

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial



Manual of Operations

ALLHAT MANUAL OF OPERATIONS
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Added:

Doxazosin Closeout Procedures
Study Closeout Procedures

OVERVIEW

ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT)

SUMMARY

I. Overview

ALLHAT consists of two randomized clinical trials containing patients aged 55 years and older including at least 55% African-Americans (self-described "Blacks"). The high blood pressure part will enroll 40,000 patients. Its purpose is to determine whether combined fatal coronary heart disease (CHD) plus non-fatal myocardial infarction differs between diuretic treatment and three alternative treatments (calcium antagonist, ACE inhibitor, and alpha blocker).* Because of the established benefit of antihypertensive treatment in reduction of stroke, illness and death from cardiovascular diseases, and death from all causes combined, the trial will *not* include a placebo or no-treatment control group.

The cholesterol-lowering treatment part will enroll 20,000 of the 40,000 patients in the high blood pressure part. Based on the results of a screening blood lipid profile, men and women with moderately elevated LDL-cholesterol will be randomized to receive a cholesterol-lowering diet plus pravastatin, or the diet plus any cholesterol-lowering therapy that their doctor might prescribe, if any ("usual care"). The purpose of the cholesterol-lowering trial is to determine whether lowering serum cholesterol with pravastatin will reduce death from all causes combined as compared to a control group receiving "usual care".

Table I.1: Design of ALLHAT

Cholesterol-Lowering Trial (2 Arms)	Antihypertensive Trial (4 Arms)*				Total
	Chlorthalidone	Amlodipine	Lisinopril	Doxazosin*	
Pravastatin	3,655	2,115	2,115	2,115	10,000
Usual Care	3,655	2,115	2,115	2,115	10,000
Not Eligible	7,310	4,230	4,230	4,230	20,000
Total	14,620	8,460	8,460	8,460	40,000

Other objectