to the front of the mounted record in the upper left hand corner. The mounted ECGs are independently graded according to a revised version of the Minnesota Code by three technicians. Disagreements are adjudicated at the Reading Center by a senior coder. The adjudicated readings are recorded on an ECG reporting form (SH10) and forwarded to the Coordinating Center with the original tracing. A

mounted Xerox copy of each electrocardiogram is stored at the ECG center.

C.4 ECG Certification

As indicated in the Quality Control Section of this Manual, the technicians responsible for recording ECGs must be officially certified as capable of recording high-quality ECGs by the ECG Center. Certification ECGs must be done on age-eligible participants in the manner described above. One ECG must be obtained, at least one minute in "length"--approximately five seconds per lead. Label each lead "I" through "V6" and fold as instructed in Figure C-1 or C-2. The two-minute strip should also be obtained. Three calibration pulses and the name and ID number of the technician should appear at the beginning of each ECG and two-minute strip. Send the ECGs and the certification form to the Coordinating Center. The tracing will be logged and forwarded to the ECG Laboratory for review. Notification of the technician's certification status will be made by the Coordinating Center after this review is complete.

C.5 ECG Coding Instructions for SHEP Physicians

The baseline electrocardiograms are to be read locally by SHEP physicians for exclusion criteria. In order to enhance comparability with the ECG Center reading, clinic physicians should become familiar with certain Minnesota Codes corresponding to Q wave abnormalities, ST depression, T wave inversion and tall R-waves.

C.5.1 Minnesota Code

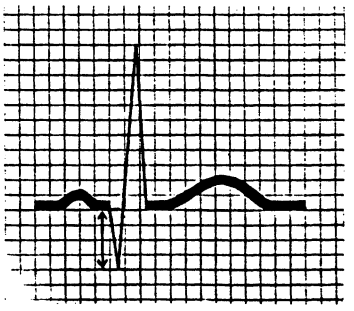
The Minnesota Code is a classification method for the electrocardiogram in epidemiologic studies. As such it provides a system for reporting ECG findings in a uniform, clearly defined manner and in objective terms with the least confusion in regard to interpretation. Emphasis is placed on reporting the actual ECG wave form deviations without recourse to interpretation. The Minnesota Code is adaptable to the usual ECG reading techniques of the electrocardiographer. Though the first impression of the code may be that of a maze of detail, it has been found on application by a number of electrocardiographers to be practicable. The electrocardiographer makes an inspection of the specific tracing at his/her accustomed speed. An estimate is then made for items of rate, rhythm, and axis, and deviations detected in interval, amplitude, and configuration of the ECG wave form. A search is made within the Minnesota classification system for the numerical code for the abnormality to be reported. The organization and numbers of the Minnesota Code soon become familiar. Classifications will be required for the SHEP, namely Q wave deviations indicative of old myocardial infarction and tall R waves together with ST depression or negative T wave indicating left ventricular hypertrophy (LVH). These codes correspond to one (1-1-1 through 1-3-6) Q codes, three codes (3.1 or 3.4) (R amplitude greater than 26 mm in either V5 or V6 or R amplitude greater than 20 mm in any of leads I, II, III, aVF, or R amplitude greater than 12 mm in lead aVL), four codes (4-1, 4-2) (ST depression--at least 0.5 mm of horizontal depression with horizontal or downsloping ST segment in any of leads I, II, aVL, aVF,

V1-V6), and five codes (51, 5-2) (T wave inversion--T amplitude negative at least 1 mm in any of leads I, II, V2-V6 or in a VL when R wave >5 mm). The codes are arranged in order of descending severity, i.e., the 1-1 Q codes are more severe than the 1-2 Q codes which are more severe than the 1-3 Q codes. Similarly, a 4-1 code is more severe than 4-2 code, etc. In order to simplify the use of the code, we have arranged the Q codes by anatomic location into anterior, inferior, and lateral sites. We suggest that the SHEP clinic physician interpret the electrocardiogram in his/her usual manner and, after determining the site of myocardial involvement, determine which Minnesota Code corresponds to the ECG analysis for Q codes or left ventricular hypertrophy. Presence of excluding arrhythmias, A-V block or pacemaker presence are determined by a clinic cardiologist using our definitions or reference to 6- and 8- codes. It is felt that local criteria for these abnormalities will not lead to non-standard exclusions.

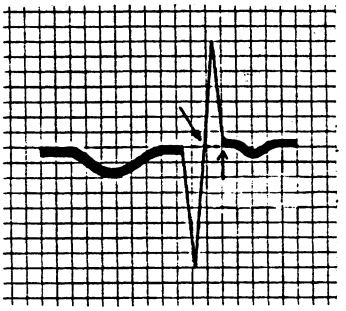
C.5.2 Abbreviated Measurement Rules for Minnesota Coding

In order to standardize clinical ECG exclusion criteria with Minnesota Code measurements, a set of measurement abbreviated rules are indicated which will aid the clinic physician in measuring the ECG wave forms of interest (Q, R, ST and T). These measurement rules should be familiarized by the physician in order that local ECG measurements correspond with measurements at the central ECG laboratory. Although the Minnesota measurement rules may be at variance with some physicians' usual way of measuring ECG wave forms, it is essential that they are followed in order to maintain consistency.

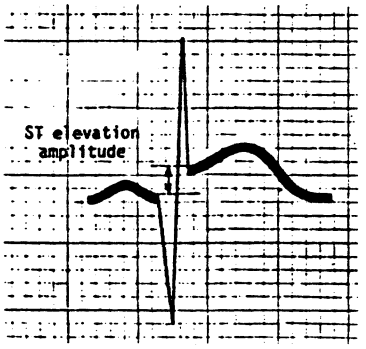
- Q wave depth is measured from the bottom of the isoelectric line to the bottom of the Q wave from the beginning of the QRS complex. Only initial negative QRS waves of ≥1 mv are considered as Q waves.

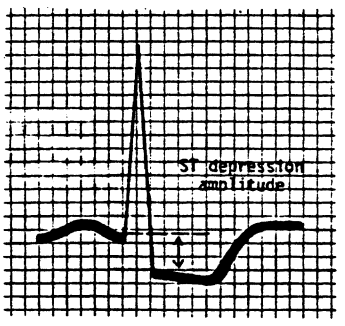


- The width of the Q waves are measured from the top of the baseline.

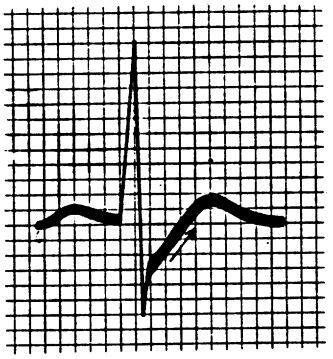


- The Q wave ST segment and T wave dimension in the majority (i.e., 2 out of 3 or 3 out of five, etc.) of beats in any one lead are taken to characterize the Q wave abnormality.
- The presence of a sharp positive deflection ≥0.25 mv at the beginning of any QRS complex in any lead is taken to be an R wave and no Q waves are then considered to be present in that lead.
- ST segment elevation or depression amplitude is measured from the top of the isoelectric line at the beginning of the QRS complex.

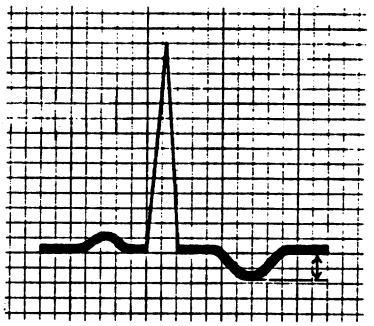




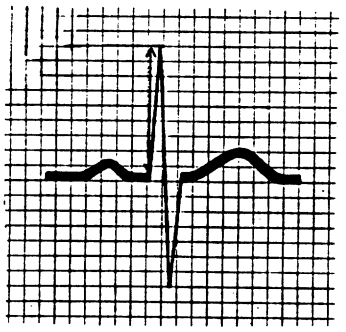
- ST segment depression is not recorded if the ST segment is upward sloping.

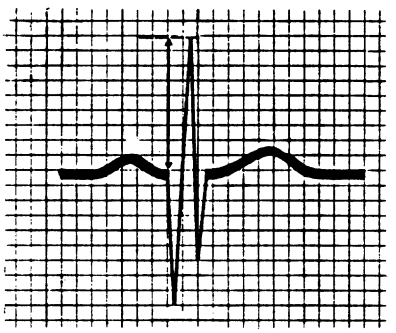


- T wave inversion amplitude is measured from the bottom of the T-P baseline to the bottom of the T wave.



- R wave amplitude for 3-codes is measured from the top of the isoelectric line at the onset of the QRS vertically to the peak of the R-wave.





- The R-wave amplitude is measured on the second to last complete beat in the appropriate lead.

TABLE C-1

Self-Evaluation of Technical Quality Performance Grade

QUALITY GRADE LEVAL	NOISE mms	DRIFT OVERALL mms	DRIFT BEAT-TO-BEAT mms
1	≤1	≤7	≤1 3/4
2	<2¼	≤8	≤2½
3	≤3½	≤9	≤3
4	≤4½	≤10	≤3½
5	>4½	>10	>3½

Examples of technical problems encountered in the ECG recording and remedial actions are illustrated in Figures C-4, C-5, C-6, C-7, and C-8.

FIGURE C-1

PROPER FOLDING OF ECG TRACINGS

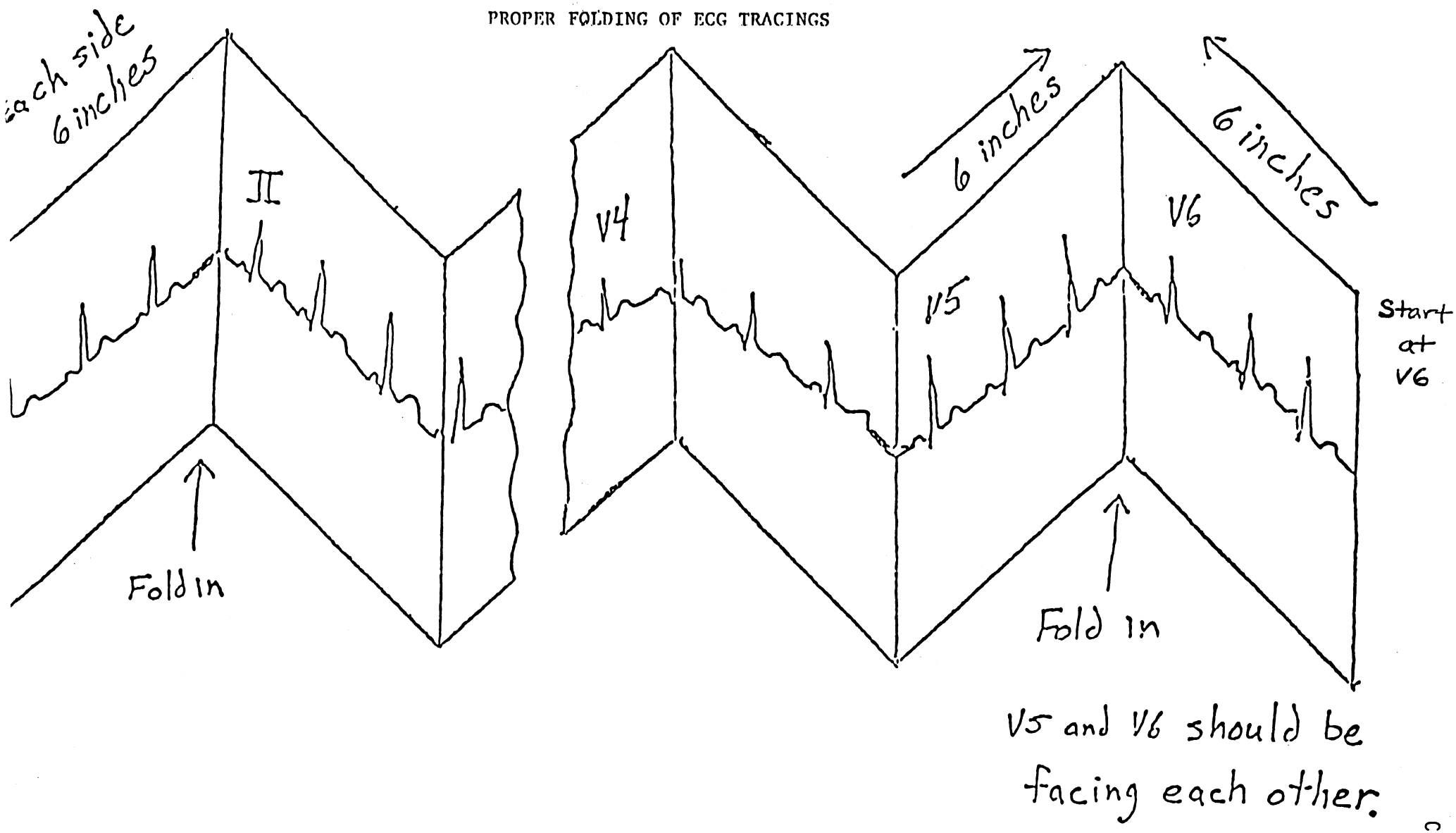


Figure C-2

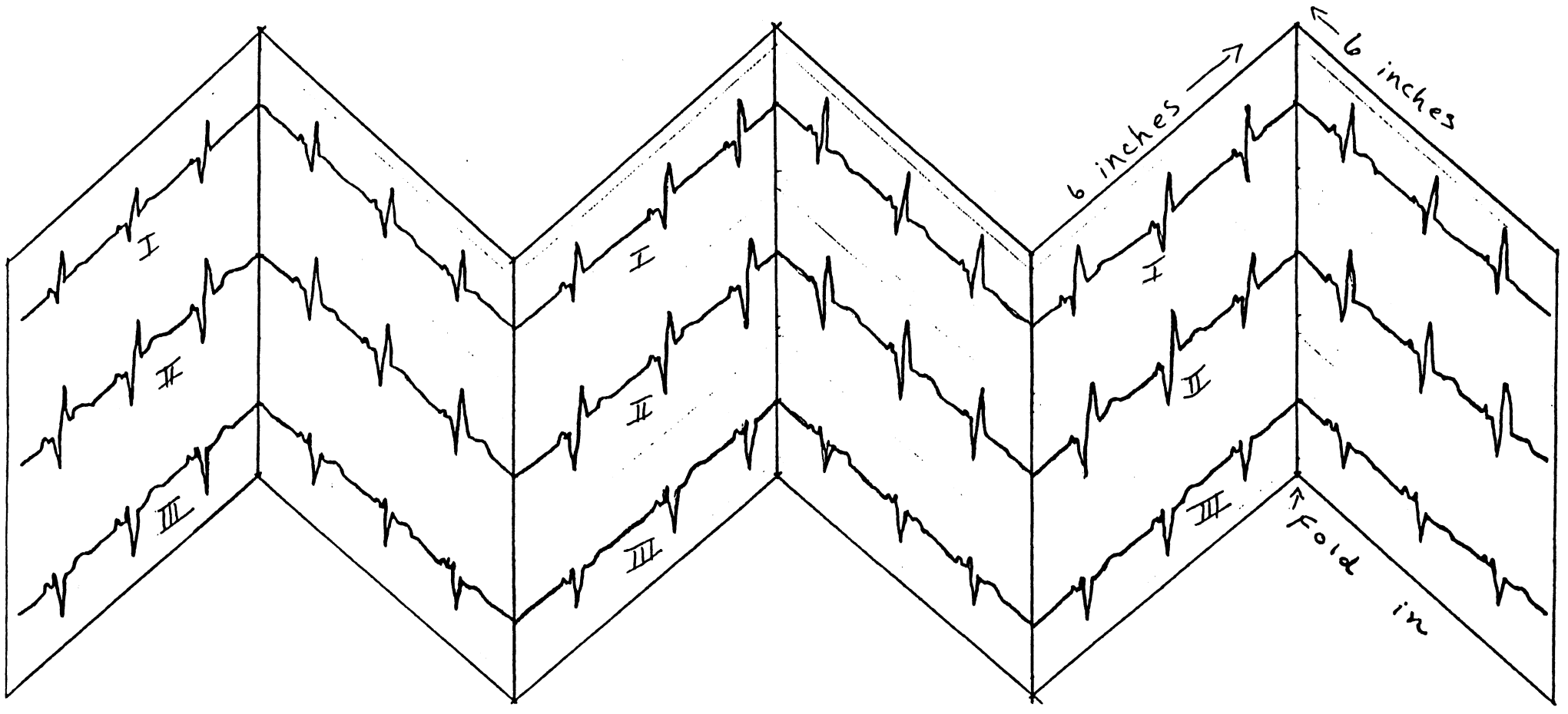
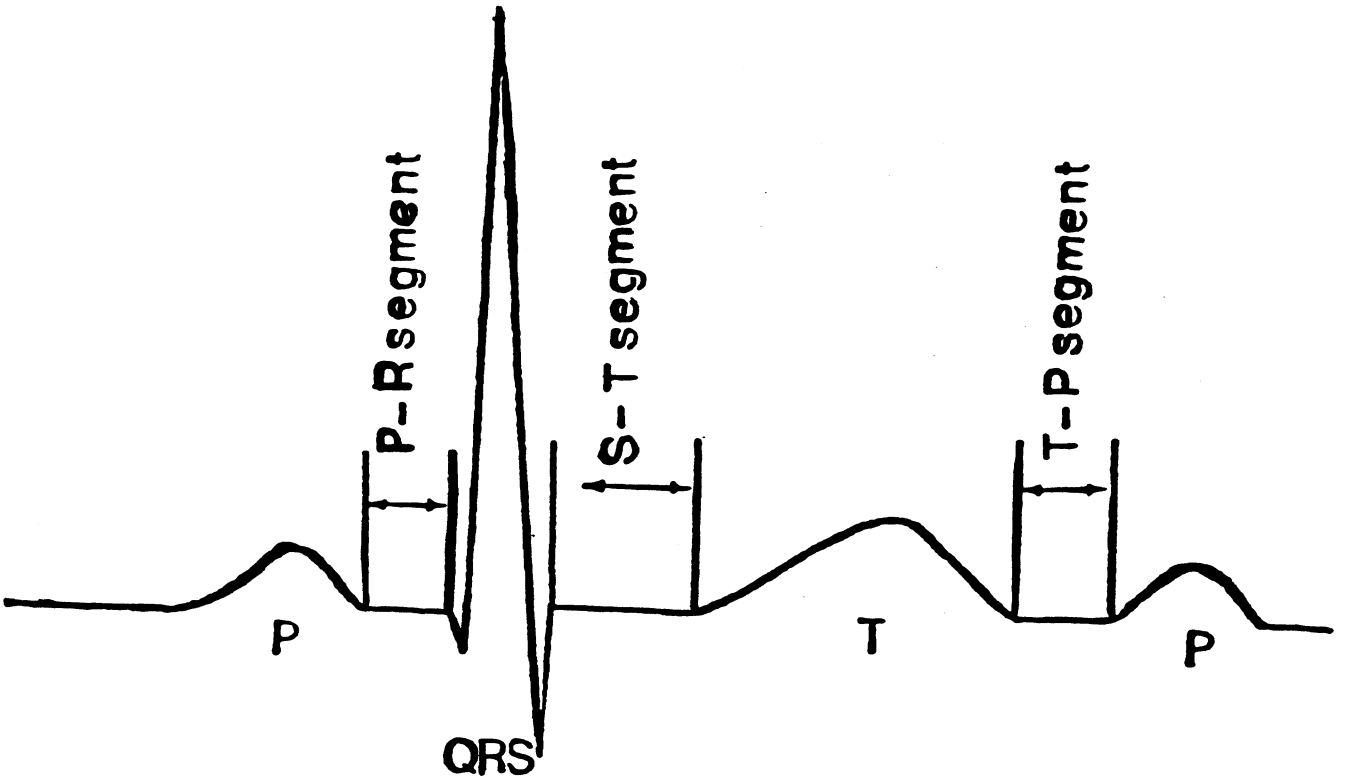


FIGURE C-3

Measurement of Noise and Drift



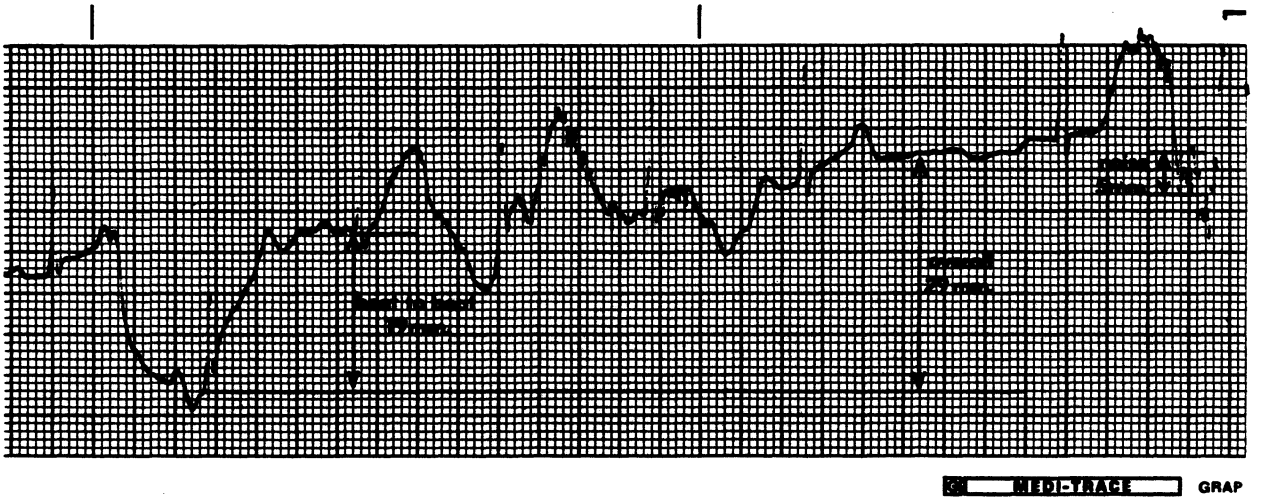
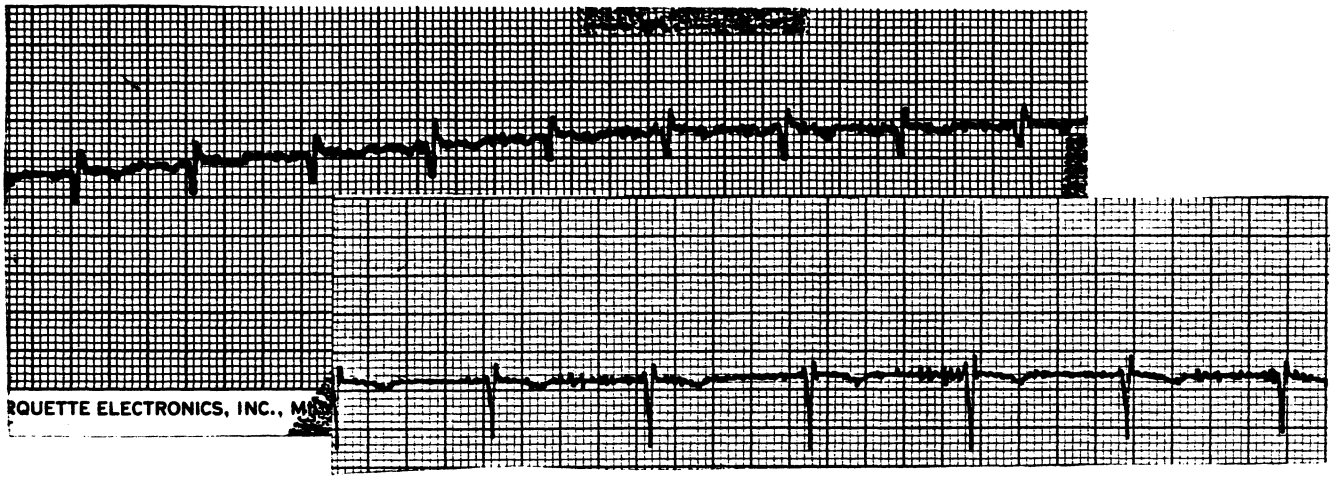


FIGURE C-4

MUSCLE TREMOR

Muscle tremor causes irregular oscillations (deflections) of low amplitude and varying rapidity; superimposed upon the ECG waveform



Remedial Actions:

Muscle tremor is the involuntary muscle activity of a participant whose state is tense, apprehensive, or uncomfortable. This is why a clear explanation of the electrocardiogram test and reassurance is necessary for the participant. The participant is asked if the temperature of the room is too low for him and is covered with a blanket if so.

FIGURE C-5

WANDERING BASELINE

Careless skin preparation or electrode application produces baseline drift, wandering baseline, or irregular or bizarre deflections (Figures C-5, C-6, C-7).

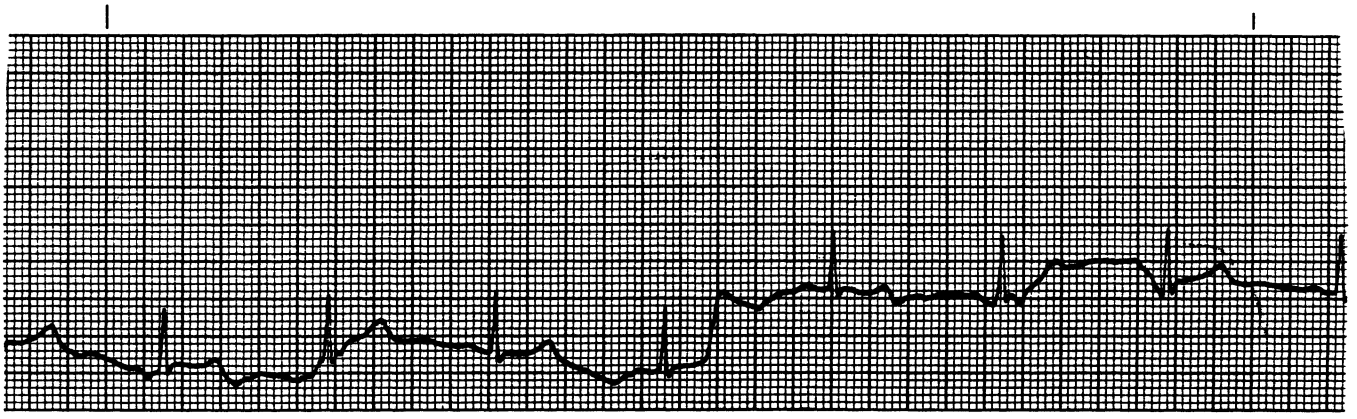


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FIGURE C-6

BASELINE DRIFT

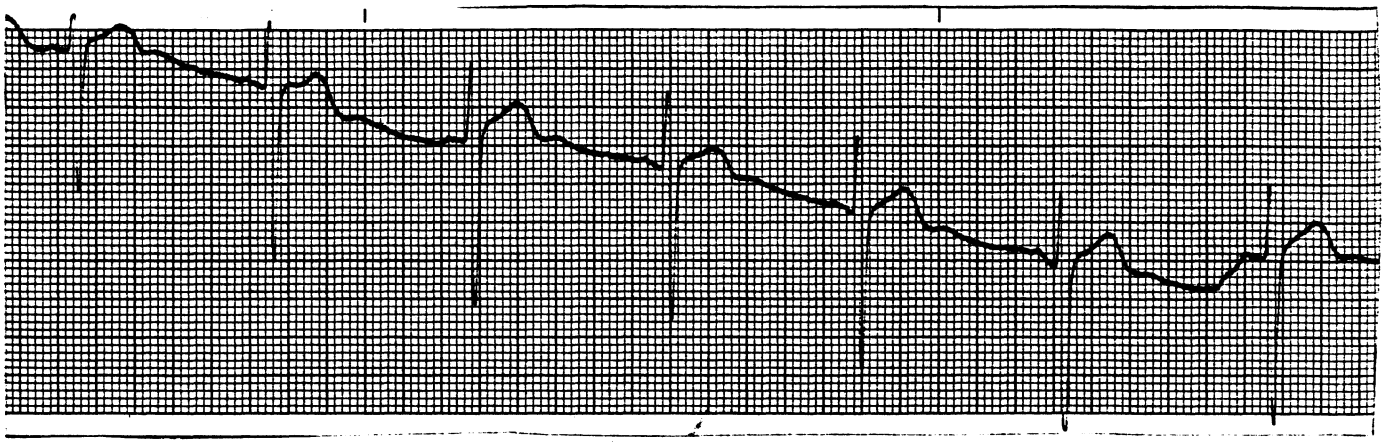
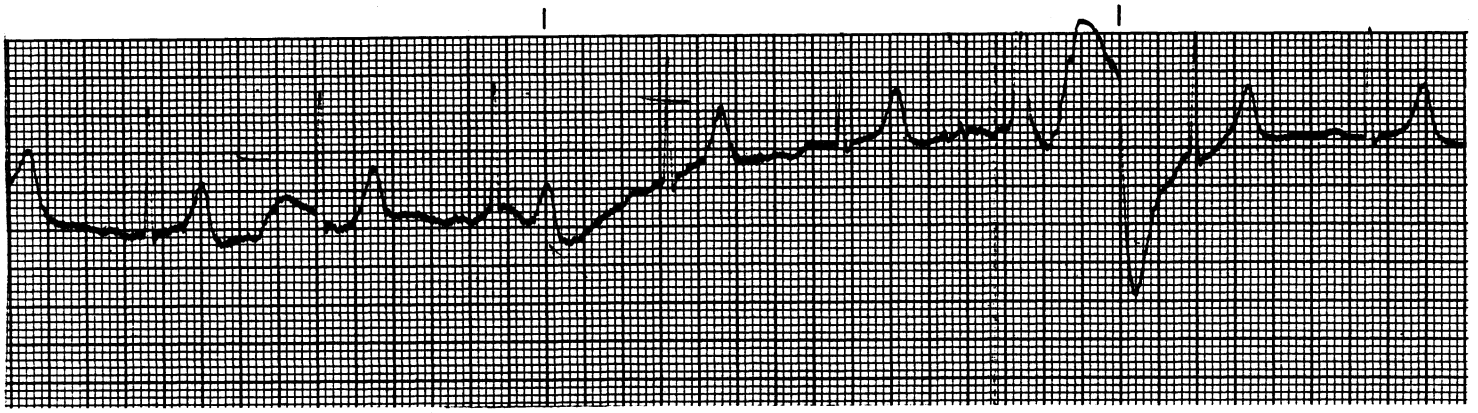


FIGURE C-7

IRREGULAR OR BIZARRE DEFLECTIONS



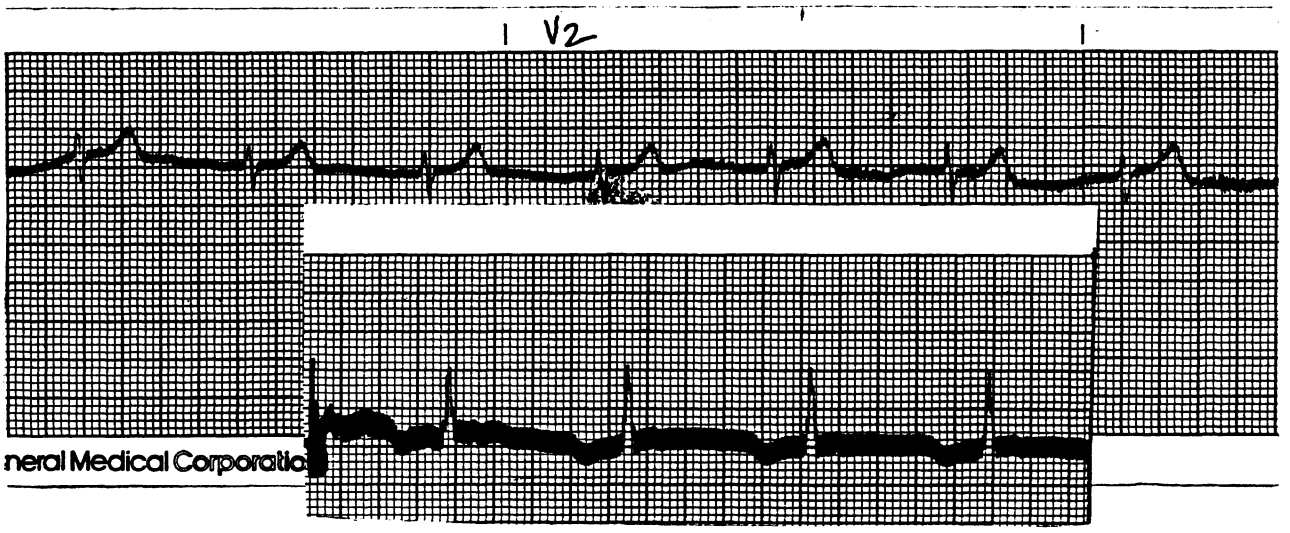
Remedial Action:

Faulty skin-electrode interface is the usual cause of the baseline wandering, drift or irregular and bizarre deflection on an ECG tracing. This may be avoided by carefully following the prescribed procedure for skin preparation and electrode placement. Similarly, tension on one or more lead wires gives the same effect because it causes interference with proper electrode contact. (However, baseline wandering or drift only in the precordial leads (V1-V6) might be due to the participant's respiratory movements). A faulty connection between an electrode and a lead wire can also be suspected.

FIGURE C-8

SIXTY-CYCLE INTERFERENCE

Sixty-cycle interference is characterized by perfectly regular fine oscillations occurring at the rate of sixty per second



Remedial Action:

Electrical equipment of any kind may be the source of AC interference on an electrocardiogram in all leads or only certain ones. AC interference appearing only in two standard limb leads (i.e., in two of leads I, II, and III) brings suspicion to the extremity which is common to them.

Lead I is the potential difference between LA and RA.

Lead II is the potential difference between LL and RA.

Lead III is the potential difference between LL and LA.

Therefore, if only leads II and III show AC interference, the left leg, being the common member, must be at fault. It must, therefore, be checked with regard to:

(1) quality of skin preparation and electrode contact;

(2) secure attachment of the LL cable tip to the electrode;

(3) possible contact to left leg with any metal part of bed or other equipment (or proximity to a wall with hidden wiring);

(4) a partially broken cable.

Systolic Hypertension in the Elderly Program

(Each Center to Xerox 1 copy for files)

ECG CERTIFICATION

(To be filled in by Clinic)

ECG Technician Name: _____ ☐☐ Code

Clinic: _____ ☐☐ Number

Date Certification Tracing Taken: _____

Date Tracing Sent to Coordinating Center: _____

Instructions:

Obtain one electrocardiogram (approximately five seconds per lead) and two-minute rhythm strip as specified in the SHEP MOO. Label each lead 1 through V6. Fold as instructed. Each ECG must also contain at the beginning (a) three calibration pulses and (b) name and code of the ECG technician.

Send ECG and this form to the SHEP Coordinating Center. Tracings will be forwarded to the ECG Center for approval of certification. Notification of the technician's certification status will be made by the Coordinating Center upon receipt of this completed form from the ECG Center.

(To be filled in by Coordinating Center)

Date Tracing and Form Received by Coordinating Center: _____

Date Tracings sent to ECG Center: _____

(To be filled in by ECG Center)

Date Tracings Received: _____

Comments:

Certified Yes _____ No _____ Date Certified: _____

_____
(Signature of Certifying Agent)

Date Sent to Coordinating Center: _____

Date Received by the Coordinating Center: _____

SHEP ECG CODING FORM

1. SHEP ID: ☐☐ - ☐☐☐☐ - ☐☐ 2. Acrostic: ☐☐☐☐☐☐

3. Date ECG recorded at Clinical Center: ☐☐ Month ☐☐ Day ☐☐ Year

4. Type of visit: 1 ☐ Baseline Visit 1
   2 ☐ Second Annual
   3 ☐ Final Annual

5. ECG Technician Code: ☐☐

6. Date sent to Coordinating Center: ☐☐ Month ☐☐ Day ☐☐ Year

7. Date Coordinating Center sends to ECG Reading Center: ☐☐ Month ☐☐ Day ☐☐ Year

8. Date of coding: ☐☐ Month ☐☐ Day ☐☐ Year

Twelve-lead ECG:

Q and QS Patterns (1X)			S - T Junction and Segment Depression (4X)			T Wave Items (5X)			ST Segment Elevation (9.2)			R	A-V Conduction Defect	Ventricular Conduction Defect	Arrhythmias (8X)						Ectopic Codes					
1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	1L V_6	23 F	V_1 V_5	3 X	(6X)	(7X)	1 X	2 X	3 X	4 X	5 X	6 X	SVPB	VPB	RN BG	M F	T-R	

Miscellaneous Items				Heart Rate (per minute)	+ or −	QRS Axis	Max. R Height (mms)		Max. S Depth (mms)		+ or −	T Hgt. (mms)	R Hgt. (mms)	Tech Prob 98	Terminal P V1		CLEAR 1.0
91	93	95	U				Lead I II III	Lead $V_4 V_5 V_6$	Lead I II III	Lead $V_1 V_2 V_3$		V5	AVL		Duration	Depth (mms)	

Two-minute rhythm strip:

→ Specify: _____

Heart Rate (per minute)	QT Duration (m. sec.)	Coupling Interval (m. sec.)	R-R (m.m.)	Ectopic Codes		
				VPB	RN BG	M F

White - Coordinating Center
Yellow - ECG Center
Pink - Coordinating Center
Goldenrod - Clinic

MINNESOTA CODES USED IN THE SHEP

In the remaining sections of this appendix are listed the Minnesota Codes as used in describing the standardized 12-lead one minute electrocardiograms (ECGs) and two-minute rhythm strips in the Systolic Hypertension in the Elderly Program (SHEP). The appendix is broken into the following fourteen sections:

I. Q and QS Pattern Codes
II. ST Junction and ST Segment Depression Codes
III. T Wave Change Codes
IV. ST Segment Elevation Codes
V. High Amplitude R Wave Codes
VI. AV Conduction Defect Codes
VII. Ventricular Conduction Defect Codes
VIII. Estes' Code
IX. Arrhythmia Codes
X. Ectopic Codes
XI. Miscellaneous Items
XII. Special Measurements
XIII. Two-Minute Rhythm Strip Measurements
XIV. Inconsistent Codes

Except where indicated, zeros are acceptable codes. They indicate that the abnormality is absent.

For further information on the Minnesota Code, see The Minnesota Code Manual of Electrocardiographic Findings by Ronald J. Prineas, Richard S. Crow, and Henry Blackburn (John Wright-PSG, Inc, Boston, 1982).

Section I: Q and QS Pattern Codes

(1) Lateral (Anterolateral) Infarction Pattern (leads I, aVL, V_6)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 seconds or more in any of leads I, V_6, or QS in leads I or V_6.

1-1-2 Q duration 0.04 seconds or more in any of leads I, V_6.

1-1-3 Q duration 0.04 seconds or more, plus R amplitude of 3 mm or more in lead aVL.

1-2-1 Q/R amplitude ratio 1/3 or more plus Q duration at least 0.02 seconds and less than 0.03 seconds in any of leads I, V_6.

1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in any of leads I, V_6.

1-2-8 Amplitude of initial R decreasing to 2 mm or less in every beat between leads V_5 - V_6. Do not code in the presence of 3-2, 7-1-1, 7-2-1, 7-3. All beats in the lead immediately adjacent to the right must have an initial RS > 2 mm.

1-3-1 Q/R amplitude ratio at least 1/4 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in any of leads I, V_6.

1-3-3 Q duration of at least 0.03 seconds and less than 0.04 seconds plus R amplitude of 3 mm or more in lead aVL.

(2) Inferior Infarction Pattern (leads II, III, aVF).

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 seconds or more in lead II.

1-1-2 Q duration 0.04 seconds or more in lead II.

1-1-4 Q duration 0.05 seconds or more in lead III plus any Q wave of at least 1.0 mm amplitude in aVF.

1-1-5 Q duration 0.05 seconds or more in lead aVF.

1-2-1 Q/R amplitude ratio 1/3 or more, plus Q duration at least 0.02 seconds and less than 0.03 seconds in lead II.

1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in lead II.

1-2-3 QS pattern in lead II.

1-2-4 Q duration of at least 0.04 seconds and less than 0.05 seconds in lead III, plus a Q wave of at least 1.0 mm amplitude in aVF.

1-2-5 Q duration at least 0.04 seconds and less than 0.05 seconds in lead aVF.

1-2-6 Q amplitude of 5 mm or more in either of leads III, aVF.

1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in lead II.

1-3-4 Q duration of at least 0.03 seconds and less than .04 seconds in lead III, plus any Q wave at last 1.0 mm amplitude in lead aVF.

1-3-5 Q duration of at least 0.03 seconds and less than 0.04 seconds in lead aVF.

1-3-6 QS pattern in each of leads III and aVF.

(3) Anteroseptal and Anterior Infarction Pattern (leads V_1-V_5)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 seconds or more in any of leads V_2-V_5.

1-1-2 Q duration 0.04 seconds or more in any of leads V_1-V_5.

1-1-6 QS pattern in any of leads V_2-V_5, when an initial R wave is present in any beat in the adjacent lead to the right on the chest. For lead V_1, an initial R is considered present when the majority of beats have an initial positive inflection in the QRS of ≧ 1/4 mm in that lead. For leads V_2-V_5, an initial R wave is considered present in a lead when any initial positive inflection in the QRS measures ≧ 1/4 mm in that lead.

1-1-7 QS pattern in all of leads V_1 to V_4, or V_1 to V_5.

1-2-1 Q/R amplitude ratio 1/3 or more, plus Q duration at least 0.02 seconds and less than 0.03 seconds in any of leads V_2-V_5.

1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in any of leads V_2-V_5.

1-2-7 QS pattern in all of leads V_1-V_3.

1-2-8 Amplitude of initial R decreasing to 2 mm or less in every beat between leads V_2-V_3, V_3-V_4, V_4-V_5, V_5 - V_6. Do not code in the presence of 3-2, 7-1-1, 7-2-1, 7-3. All beats in the lead immediately adjacent to the right must have an initial RS > 2 mm.

1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in any of leads V_2-V_5.

1-3-2 Qs pattern in absence of code 3-1, in each of leads V_1 and V_2.

Section II: ST Junction (J point) and ST Segment Depression Codes (subendocardial ischemia)

(1) Lateral (Anterolateral) ST Segment Depression (leads I, aVL, V_6)

4-1-1 S-T-J depression at least 2.0 mm or more and ST segment horizontal or downward sloping in any of leads I, aVL, V_6.

4-1-2 S-T-J depression at least 1.0 mm but less than 2.0 mm and ST segment horizontal or downward sloping in any of leads I, aVL, V_6.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in any of leads I, aVL, V_6.

4-3 No S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of leads I, aVL, V_6.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping, or U-shaped, in any of leads I, aVL, V_6.

(2) Inferior ST Segment Depression (leads II, III, aVF)

4-1-1 S-T-J depression at least 2.0 mm or more and S-T segment horizontal or downward sloping in lead II, III, or aVF.

4-1-2 S-T-J depression at least 1.0 mm but less than 2.0 mm and S-T segment horizontal or downward sloping in any of leads II, III, or aVF.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in leads II or aVF.

4-3 No S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in lead II.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping, or U-shaped, in lead II.

(3) Anteroseptal and Anterior ST Segment Depression (leads V_1-V_5)

4-1-1 S-T-J depression at least 2.0 mm or more and S-T segment horizontal or downward sloping in any of leads V_1-V_5.

4-1-2 S-T-J depression at least 1.0 mm but less than 2.0 mm and S-T segment horizontal or downward sloping in any of leads V_1-V_5.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in any of leads V_1-V_5.

4-3 No S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of leads V_2-V_5.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping, or U-shaped, in any of leads V_1-V_5.

Section III: T Wave Change Codes (myocardial ischemia)

(1) Lateral (Anterolateral) Ischemia (leads I, aVL, V_6)

5-1 T amplitude negative, minus 5.0 mm or more in any of leads I, V_6, or in lead aVL when R-amplitude is 5.0 mm or more.

5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least minus 1.0 mm but not as deep as minus 5.0 mm in any of leads I, V_6, or lead aVL when R amplitude is 5.0 mm or more.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in any of leads I, V_6, or in lead aVL when R amplitude is 5.0 mm or more.

5-4 Optional Code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads I, aVL, V_6; R wave amplitude must be 10.0 mm or more.

(2) Inferior Ischemia (leads II, III, aVF)

5-1 T amplitude negative, minus 5.0 mm or more in lead II, or in lead aVF when QRS is mainly upright.

5-2 T amplitude negative or diphasic (positive-negative type) with negative phase at least minus 1.0 mm but not as deep as minus 5.0 mm in lead II, or in lead aVF when QRS is mainly upright.

(3) Anteroseptal and anterior ischemia (leads V_2-V_5)

5-1 T amplitude negative, minus 5.0 mm or more in any of leads V_2-V_5.

5-2 T amplitude negative or diphasic (positive-negative type) with negative phase at least minus 1.0 mm but not as deep as minus 5.0 mm in any of leads V_2-V_5.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in any of leads V_3-V_5.

5-4 Optional Code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads V_3-V_5; R wave amplitude must be 10.0 mm or more.

Section IV: ST Segment Elevation Codes (Injury)

(1) Lateral (Anterolateral) (leads I, aVL, V_6)

9-2 S-T segment elevation 1.0 mm or more in any of leads I, aVL, V_6.

(2) Inferior (leads II, III, aVF)

9-2 S-T segment elevation of 1.0 mm or more in leads II, III, aVF.

(3) Anteroseptal and Anterior (leads V_1-V_4)

9-2 S-T segment elevation of 2.0 mm or more in any of leads V_1-V_4.

Section V: High Amplitude R Wave Codes

3-1 Left:
R amplitude greater than 26 mm in either of leads V_5 or V_6, or R amplitude greater than 20 mm in any of leads I, II, III, aVF, or R amplitude greater than 12 mm in lead aVL. Suppresses code 1-3-2.

3-2 Right:
R amplitude equal to or greater than 5.0 mm and R amplitude equal to or greater than S amplitude in the majority of beats in lead V_1, and there is an S wave greater than R somewhere to the left of V_1 on the chest. (Includes code 7-3 which meets the above criteria. Code 3-2 suppresses code 1-2-8.)

3-3 Left (optional code when 3-1 is not present):
R amplitude greater than 15 mm but $\leq$ 20 mm in lead I, or R amplitude in V_5 or V_6 plus S or QS amplitude in V_1 greater than 35 mm.

3-4 Criteria for 3-1 and 3-2 both present.

Section VI: AV Conduction Defect Codes

6-1 Complete (third degree) AV block (permanent or intermittent) in any lead. Atrial and ventricular complexes firing independently and atrial rate faster than ventricular rate, with ventricular rate <60.

6-2-1 Mobitz Type II.

6-2-2 Partial (second degree) AV block in any lead. (2:1 or 3:1 block.)

6-2-3 Wenckebach.

6-3 P-R (P-Q) interval 0.22 seconds or more in the majority of beats in any of leads I, II, III, aVL, aVF.

6-4-1 Persistent Wolff-Parkinson-White Syndrome:
Normal P wave. P-R interval less than or equal to 0.12 seconds plus QRS duration 0.12 seconds or more plus R peak duration 0.06 seconds or more, coexisting in the same beat and present in the majority of beats in any of leads I, II, aVL, V_4-V_6.

6-4-2 Intermittent Wolff-Parkinson-White Syndrome:
WPW pattern in ≦50% of beats in appropriate leads.

6-5 Short P-R Interval:
P-R interval less than 0.12 seconds in all beats of any two of leads I, II, III, aVL, aVF.

6-6 Intermittent aberrant ventricular conduction:
1. P-R > 0.12 seconds (Except in presence of 6-5 or heart rate > 100.)
2. Bizarre QRS complex ≧ 0.12 seconds (measure QRS duration outside to inside)
3. Normal P wave. (Suppressed by 6-4-1, 6-4-2.)
4. When most beats are normal sinus rhythm.

6-8 Artificial Pacemaker:
A sharp (spiked) amplitude occurring regularly when deflection is immediately followed by a wide, slurred QRS and a highly regular heart rate.

Section VII: Ventricular Conduction Defect Codes

7-1-1 Complete left bundle branch block (LBBB). Suppressed by 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.

1. QRS duration≧0.12 seconds in a majority of beats (of the same QRS pattern) in any of leads I, II, III, aVL, aVF PLUS
2. R peak duration ≧0.06 seconds in a majority of beats in any of leads I, II, aVL, V_5, V_6.

Code 7-1-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 3, 4, 5, 9-2, 9-4, and 9-5 codes. If any other Q wave coexists with the LBBB pattern, code the Q and drop the 7-1-1 to 7-4 code.

7-1-2 Intermittent left bundle branch block. Same as 7-1-1 but with presence of normally conducted QRS complexes of different shape to the LBBB pattern.

7-2-1 Complete right bundle branch block (RBBB). Suppressed by 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2.

1. QRS duration ≧0.12 seconds in a majority of beats (of the same QRS pattern) in any of leads I, II, III, aVL, aVF PLUS
2. R' > R in V_1 or V_2 OR
3. QRS mainly upright plus R peak duration ≧0.06 seconds in V_1 or V_2 OR
4. S duration >R duration in all beats of either leads I or II.

Code 7-2 suppresses 1-2-8, all 2, 3, 4 and 5 codes, 9-2, 9-4, and 9-5.

7-2-2 Intermittent right bundle branch block. Same as 7-2-1 but with presence of normally conducted QRS complexes of different shape to the RBBB pattern.

7-3 Incomplete right bundle branch block.
QRS duration less than 0.12 seconds in each of leads I, II, III, aVL, aVF, and R' greater than R in either of leads V_1, V_2. Code as 3-2 if those criteria are met. Code 7-3 suppresses 1-2-8 code.

7-4 Intraventricular block. Code 7-4 suppresses all 2, 3, 4, 5, 9-2, 9-4, 9-5 codes. QRS duration 0.12 seconds or more in a majority of beats in any of leads I, II, III, aVL, aVF.

7-5 R-R' pattern in either of leads V_1, V_2 with R' less than or equal to R.

7-6 Incomplete left bundle branch block.
QRS duration at least 0.10 seconds and less than 0.12 seconds in majority of beats in each of leads I, aVL, and V_5 or V_6. Do not code in the presence of any codable Q or QS wave.

7-7 Left Anterior Hemiblock (LAH).
QRS duration less than 0.12 seconds in the majority of beats in any of leads I, II, III, aVL, aVF, plus a Q wave that is greater than or equal to 1/4 mm amplitude and less than 0.03 seconds duration in lead I plus axis less than -45 degrees. In presence of 7-2, code 7-8 if axis is less than -45 degrees and Q wave in lead I meets the above criteria.

7-8 Combination of 7-7 and 7-2.

Section VIII: Estes' Code

7 QRS interval at least 0.09 seconds or more and R peak duration 0.04 seconds or more, coexisting in the second-to-the-last beat in lead V_5 or V_6.

Section IX: Arrhythmia Codes

8-1-1 Presence of any atrial or junctional premature beat. (Prematurity has to be at least 10% of normal R-R interval.)

1. Different P without QRS.
OR 2. Absent P with normal QRS.
OR 3. Different preceding P with prolonged QRS
OR 4. Different P with normal QRS
OR 5. Absent P with QRS < .12 seconds

8-1-2 Presence of any ventricular premature beat.

1. Bizarre QRS-T.
PLUS 2. Prolonged QRS ≧ .12 seconds.
PLUS 3. P wave absent.
OR 4. All fusion beats in presence of VPBs.

8-1-3 Presence of both atrial and/or junctional premature beats and ventricular premature beats (so that individual frequencies are <10% but combined premature beats are ≥10% of complexes).

8-1-4 Wandering atrial pacemaker

1. Varying normal and different P waves associated with both long and short R-R' intervals without premature beats.
2. Varying P-R interval may be present.
3. Varying ventricular rate with one P activity for each QRS.
4. Normal QRS-T (or unchanged QRS).

8-1-5 Presence of 8-1-2 and 8-1-4.

8-2-1 Ventricular Fibrillation or Ventricular Asystole.

8-2-2 Persistent Ventricular Rhythm

1. Wide QRS (greater than or equal to 0.12 seconds).
2. Absence of preceding P waves.

8-2-3 Intermittent Ventricular Tachycardia. Three or more consecutive ventricular premature beats occurring at a rate greater than or equal to 100.

8-2-4 Ventricular Parasystole (should not be coded in presence of code 8-3-1).

1. Unifocal ventricular premature beats.
2. Coupling intervals (shortest to longest) vary by greater than 0.12 seconds. (If multiform VPBs exist in any lead regardless of coupling interval, code 8-1-2.) Fusion beats can be used to measure coupling interval. Measure coupling interval from beginning of QRS.

8-3-1 Atrial Fibrillation (persistent in all leads).

1. Absent P waves.
2. Irregular undulations of the baseline.
3. Normal QRS.
4. Totally irregular ventricular rate.

8-3-2 Atrial Flutter (persistent).

1. Saw-toothed F waves or regularly undulating baseline.
2. Normal QRS.
3. Ratio of 2:1 to 8:1 A-V block.

8-3-3 Intermittent Atrial Fibrillation. Code if three or more clear-cut, consecutive sinus beats present in any lead in the presence of atrial fibrillation.

8-3-4 Intermittent Atrial Flutter. Code if three or more clear-cut, consecutive sinus beats present in any lead in the presence of atrial fibrillation.

8-4-1 Persistent Supraventricular Rhythm.

1. QRS duration less than 0.12 seconds
2. Absent P waves or presence of abnormal P waves
3. Regular rhythm.

8-4-2 Intermittent Supraventriuclar Tachycardia. Three consecutive atrial or junctional premature beats occurrring at a rate ≧100.

8-5-1 Sino-atrial Arrest.

1. Unexpected absence of P, QRS and T.
2. R-R interval fixed multiple of normal interval plus or minus 10%.

8-5-2 Sino-atrial Block. R-R interval fixed multiple of normal interval plus or minus 10%. Unexpected absence of P, QRS, and T preceded by progressive shortening of P-P intervals.

8-6-1 AV Dissociation with Ventricular Pacemaker Without Capture.

1. P-P and R-R occur at variable rates with ventricular rate as fast or faster than the atrial rate.
2. Variable P-R intervals.
3. No capture beats.

8-6-2 AV Dissociation with Ventricular Pacemaker with Capture.

8-6-3 AV Dissociation with Atrial Pacemaker and with No Capture Beats.

8-6-4 AV Dissociation with Atrial Pacemaker with Capture Beats.

Section X: Ectopic Codes

SVPB: Total number of SVPB's on the record (acceptable Minnesota Code range = 0 to 90.)

VPB: Total number of VPB's on the record (acceptable Minnesota Code range = 0 to 90.)

Runs and Bigeminy:

Blank = No ectopic beats
1 = No runs, and non-bigeminy, trigeminy.
2 = SVPB runs.
3 = VPB runs.
4 = Both VPB and SVPB runs.
5 = SVPB bigminy or trigeminy.
6 = VPB bigminy or trigeminy.
7 = SVPB bigeminy or trigeminy with SVPB runs
8 = VPB bigeminy or trigeminy with SVPB runs.
9 = Other combinations of bigeminy or trigeminy.

Multiform Ectopic Beats:

Blank = No ectopic beats
1 = Unifocal VPB or SVPB ectopic beats.
2 = Multiform SVPB.
3 = Multiform VPB.
4 = Both uniform VPB and multiform SVPB.
5 = Multiform SVPB and unifocal VPB.
6 = Unifocal SVPB and multiform VPB.

T-R' Interval:

Measurement of the shortest T-R' interval to the nearest whole mm. Peak of T to peak of R'. Blank means no VPB or SVPB. (Acceptable Minnesota Code range = 1 to 20.)

99 = Unmeasurable
If the T-R' interval is zero, code 88

These codes are applicable only to ectopic beats.

A normal ECG (coded 1.0) may have ectopic codes.

One must be able to determine the degree of prematurity on any ectopic beat--therefore we do not count or code ectopics unless they have a preceding normal sinus T wave.

To code multiform ectopic beats the following conditions must be present:

Unifocal

- Only one ectopic beat in a lead.
- When 2 or more ectopic beats are present in the same lead that are the same direction and form.

Multiform

- When two or more ectopic beats are present in the same lead that are of different direction and form.

Section XI: Miscellaneous Items

9-1 Low QRS amplitude: QRS peak-to-peak amplitude less than 5 mm in all beats in each of leads I, II, III, or less than 10 mm in all beats in each of leads $V_{1,2,3,4,5,6}$. Check calibration before coding.

9-2 S-T elevation 1.0 mm or more in any of leads I, II, III, aVL, aVF, V_5 or V_6, or S-T elevation 2.0 mm or more in any of leads $V_{1,2,3,4}$.

9-3 P wave amplitude of 2.5 mm or more in any of leads II, III, aVF, on a majority of beats.

9-4-1 QRS transition zone at V_3 or to the right of V_3 on the chest.

9-4-2 QRS transition zone at V_4 or to the left of V_4 on the chest.

9-5 T wave amplitude greater than +12 mm in any of leads I, II, III, aVL, aVF, $V_{1,2,3,4,5,6}$.

9-8-1 Findings questionable due to wandering baseline, noise, or other technical defect in the record.

9-8-2 Poor quality record due to wandering baseline, noise, or other technical defect but record codable.
(Record codable 1 through 9-4 but measurements cannot be taken.)

Section XII: Special Measurements

Heart Rate: To be determined in lead I. When 48 to 52, or 96 to 104, average the heart rate in I and V_6. With 8-2-2, 8-3-1 and 8-3-2 code heart rate by QRS complexes.

Heart rate--take first three R-R intervals (four beats) in Lead I. If there are not four beats in LI, average with V_6. Also average with V_6 when HR in LI is between 48-52 and 96-104.

Axis: Measured as usual on the second-to-the-last beats in leads I and III.

Units: -179 to +180

Axis--using the second to last complete beat in Leads I and III, measure the algebraic sum for the positive and negative deflections of the QRS in LI. Do the same for LIII. Take any fraction for either of these values to nearest even number before using the axis chart.

Maximum R: Measure the highest R wave in I, II, or III on the second-to-the-last beat.* Measure the highest R wave in V_4, V_5, or V_6 on the second-to-the-last beat.*

Maximum S: Measure the deepest S wave in I, II, or III on the second-to-the-last beat.* Measure the deepest S wave in V_1, V_2, or V_3 on the second-to-the-last beat.*

T: Measure the T wave in V_5 on the second-to-the-last beat.* (R, S, and T waves should be measured to the nearest mm; code "0" if absent.)

R, T, S measurement--take fractions to nearest whole number. If a fraction is $\geq 1/2$, round up. If a fraction is $<1/2$, round down. For 3rd reader, correct if they differ by more than 1.

Terminal P: (To be completed.)

Code 1.0 in last column on worksheet if record is normal.

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*The second-to-last beat is defined as that normal beat which immediately precedes the last normal codable beat. If there are only two beats in a lead, the measurement should be taken on the last complete normal beat.

Section XIII: Two-Minute Rhythm Strip Measurements

(To be completed.)

Section XIV: Inconsistent Codes

The codes listed in the left column cancel or suppress the codes mentioned in the right column. The appropriate columns are indicated by parentheses.

Code	Suppresses this code(s)
All codable Q, QS	7-6
Q more than 0.03 in lead I.	7-7
3-1	1-3-2
3-2	1-2-8 7-3
6-1	All except 8-2
6-4-1	All other codes
6-8	All other codes
7-1-1	1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 3s, all 4s, all 5s, 9-2, 9-4-x, 9-5, 7-7
7-2-1	1-2-8, all 3s, all 4s, all 5s, 9-2, 9-4-x, 9-5
7-3	1-2-8
7-4	All 3s, all 4s, all 5s, 9-2, 9-4-x, 9-5
8-1-4	8-1-1
8-3-1, 8-3-2, 8-3-3	8-1-1, 8-1-2
8-2-1	All codes
8-2-2	All codes
8-4-1	6-5
8-4-1 + heart rate ≧140	All codes except 7-4 or 6-2.
Heart rate >100	6-5
8-2-3	8-1-2
8-4-2	8-1-1
8-1-4	9-3

APPENDIX D

CENTRAL AND LOCAL LABORATORY PROCEDURES

D.1 Urinalysis

D.1.1 Introduction

Examination of the urine is an important part of the evaluation of people with high blood pressure. By examining the urine we can often tell things about why people have high blood pressure as well as determining what effect the high blood pressure may be having on the body.

The dipstick urinalyses are performed as a part of good medical care and to detect problems that may be caused by high blood pressure or the SHEP medications. Abnormalities should be followed up according to the judgment of the SHEP clinician. At Baseline Visit 1, proteinuria or hematuria may prompt the drawing of a blood sample for local analysis of serum creatinine.

The urine chlorthalidone determinations are done for evaluation of compliance to the SHEP Step 1 medication, and the results will not be available to the investigators or Clinical Center staff during the trial.

D.1.2 Dipstick Urinalysis

Dipstick urinalyses are performed at Baseline Visit 1, and at all annual visits. It is recommended that any of the the Ames dipsticks be used for this purpose, as long as results may be obtained for blood, protein, and glucose. These include:

Hema-Combistix	--	also measures pH
Labstix	--	also measures pH and ketones
Bili-Labstix	--	also measures pH, ketones and bilirubin
Bili-Labstix SG	--	also measures pH, ketones, bilirubin and specific gravity
Multistix	--	also measures pH, ketones, bilirubin, and urobilinogen
Multistix SG	--	also measures pH, ketones, bilirubin, urobilinogen and specific gravity
N-Multistix	--	also measures pH, ketones, bilirubin, urobilinogen and nitrite
N-Multistix SG	--	also measures pH, ketones, bilirubin, urobilinogen, nitrite, and specific gravity

Other supplies required for the dipstick urinalysis are plastic cups of the type usually used for urine collection.

The following directions are from an Ames dipstick package insert.

Summary and Explanation: AMES REAGENT STRIPS for Urinalysis are firm plastic strips to which are affixed several separate reagent areas. Depending on the product being used, AMES REAGENT STRIPS provide tests for pH, protein, glucose, blood, and nitrite in urine. Please refer to the carton and bottle label for specific reagent areas on the product you are using. Test results may provide information regarding the status of carbohydrate metabolism, kidney function, acid base balance, and bacteriuria.[1-3]

The reagent test areas on AMES REAGENT STRIPS are stable and ready to use upon removal from the bottle. The entire reagent strip is disposable; no additional laboratory equipment is necessary for testing. The directions must be followed exactly. Accurate timing is essential to provide quantitative results. The reagent strips must be kept in the bottle with the cap tightly closed (as specified on the cap) to maintain reagent reactivity. To obtain optimum results, it is necessary to use FRESH, well-mixed, uncentrifuged urine.

Revised 4-86

Storage: Store at temperatures under 30°C (86°F). Do not store in a refrigerator. Do not use after expiration date.

Recommended Procedures for Handling AMES REAGENT STRIPS: All unused strips must remain in the original bottle. Transfer to any other container may cause reagent strips to deteriorate and become unreactive. Do not remove desiccant(s) from bottle. Replace cap immediately and tightly after removing reagent strip. Do not touch test areas of the reagent strip. Work areas and specimen container should be free of detergents and other contaminating substances.

Dip test areas in urine completely, but briefly, to avoid dissolving out the reagents. Read test results carefully at the times specified, in a good light and with the test area held near the appropriate Color Chart on the bottle label.

IMPORTANT: PROTECTION AGAINST AMBIENT MOISTURE, LIGHT AND HEAT IS ESSENTIAL TO GUARD AGAINST ALTERED REAGENT REACTIVITY. Discoloration or darkening of reagent areas may indicate deterioration. If this is evident, or if test results are questionable or inconsistent with expected findings, the following steps are recommended: (1) confirm that the product is within the expiration date shown on the label; (2) check performance against known positive control materials (e.g., CHEK-STIX® Control Strips); (3) retest with fresh product. If proper results are not obtained, consult your local Ames Representative, or contact Ames Customer Service Communications by calling toll free 1-800-348-8100, for advice on testing technique and results.

Specimen Collection and Preparation: Collect urine in a clean container and test it as soon as possible. If testing cannot be done within an hour after voiding, refrigerate the specimen immediately and let it return to room temperature before testing.

Prolonged exposure of unpreserved urine to room temperature may result in microbial proliferation with resultant changes in pH. A shift to alkaline pH may cause false positive results with the protein test area. Urine containing glucose may decrease in pH as organisms metabolize the glucose. Bacterial growth from contaminating organisms may cause positive blood reactions from the peroxidases produced.

Procedure: MUST BE FOLLOWED EXACTLY TO ACHIEVE RELIABLE TEST RESULTS.

1. Collect FRESH urine specimen in a clean, dry container.

2. Remove one strip from bottle and replace cap. Completely immerse reagent areas of the strip in FRESH urine and remove immediately to avoid dissolving out reagents.

3. While removing, run the edge of the strip against the rim of the urine container to remove excess urine. Hold the strip in a horizontal position to prevent possible mixing of chemicals from adjacent reagent areas and/or soiling of hands with urine.

4. Compare test areas to corresponding Color Chart on the bottle label at the time specified. HOLD STRIP CLOSE TO COLOR BLOCKS AND MATCH CAREFULLY.

Limitations of Procedures: As with all laboratory tests, definitive diagnostic or therapeutic decisions should not be based on any single result or method. Limitations are given here for pH, protein, glucose, and blood.

- pH: If proper procedure is not followed and excess urine remains on the strip, a phenomenon known as "runover" may occur, in which the acid buffer from the protein reagent will run onto the pH area, causing a false lowering of the pH reading.

- Protein: False positive results may be obtained with highly buffered alkaline urines. Contamination of the urine specimen with quaternary ammonium compounds (e.g., from some antiseptics and detergents) or with skin cleansers containing chlorhexidine may also produce false positive results.

- Glucose: Ascorbic acid concentrations of 50 mg/dL or greater may cause false negatives for specimens containing small amounts of glucose (100 mg/dL). Ketone bodies reduce the sensitivity of the test; moderately high ketone levels (40 mg/dL) may cause false negatives for specimens containing small amounts of glucose (100 mg/dL) but the combination of such ketone levels and low glucose levels is metabolically improbable in screening.

- Blood: Elevated specific gravity or elevated protein may reduce the reactivity of the blood rest. Certain oxidizing contaminants, such as hypochlorite, may produce false positive results. Microbial peroxidase associated with urinary tract infection may cause a false positive reaction. Ascorbic acid concentrations of 5 mg/dL or greater may cause false negatives at the Trace level.

Expected Values: Expected values for the typical "normal" healthy population and the abnormal population are listed below for pH, protein, glucose and blood.

- pH: Both the normal and abnormal urinary pH range is from 5 to 9.

- Protein: Normally no protein is detectable in urine, although a minute amount is excreted by the normal kidney. A color matching any block greater than Trace indicates significant proteinuria. For urine of high specific gravity, the test area may most closely match the Trace color block even though only normal concentrations of protein are present. Clinical judgment is needed to evaluate the significance of Trace results.

- Glucose: Minute amounts of glucose may normally be excreted by the kidney; however, these amounts are below the sensitivity level of this test. Concentrations of as little as 100 mg/dL may be significantly abnormal if found consistently. Results must be read at 30 seconds for quantitation.

- Blood: The significance of the trace reaction may vary among patients, and clinical judgment is required for assessment in an individual case. Development of green spots (intact erythrocytes) or green color (free hemoglobin/myoglobin) on the reagent area within 40 seconds indicates the need for further investigation. Blood is often, but not always, found in the urine of menstruating females. This test is highly sensitive to hemoglobin (it is slightly less so to intact erythrocytes) and thus complements the microscopic examination.

Specific Performance Characteristics:

- pH: The pH test area permits quantitative differentiation of pH values within the range of 5-8.5. pH readings are not affected by variations in the urinary buffer concentration.

- Protein: Quantitative results are obtained with the protein test. Five to 20 mg/dL of albumin may be detected as a Trace result. The test area is more sensitive to albumin than to globulins, hemoglobin, Bence-Jones Protein and muco-protein; a negative result does not rule out the presence of these other proteins.

- Glucose: Quantitiative results are obtained with the glucose test when read at 30 seconds. The test is specific for glucose; no substance excreted in urine other than glucose is known to give a positive result. The reagent area does not react with lactose, galactose, fructose nor reducing metabolites of drugs (e.g., salicylates and nalidixic acid). This test may be used to determine whether the reducing substance found in urine is glucose. Approximately 100 mg/dL of glucose is detectable. Reactivity may be influenced by urine specific gravity and temperature. The test is more sensitive than the copper reduction test (e.g., CLINITEST® Reagent Tablets). If the color appears somewhat mottled at the higher glucose concentrations, match the darkest color to the color blocks.

- Blood: The test is generally capable of detecting 0.015 to 0.062 mg/dL free hemoglobin or 5 to 20 intact red blood cells per microliter in urines with specific gravity of 1.005 and ascorbic acid concentrations of less than 5 mg/dL. The sensitivity is less in urines with high specific gravity and ascorbic acid content. The test is slightly more sensitive to free hemoglobin and myoglobin than to intact erythrocytes. The appearance of green spots on the reacted reagent area indicates the presence of intact erythrocytes in the urine.

Bibliography:

1. Free, A.H. and Fee, H.M.: Urinalysis. Critical Discipline of Clinical Science. CRC Crit. Rev. Clin. Lab. Sci. 3(4):481-531; 1972.

2. Kark, R.M. et al.: A Primer of Urinalysis, 2nd ed. New York: Haper and Row; 1963.

3. Yoder, J., Adams, E.C., and Free, H.M.: Simultaneous screening for urinary occult blood, protein, glucose and pH. Amer. J. Med. Tech. 31:285; 1965.

The Ames Multistix, which is the dipstick that many Clinical Centers plan on using, gives semi-quantitative results for the following:

a. Glucose--Read at 30 seconds

Negative
1/10 g/dL (100 mg/dL)
¼ g/dL (250 mg/dL)
½ g/dL (500 mg/dL)
1 g/dL (1000 mg/dL)
2+ g/dL (≧2000 mg/dL)

b. Protein--Time not critical, may be read immediately

Negative
Trace
30 mg/dL (+)
100 mg/dL (++)
300 mg/dL (+++)
>2000 mg/dL (++++)

c. pH--Time not critical; may be read immediately

5, 6, 6.5, 7, 7.5, 8, 8.5

d. Blood--Read at 40 seconds

Negative
Non-hemolyzed trace
Hemolyzed trace
Small (+)
Moderate (++)
Large (+++)

e. Bilirubin--Read at 20 seconds

Negative
Small (+)
Moderate (++)
Large (+++)

f. Ketones--Read at 15 seconds

Negative
Trace (5 mg/dl)
Small (15 mg/dl)
Moderate (40 mg/dl)
Large (80 mg/dl)
Large (160 mg/dl)

g. Urobilinogen--Read at 45 seconds

Negative
1 Ehrlich units/dl } Normal range
2 Ehrlich units/dl
4 Ehrlich units/dl
8 Ehrlich units/dl
12 Ehrlich units/dl

D.1.3 Urine Chlorthalidone Determinations (Qualitative)

These determinations will be made by the Central Laboratory on urines collected at Year 1 and Year 4. Urine for these determinations may be collected at the same time as that for the urine dipstick analysis.

Prior to dipstick analysis, at least 15 ml of urine should be poured off into a plastic 100 cc aliquot bottle (provided by MetPath). This is the minimum amount of urine required for the qualitative urine chlorthalidone analysis. (This bottle contains no preservative.) Make sure that the cap is secure. With a black permanent marker, write the participant's SHEP ID and acrostic on the bottle (this could be accomplished prior to the visit).

Two types of MetPath request slips are used for SHEP: (1) the yellow request slip for the urine chlorthalidone analysis, and (2) the white request slip for the serum analyses. For the urine chlorthalidone analysis, the participant's ID number should be filled in on the urine chlorthalidone request slip in the first 8 spaces of "Patient ID"; these spaces are marked off for your ease of reference. The remaining two spaces of "Patient ID" are for the sequence number of the clinic visit. Fill in the participant's acrostic in "Other Identification," being sure that it matches the acrostic on the SH06. The date that the specimen was collected should be entered into the space provided on the right-hand side of the request slip. Check the box in front of "Urine Chlorthalidone (Year 1 and Year 4)," at the bottom of the request slip.

Envelopes are provided by MetPath for the specimens. Fold the urine chlorthalidone requisition slip and place the slip and the urine specimen in the envelope and close the envelope. If a blood specimen has been drawn and prepared for the same participant, it should not be included in the same envelope.

A MetPath courier will pick up the samples on a schedule determined by the Clinical Centers and their local MetPath representative. If the specimens will not be picked up by MetPath on the same day they are obtained, they should be refrigerated until pick-up.

SHEP urine chlorthalidone determinations were stopped February 28, 1988.

D.2 Venipuncture, Collecting, Storing and Shipping the Samples

D.2.1 Techniques:

One of the most common clinical procedures, other than blood pressure determination, that will occur during the SHEP is the drawing of blood samples, for local or central analysis. Since it involves a small amount of pain for the participant, it is very important that the techniques be seriously considered and reviewed by clinic staff involved in this process. These techniques, and some special considerations for drawing blood from the elderly, are reviewed here.

a. General policies

1) All patients will be seated for 5 minutes prior to venipuncture.
2) Tourniquet must not be in place more than two minutes.
3) Blood samples will be centrifuged within 30-60 minutes.
4) All venoject tubes with additive must be completely filled with blood and inverted gently until additive is dissolved (see section 2a below).
5) No single staff member will attempt more than 2 venipunctures on the same patient. After two failures another person will be asked to make any further attempts.
6) Antecubital site of either arm will be used as first choice for venipuncture.
7) Prior to venipuncture, the participant's ID and acrostic should be written on the tube label with a permanent black marker.

b. Supplies needed for routine procedure

- 21G 1½" mutliple sample needle
- needle holder, adult size
- vacutainer tubes--

  red and grey top barrier tube
- alcohol prep
- gauze
- tourniquet
- band-aid

c. Procedure for routine drawing of blood sample

1) Wash hands.
2) Explain procedure to patient; for example: "I will be drawing a blood sample from your arm. You will probably feel a small prick when I insert the needle."
3) Fill out appropriate lab forms, if not already filled out.
4) Prepare equipment, if not already prepared.
5) Position participant's arm on drawing table. Extend the arm towards you, palm up. Use padded cushion under elbow for comfort.
6) Apply tourniquet 3 inches above venipuncture site. If no radial pulse, tourniquet is too tight.
7) Request participant to make a fist.
8) Palpate vein. If no vein is felt, try other arm or site (see section on "Difficult Venipunctures").
9) Clean site with alcohol swab or prep.

10) Insert needle, bevel up, parallel to vein. Use straight stab, do not poke around. The needle is sterile, do not touch while performing venipuncture. If vein rolls, withdraw needle slightly and try second thrust. If the vein collapses, remove vacutainer tube, call over staff person to reapply tourniquet, have participant open and close fist, then reinsert tube. If still no blood, stop procedure and use techniques in section on "Difficult Venipunctures."

11) Release tourniquet. If tourniquet is on longer than two minutes, start over in the other arm.

12) Observe participant for fainting. If participant faints:

- Withdraw needle.
- Maintain pressure at site.
- Hold arms over table.
- Call for help.
- Prevent injuries from falls or seizures.
- Apply cool compress to forehead.
- Use ammonia capsule if needed.
- Have participant lie down on exam table for 5-10 minutes.

If participant is dizzy:

- Have participant lay head on table.
- Continue talking to participant to assess level of consciousness.
- Finish drawing blood if possible.
- Have participant lie down on exam table for 5-10 minutes.
- Apply cool compress to forehead.

13) Draw required blood tubes and prepare for processing.

14) Apply slight pressure to gauze and withdraw needle, then immediately apply pressure to site.

15) Request participant to apply pressure at site for 3-5 minutes.

16) Dispose of entire needle set-up into disposal container. If using syringe/needle dispose entire set-up into disposable container.

17) Check site and apply band-aid. If bleeding occurs have participant hold site 1-2 minutes longer.

d. Difficult venipunctures

1) Start with procedure above.

2) Determine if vein is difficult:

- Palpated vein feels small or rolls
- Participant complains of being stuck more than once or previous staff problems (no single staff person will attempt more than two venipunctures on a single participant at a single clinic visit)
- Participant has been stuck once already.

3) Check back of hand and forearm for venipuncture sites with larger veins.

4) Attempt one or more vein dilation methods:

- Hot pack venipuncture site with warm, wet towel for 3-5 minutes.
- If vein is small, try disposable syringe and 22G needle.
- Have participant wash hand in warm water for 3-5 minutes.

- Have participant dangle arm at side with tourniquet in place for one minute.
- Use blood pressure cuff for tourniquet by pumping pressure to 60-80 mm Hg.

5) Finish venipuncture following procedures outlined above.

e. Special considerations for drawing blood in the elderly

The elderly pose some special blood drawing problems due to vein fragility and small veins, especially if the samples are drawn fasting. The system of drawing blood by using vacuum tubes can accentuate this problem, causing veins to collapse due to high pressure exerted by the vacuum tubes. Steps outlined in section (d) above may help to alleviate some of the problems.

An important point in drawing blood is that the tourniquet must not occlude arterial flow, otherwise the problems of veins collapsing during the venipuncture amy be accentuated. By using a syringe the pressure can be controlled and this problem almost eliminated. When using a smaller needle (e.g., 22G 1") there is less chance of blowing (hematoma formation) the vein due to fragility.

D.2.2 Supplies

METPATH, the Central Laboratory for the SHEP, will supply:

vacutainer tubes (red and gray top barrier tubes), 15 ml

multiple sample needles (21G 1½" suggested; you may use other sizes as necessary--METPATH will still supply them)

needle holder, adult size (hollow plastic tube used to hold needle and house vacuum tube)

syringes

plastic serum vials and caps (white cap)

extra tourniquets, if you need them

alcohol preps

centrifuge (a loan for the duration of the study)

request slips

shipping envelopes

These supplies should be requested using the supply requisition form provided by MetPath. Supplies not specifically listed on the requisition may be written on the blank lines at the end. When additional SHEP request slips are ordered, be sure to indicate that your request slip is a "Clinical Studies" request slip; also, attach a copy of your SHEP request slip. Otherwise, you may receive the regular MetPath request slip (blue and white), which should not be used to request SHEP Central Laboratory analyses.

D.2.3 Preparing the Samples for Shipping

(1) Collect blood specimen using the usual venipuncture technique. Fill tube completely. If a single tube cannot be completely filled, two tubes may be submitted.

(2) Gently invert barrier tube five times to mix clot activator with blood.

(3) Allow blood to clot for 30 minutes (no longer than 45 minutes).

(4) Centrifuge at 1100 RCF for 10 minutes (full speed for centrifuges suppled by MetPath).

(5) Remove from centrifuge. Barrier will have formed, separating cells from serum. All of the separation gel should have moved from the bottom of the tube to form a barrier layer.

(6) Remove the red and grey stopper. Pour off the serum into a plastic serum vial. Snap the white cap onto the vial, making sure that the cap is in the whole way. With a black permanent marker, write the participant's SHEP ID and acrostic on the plastic tube.

(7) If the specimens will not be picked up by METPATH on the same day as they are drawn, they should be prepared as above and refrigerated upright. Tubes may be refrigerated for up to one week.

The required information should then be filled in on the white requisition slip for serum analyses if this has not been done prior to the visit. The participant's ID number should be filled in, in the first 8 spaces of "Patient ID"; these spaces are marked off for your ease of reference. The remaining two spaces of "Patient ID" are for the sequence number of the clinic visit. Fill in the participant's acrostic in "Other Identification," being sure that it matches the acrostic on the SH06. The date that the specimen was collected should be entered into the space provided on the right hand side of the request slip. Be sure to check the tests requested (Chem-Screen Profile, Lipid Analysis or Serum Potassium). The Chem-Screen Profile includes a serum potassium, so these two tests should not be requested at the same time.

Envelopes will be provided by the Central Laboratory for the specimens. Place the folded requisition and the serum specimen in the envelope and close. (As many serum specimens as needed for one participant may go on one serum analysis requisition and in one envelope.)

If a urine specimen has been collected for central analysis of urine chlorthalidone, the urine sample and the yellow request slip for urine chlorthalidone should be submitted in an envelope separate from the serum sample and its request slip.

A METPATH courier will pick up the samples on a schedule determined by the Clinical Centers and their local METPATH representative.

D.2.4 Receipt of Hardcopy Reports from MetPath

Due to the requirement that the potassium values from MetPath be blinded, except for out-of-range values, each Clinical Center has assigned a person to receive hardcopy reports. These persons are not involved in the medical care of SHEP participants. These persons will review the potassium result on each report, blind the values that are in the reference range (3.50-5.30 mmol/l) and pass the report on to the SHEP clinicians.

Specific instructions for this procedure are at the end of this appendix.

D.2.5 Missing Reports

If reports of any SHEP Central Laboratory procedures are missing after a reasonable period of time elapses, results may possibly be obtained by calling:

Industrial Client Services

1-800-828-8883 or 1-800-631-1390

Ask for any of the following:

Joy Cunningham
Karen Johnson
Jerry Panasuik

The missing report may be regenerated or, if within 7 days, the procedures may be rerun on the blood or urine sample.

D.2.6 Central Laboratory Procedures

(To be completed.)

D.2.7 Local Laboratory Determinations

The following determinations will be done locally:

hemoglobin
hematocrit
WBC count
} BL2 and annually

serum potassium
and other determinations -- as needed in the judgment of the clinician

The serum potassium required at visits after a Step 1 start or increase is not a local determination.

The Principal Investigator of each Clinical Center will be responsible for establishing the mechanism to obtain these test results. If METPATH is to be used for the local determinations, do not use the SHEP request slip--use the requisition slip normally provided by METPATH.

INSTRUCTIONS FOR HANDLING HARDCOPIES

OF SHEP LABORATORY REPORTS FROM METPATH

Two types of laboratory reports should be delivered to you:

- Chem-Screen Profiles
- Single tests of serum potassiums

Several examples of each of these are attached for your reference. The participant identifying information has been covered on these examples, but will be printed on the copies that you receive.

Within 24-hours of receiving any hardcopies of SHEP laboratory reports from METPATH, the following must be accomplished:

1. Using a copy of the attached log sheet, log in each report, copying the SHEP participant ID number ("Patient" on the report), the acrostic ("Patient Soc. Sec. No." on report) and the date drawn from each report. Indicate the date that you received the hardcopy reports.

2. Review the potassium result on each report.

   a. If any potassium values are not in the reference range (i.e., outside the range of 3.50-5.30 mmol/l), they will be listed below a line of asterisks (*) with the heading, "Test results outside established reference range" (refer to Examples 3 and 5). If a potassium result is outside the reference range, the results should be sent to the clinic without alteration.

   b. Potassium values within the reference range (3.50-5.30 mmol/l) will be listed as per Examples 1, 2 and 4. These values should be covered using a wide, black permanent marker, taking care not to cover the results that may be above or below the potassium value. (Three black markers are enclosed for your use.)

3. Make a copy of the log sheet to keep for your records. Enclose the original log sheet and the laboratory reports in an envelope and get them to the SHEP Clinic as quickly as possible.

4. If you should ever receive a report for presence of urine chlorthalidone, do not, under any circumstances, forward it to the SHEP Clinic. These reports should be discarded. If you receive any of these reports, please call Dr. Barry Davis or Sara Pressel at (713) 792-4480.

5. If you will be out of your office for more than one day, please arrange for another person who is not responsible for the care of SHEP participants to receive the laboratory reports and process them according to Steps 1 through 3 above.

LOG SHEET

RECEIPT OF HARDCOPIES

OF SHEP LABORATORY REPORTS FROM METPATH

Date received: _____

The following laboratory reports from METPATH are attached:

SHEP Participant ID ("Patient")	Acrostic ("Patient Soc. Sec. No.")	Date Drawn

_____

Signature of person receiving reports

MetPath
CENTRAL LABORATORY FACILITY
ONE MALCOLM AVE.
TETERBORO, NEW JERSEY 07608
CLIENT SERVICE: 800-631-1390
800-652-2870
RAYMOND GAMBINO, M.D.
PAUL A. KRIEGER, M.D.
JOSEPH E. O'BRIEN, M.D.

PATIENT | DATE DRAWN | DATE REC'D | DATE OF REPORT
SEX | AGE | ACCT. NO.
PATIENT SOC. SEC. NO. | SPEC. NO.

TEST NAME		RESULT	UNITS	REFERENCE RANGE
CHEM-SCREEN PROFILE		.....		
CALCIUM		9.70	MG/DL	8.80-10.5
BUN		11.0	MG/DL	6.00-23.0
CREATININE		0.90	MG/DL	.60-1.30
URIC ACID		3.90	MG/DL	2.20-8.30
GLUCOSE (CS)		112.0	MG/DL	65.0- 130
TRANSAMINASE, SGO		22.0	I.U./L	10.0-50.0
ALK. PHOSPHATASE		19.0	I.U./L	10.0-45.0
SODIUM		140.0	MMOL/L	134- 143
POTASSIUM		[redacted]	MMOL/L	3.50-5.30
G-GLUTAMYL TRANSPEP.		20.0	UNITS/L	5.00-60.0
HDL CHOLESTEROL		54.0	MG/DL	
PERCENT HDL CHOL.	*(01)	21.2		
LIPOPROTEIN TYPE		NORMAL PATTERN		NORMAL
CHOLESTEROL, SERUM		255.0	MG/DL	120- 290
TRIGLYCERIDES		153.0	MG/DL	50.0- 200

(01) PERCENT HDL CHOLESTEROL

CORONARY HEART DISEASE (CHD) RISK GROUPS	MALE	FEMALE
LOWEST RISK	GREATER THAN 28	GREATER THAN 28
BELOW AVERAGE CHD RISK	22.1-28.0	22.1-28.0
AVERAGE CHD RISK	15.1-22.0	17.1-22.0
HIGH CHD RISK	7.0-15.0	9.0-17.0
HIGHEST RISK	LESS THAN 7	LESS THAN 9

EXAMPLE 1:

Chem Screen Profile with all values in reference range.

Black out the potassium value.

METPATH [redacted]

CENTRAL LABORATORY FACILITY
ONE MALCOLM AVE.
TETERBORO, NEW JERSEY 07608
CLIENT SERVICE 800-631-1390
800-652-2870

RAYMOND GAMBINO, M.D.
PAUL A. KRIEGER, M.D.
JOSEPH E. O'BRIEN, M.D.

[redacted] | [redacted] | DATE DRAWN | DATE RECEIVED | DATE OF REPORT

PATIENT | SEX | AGE | ACCT. NO.

PATIENT SOC. SEC. NO. | SPEC. NO.

TEST NAME		RESULT	UNITS	REFERENCE RANGE
CHEM-SCREEN PROFILE		.....		
CALCIUM		9.50	MG/DL	8.80-10.5
BUN		12.0	MG/DL	6.00-23.0
CREATININE		1.10	MG/DL	.60-1.30
URIC ACID		7.20	MG/DL	2.20-8.30
GLUCOSE (CS)		109.0	MG/DL	65.0- 130
TRANSAMINASE, SGO		34.0	I.U./L	10.0-50.0
SODIUM		137.0	MMOL/L	134- 143
POTASSIUM		[redacted]	MMOL/L	3.50-5.30
HDL CHOLESTEROL		72.0	MG/DL	
PERCENT HDL CHOL.	*(01)	27.2		
LIPOPROTEIN TYPE		NORMAL PATTERN		NORMAL
CHOLESTEROL, SERUM		265.0	MG/DL	120- 290
TRIGLYCERIDES		141.0	MG/DL	50.0- 200

****

TEST RESULTS OUTSIDE ESTABLISHED REFERENCE RANGE

ALK. PHOSPHATASE	111.0	I.U./L	10.0-45.0
G-GLUTAMYL TRANSPEP.	81.0	UNITS/L	5.00-60.0

(01) PERCENT HDL CHOLESTEROL

CORONARY HEART DISEASE (CHD) RISK GROUPS	MALE	FEMALE
LOWEST RISK	GREATER THAN 28	GREATER THAN 28
BELOW AVERAGE CHD RISK	22.1-28.0	22.1-28.0
AVERAGE CHD RISK	15.1-22.0	17.1-22.0
HIGH CHD RISK	7.0-15.0	9.0-17.0
HIGHEST RISK	LESS THAN 7	LESS THAN 9

EXAMPLE 2:

Chem Screen Profile with several values outside of the reference range, with potassium value in the reference range. Values outside of the reference range are listed below the line of asterisks (*).

Black out potassium.

MetPath
CENTRAL LABORATORY FACILITY
ONE MALCOLM AVE.
TETERBORO, NEW JERSEY 07608
CLIENT SERVICE 800-631-1390
800-652-2870
RAYMOND GAMBINO, M.D.
JOSEPH E. O'BRIEN, M.D.
PAUL A. KRIEGER, M.D.

PATIENT | DATE DRAWN | DATE REC'D | DATE OF REPORT

SEX | AGE | ACCT. NO.

PATIENT SOC. SEC. NO. | SPEC. NO.

TEST NAME		RESULT	UNITS	REFERENCE RANGE
CHEM-SCREEN PROFILE		.....		
CALCIUM		9.20	MG/DL	8.80-10.5
BUN		15.0	MG/DL	6.00-23.0
CREATININE		1.00	MG/DL	.60-1.30
URIC ACID		6.10	MG/DL	2.20-8.30
GLUCOSE (CS)		93.0	MG/DL	65.0- 130
TRANSAMINASE, SGO		21.0	I.U./L	10.0-50.0
ALK. PHOSPHATASE		24.0	I.U./L	10.0-45.0
SODIUM		141.0	MMOL/L	134- 143
G-GLUTAMYL TRANSPEP.		15.0	UNITS/L	5.00-60.0
LIPOPROTEIN TYPE		NORMAL PATTERN		NORMAL
CHOLESTEROL, SERUM		222.0	MG/DL	120- 290
TRIGLYCERIDES		96.0	MG/DL	50.0- 200
HDL CHOLESTEROL		42.0	MG/DL	
PERCENT HDL CHOL.	*(01)	18.9		

****

TEST RESULTS OUTSIDE ESTABLISHED REFERENCE RANGE

POTASSIUM	5.50	MMOL/L	3.50-5.30

(01) PERCENT HDL CHOLESTEROL

CORONARY HEART DISEASE (CHD) RISK GROUPS	MALE	FEMALE
LOWEST RISK	GREATER THAN 28	GREATER THAN 28
BELOW AVERAGE CHD RISK	22.1-28.0	22.1-28.0
AVERAGE CHD RISK	15.1-22.0	17.1-22.0
HIGH CHD RISK	7.0-15.0	9.0-17.0
HIGHEST RISK	LESS THAN 7	LESS THAN 9

EXAMPLE 3:

Chem-Screen Profile with potassium value outside of the reference range. Values outside of the reference range are listed below the line of asterisks (*).

Do not black out the potassium value.

[redacted]

CENTRAL LABORATORY FACILITY
ONE MALCOLM AVE.
TETERBORO, NEW JERSEY 07608
CLIENT SERVICE 800-631-1390
800-652-2870

RAYMOND GAMBINO, M.D.
PAUL A. KRIEGER, M.D.
JOSEPH E. O'BRIEN, M.D.

[redacted]

PATIENT
SEX
AGE
PATIENT SOC. SEC. NO.
DATE DRAWN
DATE REC'D.
DATE OF REPORT
ACCT. NO.
SPEC. NO.

TEST NAME	RESULT	UNITS	REFERENCE RANGE
POTASSIUM, SERUM	[redacted]	MMOL/L	3.50-5.30

EXAMPLE 4:

Single potassium in the reference range.

Black out potassium value.

MCTPATH
CENTRAL LABORATORY FACILITY
ONE MALCOLM AVE.
TETERBORO, NEW JERSEY 07608
CLIENT SERVICE 800-631-1390
800-652-2870
RAYMOND GAMBINO, M.D.
JOSEPH E. O'BRIEN, M.D.
PAUL A. KRIEGER, M.D.

PATIENT | DATE DRAWN | DATE REC'D | DATE OF REPORT

SEX | AGE | ACCT. NO.

PATIENT SOC. SEC. NO. | SPEC. NO.

TEST NAME	RESULT	UNITS	REFERENCE RANGE
**********			
TEST RESULTS OUTSIDE ESTABLISHED REFERENCE RANGE			
POTASSIUM, SERUM	2.90	MMOL/L	3.50-5.30

EXAMPLE 5:

Single potassium value outside of the reference range. Values outside of the reference range are listed below the line of asterisks (*).

Do not black out the potassium value.

APPENDIX E

PHYSICAL EXAMINATION PROCEDURES

E.1 Height and Weight

Height is measured once, at Baseline Visit 1. The participant, without shoes, should stand with his back against the measuring rod, with his heels touching it and his head against it at the top. The horizontal bar should be brought down to rest on the top of the head, snuggly but without excessive pressure. Height should be read and recorded before the participant steps off the scale.

Fractions of inches:

If the fraction is less than 1/2 inch, drop it.

If the fraction is more than 1/2 inch, raise the height to the next higher inch.

If the fraction is exactly 1/2 inch, drop it if the whole number is an even one. Raise it to the next inch if the whole number is an odd one.

Examples:
67-1/4 inches = 67 inches
67-3/4 inches = 68 inches
67-1/2 inches = 68 inches
68-1/2 inches = 68 inches

Unlike height, weight is measured regularly at every clinic visit throughout the course of the study. The weight is measured in pounds, using a standard balance beam scale, without shoes, without outer clothing or men's jacket or suit coat. The preceding rule regarding fractions in inches applies also to fractions in pounds (see above). Only whole pounds are to be recorded.

E.2 Physical Examination

The complete physical examination is required at Baseline Visit 1 and at all annual examinations. At certain other visits, short examinations will be necessary if positive responses are obtained to selected side effects on form SH42.

The physical examination should be accomplished in a well-lighted, draft-free room with air temperature adjusted so that the scantily-covered subject is comfortable. A firm mattressed bed or an examining table covered with a pad should be used. Either an adjustable examining table or pillows should be available as needed to keep the subject comfortable during examination.

In preparation for examination, the subject should disrobe completely (with the exception of undershorts or panties). Any standard type of examining gown or covering for the unclad subject that allows appropriate access to areas to be examined may be used.

a. Skin

Comment on observations that the examiner considers as abnormal.

b. Head, ears, nose, throat

The ears are to be examined with an otoscope. The throat should be examined with proper light and using tongue depressor. Comment on observations that the examiner considers abnormal.

c. Eyes

An opthalmoscope should be used to visualize the fundi. If the fundi cannot be visualized due to cataracts or other reason, "Not Visualized" should be checked on the form and a comment entered in the right-hand column. Abnormalities of the fundus include:

(1) Arteriolar spasm/focal constriction

(2) A-V nicking

(3) Hemorrhages

(4) Exudates

(5) Papilledema

If any of the above are present in either eye, the fundi should be considered as "abnormal," and comments entered into the right-hand column of the form.

Other eye abnormalities include any other observation that the examiner considers as abnormal.

d. Neck

Items of particular interest in the neck include jugular venous pressure, carotid bruits, and thyroid abnormalities.

For carotid bruits and carotid pulses, it should be indicated in the checkboxes whether the right side only, left side only, or both sides (bilateral) are affected.

Other conditions that the examiner considers to be abnormal should be noted.

e. Lymph nodes

Examine lymph nodes in the neck, axillary areas and inguinal areas. Any observations considered to be abnormal by the examiner should be noted.

f. Chest, lungs

The chest and lungs should be examined with the subject in the sitting position. Specific items that should be checked on the form include bilateral râles that do not clear with coughing, respiratory rate 20+, and wheezing. Other observations considered to be abnormal by the examiner should be noted.

g. Heart

The heart should be examined with the subject in the supine position.

Specific items that should be noted on the physical examination form are:

- PMI (point of maximal impulse) more than 2 centimeters lateral to midclavicular line
- Any murmur (specify systolic or diastolic in Comments section)
- Presence of third heart sound
- Presence of fourth heart sound
- Irregular pulse

Other conditions considered as abnormal by the examiner should be noted as "Other" and described in the Comments section.

h. Breasts

Any conditions considered as abnormal by the examiner should be described in the Comments section.

i. Abdomen

Specific items that should be noted on the physical exam form are:

- Liver span 10 centimeters or more
- Abnormal abdominal pulse
- Any mass
- Bruit

Any other conditions considered to be abnormal by the examiner should be noted as "Other" and described in the Comments section.

j. Extremities

Specific items that should be noted on the physical examination form are:

- Pitting ankle edema
- Femoral bruit
- Any peripheral pulses absent or markedly diminished--includes femoral, popliteal and tibial; if any pulses are affected, notes should be made in the Comments section.

Any other condition of the extremities considered to be abnormal by the examiner should be described in the Comments section.

k. Neurological

Specific items that should be examined are:

- Gait testing--

Ask the participant to walk in bare or stocking feet or in flat shoes for 15 feet or so. A left hemiparetic gait is marked by decreased left arm swing with the arm bent at the elbow with a stiffness to the left leg so that the leg is moved forward often without much knee bend

or foot bending upward and the foot tends to swing out and in a semicircle as it comes forward. A right hemiparetic gait would be similar on the right side. Unable to assess means that the participant is unable to walk or refuses.

- Walking on toes--

Ask the participant to walk on his or her toes (on this test and the next you can hold the hand to help balance). If they can take four or more steps on the balls of each foot without touching the heels to the floor, check normal. Unable to assess means that the participant is unable to walk or refuses.

- Walking on heels--

Ask the participant to walk on the heels. (Participants often feel more secure if you hold their hand for this.) If four or more steps can be taken with each foot on the heels without touching the ball of the foot on the floor, that is normal. Unable to assess means that the participant is unable to walk or refuses.

- Station--

Station is tested by having the participant stand with both feet together and eyes closed and maintain the stance for 30 seconds. If the participant cannot do the test with eyes closed, try with the eyes open and, if successful, the participant may try again with eyes closed. Participant confidence is often better if the clinician stands near by during test.

- Cranial Nerves--

For assessment of facial weakness, watch the participant's face during the interview. Ask the participant to show their teeth or gums (the clinician may show them how). There should be a symmetrical lateral movement of the mouth.

- Visual Fields--

Assessment of visual fields compares the participant's visual fields with the examiner's. With the participant facing the examiner, about 3 feet apart, the participant is asked to keep looking at the examiner's nose. The examiner looks at the participant's eyes and hold his or her own hands out laterally so that from the corner of his own eye he can see his fingers if they move. The examiner wiggles the fingers on one or both hands and asks the participant to identify whether the fingers are wiggled on one side or both sides. First, the hands are held above the meridian or in the upper part of the participant's gaze and then lower, in the lower part of the participant's gaze.

A simple sequence might be to wriggle fingers of both hands in the upper fields and if the response is "both sides," move the hands down and check with only the left or right fingers moving and if correctly identified, try both sides moving. If correctly identified, the test is over and normal. If the responses are inconsistent, or the participant can identify one side if moving, or either side but not both sides when fingers are moving on both sides, possible is checked. Participants who cannot identify movement on the left or on the right side have an abnormality of the visual field.

"Unable to assess" refers to other visual problems that would affect the assessment of visual fields.

- Motor Wrist Extensors--

Strength is tested by asking the participant to make a fist and bend the hand up. The examiner tries to bend the hand down against the participant's resistance. If the participant is unable to resist a mild pressure, a weakness is present in that wrist.

- Coordination--

Each hand is patted individually on the participant's knee "as fast as you can." Usually there is nearly equal speed with both hands, sometimes a little less speed with the non-dominant hand (the left hand in right-handed people). If there is a noticeable difference or slowness, or if the non-dominant hand is faster, an abnormality of coordination is present.

- Reflexes--

Patellar Tendon--With the participant sitting on a table and the legs dangling down, the patellar tendon is struck with a reflex hammer just below the knee cap. The participant should be relaxed. The reflex is the contraction of the anterior thigh muscle and forward movement of the lower leg. The speed and size of movement on one side is compared with the other side. The reflexes can be repeated as necessary.

Babinski Sign--With the participant relaxed but warned that the clinician is about to scratch the bottom of the foot, the foot is scratched along the outside edge on the bottom (using a key or similar rough but not sharp edge) from the back of the foot forward. The usual normal response is downward flexion of the toes or occasionally no response. A positive Babinski is the upward flexion of the big toe and sometimes associated with spreading the other toes.

Any other neurological condition considered to be abnormal by the examiner should be described in the Comments section. Details of the abnormalities listed above should also be described.

I. Other Physical Findings

If other findings are observed that do not belong in the above categories (e.g., comments on general appearance), or the examiner requires extra space for comments, this section of the form should be used.

APPENDIX F

ADMINISTRATIVE PROCEDURES FOR PARTICIPANT SCHEDULING AND DATA HANDLING

F.1 Introduction

The major responsibility for collecting and reporting valid and reliable data lies with the Clinical Center and its staff. To ensure consistency of the data across, as well as within the clinics, procedures for collecting and reporting information are standardized.

F.2 Preparing for a Visit

To facilitate the flow of a clinic visit, it is suggested that the following tasks be performed prior to the visit:

a. Remind the participant in advance of the upcoming appointment. The reminder can take the form of a telephone call, letter, or postcard (perhaps self-addressed by the participant at his/her previous visit). In addition, it may be helpful to follow this with a telephone call the day before the visit. When the participant is reminded to return for the next visit, he or she should also be reminded to bring all unused pills and empty bottles to the clinics.

b. Retrieve the participant's medical file.

c. Consolidate pertinent information received at or since the last completed study interview for the examining clinician's review Central or local laboratory test results, information concerning hospitalization, new medication prescription, and blood pressure at the last few visits).

d. Place the participant's ID number and acrostic on all forms pertinent to the scheduled visit.

e. Schedule laboratory test appointments, if necessary.

f. Prepare for the shipment of laboratory specimens by appropriate laboratory forwarding forms, if necessary.

g. Obtain the participant's potential supply of study medications for either continuing the same dosage or being stepped-up.

F.3 Scheduling Study Visits

At the time of randomization, a required visit schedule will be generated, containing a "target window" for the two-month and all quarterly visits. (The one-month visit will have already been scheduled by the time the visit schedule is generated.)

The two-month visit target date is exactly two months from the date of randomization (i.e., same day number, two calendar months later). The target window is ±7 days. For example, a participant randomized on April 3, 1985, would have a two-month target date of June 3, 1985, and a visit window of May 27, 1985, to June 10, 1985.

The quarterly and annual visit target dates are at exactly three-month intervals from the date of randomization (i.e., same day number, at three-month intervals). The target window is ±14 days. For example, a participant randomized on April 3, 1985, would have the following quarterly visit schedule each follow-up year:

	Earliest Date	Target Date	Latest Date
1st Quarter	June 19	July 3	July 17
2nd Quarter	September 18	October 3	October 17
3rd Quarter	December 20	January 3	January 17
Annual	March 20	April 3	April 17

The first visit scheduled in these windows will be the two-month, quarterly or annual visit as applicable. Extra visits occurring in a visit window, after a visit has already been completed in that window, is either another visit required by SHEP protocol or an interim visit. In cases where an annual visit cannot be scheduled in the appropriate target window, the annual visit may be accomplished anywhere from -6 to +6 weeks from the target (-4 to +4 weeks from the earliest and latest dates); visits scheduled outside this time frame should not be considered as annual visits. In cases where a quarterly visit cannot be scheduled in the target window, that quarterly visit is a missed visit. The remaining visit windows will, however, remain the same, and every effort should be made to keep the participant on that schedule.

For regular quarterly visits after the first annual visit, the windows initially provided will repeat each year. For example, using the windows listed above, the next quarterly visit window after the first annual (e.g., March 20-April 17, 1986) would be June 19-July 17, 1986.

F.4 Rescheduling Individual Visit Components

On rare occasions, it may be necessary to reschedule part of a visit because of equipment failure, employee absence, etc. For example, an ECG machine may fail or the primary clinician may not be available to conduct a physical exam, or the participant may not have fasted for 12 hours prior to certain annual visits. If any component of a clinic visit is missing, the visit is not considered complete; therefore, no data should be entered into the computer, and the form should not be sent to the Coordinating Center. The next visit should not be scheduled until all the necessary requirements for that visit are fulfilled. This should be done as soon as possible. The next regular visit is then scheduled from the date of completion.

The "Do Not Know" option, when it appears on a study form, must not be used for data which are going to be filled in at a later date. (This option is only used in the case of an impasse in clinical judgments.) Rather, it should be left blank, temporarily. Clinic staff are requested to call the Coordinating Center on a case-by-case basis if circumstances do not allow the above procedure to be followed.

The following situations should be reviewed when rescheduling is necessary:

- In the case of baseline visits, all eligibility information must be obtained before the BL2 visit is scheduled (for example, a local serum creatinine, if required).
- After randomization, if for any reason blood cannot be drawn or any of the behavioral evaluation cannot be obtained at BL2, the Step 1 medication cannot be started. These interviews and procedures must be rescheduled as soon as possible at which time the drug treatment can begin; a 48-hour delay is allowed in starting medications.
- In the case of post-randomization visits, rescheduling of components is less of a problem. However, it is important that components of the quarterly and annual visits be completed at the scheduled time of those respective visits, if at all possible, because they are considered evaluation points for certain measurements.

When a visit component is rescheduled, special care should be taken to copy the date of the applicable clinic visit, and the sequence number of that clinic visit, to the auxiliary forms that are required, in order that all procedures carried out at that visit may be readily identified.

F.5 Missed Visits

Every effort must be made to avoid missed visits (see Section F.2, "Preparing for a Visit"). However, if a participant fails to come in for a scheduled visit, or a visit within the window, the Clinical Center should contact him or her by telephone, mail, or as a last resort by home visit. In some cases a telephone call from the Clinic Coordinator stressing the importance of a consistent follow-up may be the incentive required for the participant to continue active participation in the study. However, some participants respond more favorably to a telephone call from the project physician. The visit may be completed at another SHEP Clinical Center, if the participant and both Clinical Centers agree.

Participants should be encouraged to report at scheduled visits, even if they are not adhering to the drug regimen. If a clinic, home, or telephone visit does not take place in a quarterly or annual window, then an SH51 (Report of Missed Quarterly or Annual Visit) should be completed (see Section 9.18).

Suggestions for maintaining rapport with the patient and preventing the patients from losing confidence in the Clinical Center study are as follows:

a. Initial Participant Orientation

It will be difficult to maintain rapport with the participant who experiences or perceives an experience of a side effect or adverse reaction, unless the possible occurrence of the problem has been explained to him or her prior to randomization. All other aspects of the study should be thoroughly explained at the initial orientation such as the expected visit schedule, lab tests, etc. A well planned, thorough orientation (see Section 2.4.4 and Appendix B) means no surprises for the participant and better study compliance.

b. Scheduled Visits

Immediately upon completion of a scheduled visit, the participant may be reminded of pre-randomization discussion of complications. The participant will then be better able to recall or recognize severe complications, if they occur.

c. Other Reasons for Loss of Cooperation

A participant's lack of cooperation and/or decreased commitment to the study may be the result of many reasons. For example, long waits may occur during the exam. If delays are unavoidable, the cause of delay should be explained to the participant. If there are problems in transportation to the clinic, assistance in making other arrangements might be offered. Although efforts have been made to format study forms to make them readable, some participants have reading and/or eyesight difficulty. Some participants will have problems with hearing. In general, impersonal treatment will tend to aggravate any problems that may exist while consideration for the participant will increase the probability that he or she will cooperate and adhere to the study protocol.

F.6 Permanent Transfer of Participant to Another Clinical Center Area

Participants who permanently move into another Clinical Center area may transfer to that Clinical Center permanently. Between-center communications should be done before the participant is approached regarding the transfer. This should involve finding out what the new center provides in the way of transportation, extra travel money, case management situation, etc. This should smooth the way, and let the participant know what to expect. With the participant's permission, his or her SHEP Clinic records and medications should be mailed to the new Clinical Center, with a cover letter from the original Clinical Center's Principal Investigator. The former Clinical Center is to be telephoned and notified of receipt of records and medication by the participant's new Clinical Center.

The Coordinating Center should be notified immediately but will not officially transfer a participant until an SH67 has been received from the old Clinical Center, changing the first two digits of the ID number.

If a participant does not agree to transfer to the new Clinical Center, he or she remains a responsibility of the former Clinical Center for telephone follow-up purposes.

F.6.1 Participants Temporarily Visiting in Another Clinical Center Area

In some cases, participants may routinely visit another Clinical Center area for a few months each year (e.g., participants with winter homes in Miami). These participants may complete their required visits at another Clinical Center if they agree and the other center agrees. Records and medications should be handled similar to a permanent transfer, except that the participant's ID does not change.

F.7 Participants Moving Within One Clinical Center Area

Participants changing their place of residence within one Clinical Center area, but who continue to attend the same Clinic, should inform the Clinic of this address change at the time of their next Clinic Visit by amending the SHEP Participant Information Sheet, form SH02. There is no need to report this change of residence to the Coordinating Center. The Participant Information Sheet should be presented to the participant at least semi-annually for his or her review to ensure that all the information is current.

F.7.1 Participants Moving to An Area With No Clinical Center

Participants changing their place of residence to an area with no Clinical Center remain the responsibility of the original Clinical Center, for telephone follow-up.

F.8 Housebound Participants

Participants unable or unwilling to attend the clinic should nonetheless be contacted quarterly and interviewed. This interview will most likely occur by telephone but in some cases a home visit may be possible. Of course, not every procedure can be carried out in these cases. Procedures that are required and procedures that may be omitted for home and telephone visits are summarized in Tables F-1 and F-2 and on the appropriate visit forms. A telephone or home contact should should be assigned a sequence number, like any other type of visit. If possible SHEP events are ascertained at a telephone visit, the participant may be willing to receive and sign an authorization for hospital or medical records and mail it back to the clinic, if a blanket authorization has not been signed at baseline, or a blanket authorization is not acceptable.

As many home visits as feasible should be carried out. However, priorities for home visits should be as follows: (2) keep those still on SHEP medications on protocol, (2) for those who have not yet had a stroke endpoint, to document a possible stroke, (3) for documentation of secondary endpoints, (4) annual follow-up.

TABLE F-1

Procedures That Are Required for Home and Telephone Visits

	Annual Visits	Other Visits
Home	Take-home form (SH44) SH02 review BP, pulse *ECG/2-minute rhythm strip Compliance, except pill count General well-being Side effects Review of medication history *Physical examination (use self-report height and weight) Clinician judgment and endpoint review Protocol review Blood pressure review Medication prescription Behavioral evaluations	BP, pulse Compliance, except pill count General well-being Side effects Protocol review Blood pressure review Medication prescription Behavioral evaluations
Telephone	(All of the above except:) BP, pulse (use self-report BP item) ECG/2-minute rhythm strip Physical examination (use self-report height and weight) Behavioral evaluations	(All of the above except:) BP, pulse Behavioral evaluations

*May be omitted if not feasible.

TABLE F-2

Procedures That May Be Omitted for Home and Telephone Visits

	Annual Visits	Other Visits
Home	Lab work (blood or urine) Pill count ECG/two-minute rhythm strip Physical examination	Lab work (blood or urine) Pill count
Telephone	(In addition to the above:)	(In addition to the above:)
	Pulse, BP, height, weight (Use self-report items as instructed on form for BP, height, weight) Any behavioral evaluation	Pulse, BP, weight Any behavioral evaluation

F.9 Documenting and Locating Participants Who Are Lost to Follow-up

In the case of those participants who miss clinic visits and cannot be contacted, follow-up efforts should be documented carefully in the following manner:

1) Attempts to contact the participant following the initial missed visit should be recorded in his/her chart. Date and method of contact should be included in the documentation.

2) An SH51 (Report of Missed Quarterly or Annual Visit) should be completed for each missed visit, carefully documenting attempts to locate and contact. Efforts to locate these participants should continue until the end of the trial.

The Clinical Centers should also regularly update the SH02 (Participant's Information Sheet) with information such as addresses of potential contacts. It is recommended that the participant be shown his/her SH02 at least semiannually as a routine part of the clinic visit, and asked to verify the information on it, especially the potential contacts. If the participant moves out of the area without contacting the Clinical Center and does not leave a forwarding address, a special effort should be made by the clinic to track down this participant. The following other sources may be helpful in identifying the whereabouts of the participant:

Neighbors
Neighborhood merchants
Unions, professional societies
Clergymen
Utility companies
Health and welfare agencies
Social Service exchanges
School boards
Voter registration offices
Public housing and relocation authorities
Car registration
Many other imaginative ways

F.10 Refusals

Participants who withdraw (refuse further participation) should remain the target of surveillance efforts every three months until the conclusion of the study. An SH51 (Report of Missed Quarterly or Annual Visit) should be completed when the upper window for each missed quarterly or annual visit is passed and the participant is still refusing.

In the case of participants who refuse further participation, and who may be antagonized by follow-up attempts, it is recommended that the participant be told at the initial refusal that the purpose of the follow-up contacts is to monitor his or her general well-being and whereabouts--not to try to talk them back into the study.

The quarterly contact may then be made by telephone, as described in Section F-8 for housebound participants.

F.11 Evaluation Summaries

Since some events require evaluation over time (e.g., escape blood pressure), it will be convenient for the clinic to have several items of data available from all clinic visits on a summary sheet. An example has been provided here; the use of this format is optional, but some type of summary will facilitate the determination of what is happening to the participant over time.

F.12 Initial Contact Visit Reports

Each SHEP Clinic will submit a summary of Initial Contact Visits as of the last Friday of each month. These reports will be cumulative (i.e., from March 1, 1985) and will contain the following information by antihypertensive medication status at Initial Contact:

- number of Initial Contact Visits
- number of participants eligible for the next visit (Baseline Visit 1 or Drug Evaluation Visit 1)
- number of participants scheduled for the next visit.

A format for these reports is attached.

An Initial Contact Visit is any personal contact by which a person is screened for participation in the SHEP using:

- the medical exclusion items on the SH01B and SH01C (this may be accomplished over the telephone); and/or,
- SHEP blood pressure procedures, completed by a SHEP certified blood pressure observer

A "pre-screen" type of procedure during which a single blood pressure is taken (e.g., at health fair screenings by the AHA or Red Cross) or a screening of medical records does not count as an Initial Contact Visit.

SHEP CLINIC VISIT SUMMARY

Name: _____

SHEP ID: _____ - _____ - _____

Acrostic: _____

Date	Seq	30-sec Pulse	SBP	DBP	Weight	Felt Unwell	Doctor	Hospital	Event	Prescribed This Visit C	A	R	Other	K	Uric Acid	SHORTCARE TS1	TS2	Other

SHEP Initial Contact Report

DAY: _____ DATE: ____/____/____

CLINIC NAME: _____ CLINIC NUMBER: _____

	Medication Status at Initial Contact		
	On Meds	Not on Meds	TOTAL
Total number of Initial Contacts as of above date			
Total eligible for next visit (see footnote)			
Total scheduled for next visit (see footnote)			

"Next visit" refers to BV1 for persons not on medications at Initial Contact, and DEV1 for persons on medications at Initial Contact.

Person completing report: _____ _____
Signature ID Code

F.13 General Directions for Data Recording

No matter how well you conduct your interviews, the information you gain will be lost for this study unless it is carefully recorded. Data well recorded, on the other hand, add measurably to the information we are gathering on the differences between the two treatment groups being studied. The following are general procedures to be followed in filling out study forms:

a. PRINT IN BOLD CAPITAL LETTERS. The importance of printing legibly cannot be overstressed. As basic as clear printing is, much information is garbled simply by sloppy handwriting. This information, if it can be retrieved at all, takes extra hours to process because it must be carefully "translated" first. Print clearly and use a black pen. Press hard enough so that information can be clearly seen on any NCR copies.

b. Dates

1) Enter dates numerically

2) Use leading zeros as necessary

Example: December 1, 1985, is recorded as:

1 2	0 1	8 5
Month	Day	Year

3) When an exact date cannot be remembered, but the month and year are known, enter the information that is known in the usual manner; enter 99 for the unknown information; e.g., "sometime during September of 1985" would be recorded as:

0 9	9 9	8 5
Month	Day	Year

c. Times

1) Hours are 1-12, with a box provided for a.m. or p.m.; do not use maritime hours (0-24).

2) Use leading zeros as necessary

Example: 2:15 p.m. would be recorded as:

0,2	:	1,5	☐ a.m. ☒ p.m.
Hour		Minute	

3) When asking the participant for time (e.g., time of event onset), and an hour cannot be remembered, but "morning," "afternoon," or "evening" is known, time should be recorded as (for example):

9,9	:	0,0	☒ a.m. ☐ p.m.
Hour		Minute	

If the minutes cannot be remembered, or approximated, 00 should be used in the space provided to record minutes.

4) Responses

(1) Check boxes

Place an "X" in the box that corresponds to the answer given by the participant or determined by the appropriate clinic staff. Do not use a "√" or other mark, as they are more difficult to find. Example:

☒ Eligible for BL1
☐ Continue evaluation
☐ Not eligible for SHEP

(2) Space for written explanation

Fill in the space with the participant's answer when an explanation or specification is required. Please print clearly.

Example:

Appointment not made; reason	WILL CALL

5) Boxes for numerical recordings (e.g., blood pressures and dates):

a) Use leading zeros as necessary; e.g.,

0,9,2

b) In the rare case of unknown numerical values, the item should be coded with 9s.

Standard SHEP forms, once completed, should be edited locally to ensure that both the original and the copy are complete and legible throughout. Any illegible sections on either copy should be corrected immediately, if necessary, by contact with the staff member who completed that portion of the form.

All corrections to forms should be made by marking through the incorrect item and writing the correct item above. Do not attempt to erase. Do not use any liquid paper product.

F.14 Data Entry and Transmission

F.14.1 General Description

Study data are being entered into microcomputer files by data entry personnel at each Clinical Center. These people will have been specially trained by the Coordinating Center programming staff, or trained by a centrally-trained operator. A complete description of the data entry and transmission system may be found in the SHEP Data Entry and Transmission Manual, under separate cover.

F.14.2 Multiple Sites in a Clinical Center area

Some centers will be seeing participants and filling out SHEP forms at more than one site. In these cases, arrangements must be made locally to periodically transfer hardcopy forms to the microcomputer location for data entry.

F.14.3 Transfer of Hardcopy Forms to the Coordinating Center

Most SHEP forms are single-copy forms (no NCR copy). Although most of these are data entered (see Summary of SHEP Forms, page F-26), the Coordinating Center will not receive a hardcopy.

Forms that are NCR forms should be separated to give two complete forms (a white copy and a yellow copy). Pages of individual copies should be stapled together immediately. Originals should always be used for data entry. The forms that are exceptions to this are the ECG Coding Form (SH10), the CT Scan Coding for Stroke (SH14) and the CT Scan Coding Form for Dementia (SH16)--these have an original and three NCR copies. In these cases, the Clinical Center should retain only the last copy (goldenrod), and the rest should be forwarded with the ECG or CT scan to the Coordinating Center. Do not separate the SH14 and SH16 forms from their cardboard backing.

Every effort should be made to enter forms onto the microcomputer files the same day that they are completed; in any case, they should be entered no later than the following Monday, so that they may be electronically transmitted to the Coordinating Center per the schedule.

With each data transmission, a listing (batch sheet) is created locally of those forms that are electroncially transmitted, listing form type, SHEP ID, acrostic, and date completed. The forms are listed by form type, in the order that they are entered. Several forms will be flagged by an asterisk (*). The flagged forms should be photocopied and sent to the Coordinating Center with the batch sheet.

Hardcopy forms are sent to the Coordinating Center in batches. There are three types of hardcopy batches: (1) forms that are electronically transmitted and the flagged hardcopies are sent to the Coordinating Center on a routine schedule; (2) morbidity and mortality forms, some of which are electronically transmitted and some are not; and (3) ECGs. The batching procedures for each of these are described below.

1. Routine batches of hardcopies--These batches include:

    Photocopies of flagged forms

    Required yellow copies--SH32, SH49

    SH67s for all except SH20-23

As soon as elecronic transmission is accomplished, the routine batches of hardcopies should be put in the same order as they are listed on the computer-generated batch sheet. They should be packaged with the batch sheet and sent to the Coordinating Center, to the attention of Barbara Raslan. A padded envelope should be sufficient for packaging. A copy of each batch sheet should be kept at the Clinical Center for their records.

2. Morbidity and mortality forms (SH14, SH16, SH20-SH28, SH31, and SH67s) for these forms--Of these forms, the SH20-23, SH31 and SH67s for these forms are data entered and electronically transmitted to the Coordinating Center. However, they should be sent to the Coordinating Center in a separate batch, within 48 hours of completion, along with ancillary documentation of the event if appropriate (SH14, SH16, SH24-28, records). A separate batch sheet is provided and should be photocopied at the Clinical Center as needed. For each hardcopy to be sent to the Coordinating Center, the form type, participant ID, acrostic and the date completed should be filled out as indicated. The hardcopy forms should be sent in the same order that they are listed on the batch sheet, packaged with the batch sheet, and sent to Terri Henry (Morbidity and Mortality Monitor) at the Coordinating Center. A copy of the batch sheet should be kept at the Clinical Center.

3. ECGs--ECGs and two-minute rhythm strips are routinely sent to the Coordinating Center at baseline (randomized participants only), two years and the final annual visit. Each participant's strips are attached to an SH10 (SHEP ECG Routing and Coding Form). These forms are not electronically transmitted and therefore are not listed on the computer-generated batch sheet. These should be listed on the separate batch sheet, listing ID, acrostic, and date of tracing and whether a two-minute strip is attached. The strips and forms should be attached to the batch sheet, and these may be sent to the Coordinating Center with regular batches of SHEP forms.

F.14.4 Problem Forms

Rarely, a form that requires data entry at the Clinical Center level will have missing or invalid data such that the SHEP data package will not accept it. When this occurs, the forms should be listed (form type, SHEP ID, acrostic, date of visit or completion) in a letter that describes the data entry problem, and the forms should be sent to the Coordinating Center in a separate envelope from any other batch of forms. The cover letter serves as the batch sheet for these forms.

SHEP BATCH SHEET

Center Name and Number: _____

Date forms mailed to Coordinating Center: ____/____/____

Form Type	SHEP ID	Acrostic	Date of Tracing	No 2-Minute Strip (√)	Form Type	SHEP ID	Acrostic	Date Form Completed	Form Type	SHEP ID	Acrostic	Date Form Completed
SH10					SH20				SH24			
									SH25			
					SH21							
									SH26			
SH14					SH22							
									SH27			
SH16												
					SH23							
									SH28			

Revised 8-88

SUMMARY OF SHEP FORMS

Form	Name	Data Entry	NCR	Coordinating Center Copy	Comments
SH01	Initial Contact	No	No	None	
SH02	Participant Information Sheet	No	No	None	
SH03	SHEP Baseline Demographic Information and Medication History	Yes*	No	None	
SH04	SHEP Baseline Medical History	Yes*	No	None	
SH05	SHEP Drug Evaluation Visit Summary	No	No	None	
SH06	Baseline Visit 1	Yes	Yes	Yellow	
SH07	Baseline Visit 2	Yes	Yes	Yellow	
SH08	Clinic Visit Documentation	Yes	No	None	
SH09	SHEP Annual Clinic Visit	Yes	No	None	
SH10	SHEP ECG Coding Form	No†	Yes (4)	White, yellow, pink	Clinic keeps goldenrod copy
SH11	Local Laboratory Results	Yes	No	None	
SH13	Receipt of Alert Level from Central Laboratory	Yes	No	None	
SH14	SHEP CT Scan Coding Form for Stroke	No†	Yes (4)	White, yellow, pink	Clinic keeps goldenrod copy (page 1 only)
SH16	SHEP CT Scan Coding Form for Dementia	No†	Yes (4)	White, yellow, pink	Clinic keeps goldenrod copy (page 1 only)
SH20	Initial Notification of Morbid Event	Yes	Yes	White	
SH21	Final Report of Morbid Event	Yes	Yes	White	
SH22	Initial Notification of Death	Yes	Yes	White	
SH23	Final Report of Death	Yes	Yes	White	
SH24	Interview with Participant, Next-of-Kin, or Personal Clinician for Morbid Event	No	Yes	White	
SH25	Interview with Participant's Physician in the Case of a Death	No	Yes	White	

*The SH03 is required for all participants who attend Baseline Visit 1; the SH04 is required for all participants who are blood pressure-eligible at Baseline Visit 1.

†Entered at Coordinating Center

SUMMARY OF SHEP FORMS
(Continued)

Form	Name	Data Entry	NCR	Coordinating Center Copy	Comments
SH26	Interview with Witness to Death or Next of Kin	No	Yes	White	
SH27	SHEP Neurological Evaluation for Stroke	No†	Yes	White	
SH28	SHEP Neurological Evaluation for TIA	No†	Yes	White	
SH30	SHEP SHORT-CARE Form	Yes	No	None	
SH31	Diagnostic Criteria for Dementia	Yes	Yes	White	
SH32	Diagnostic Criteria for Depression	Yes	Yes	Yellow	
SH33	Activities of Daily Life	Yes	No	None	
SH34	Social Network Questionnaire	Yes	No	None	
SH35	SHEP Behavioral Evaluation--Part II	Yes	No	None	
SH36	SHORT-CARE Scoring Sheet	No	No	None	
SH40	Compliance Evaluation	Yes	No	None	
SH42	Side Effects Questionnaire	Yes	No	None	
SH44	Annual Medical, Medication and Habits History	Yes	No	None	
SH49	Report of Study Drug Disclosure	Yes	Yes	Yellow	
SH51	Report of Missed Quarterly or Annual Visit	Yes	No	None	
SH62	SHEP Drug Compliance Worksheet	No	No	None	
SH66	SHEP Interviewer/Observer Codes	No	No	Copy	Re-submit as new certifications, recertifications, staff additions occur
SH67‡	Corrections to Transmitted Data	Yes	Yes	Yellow	

‡May be initiated at Coordinating Center.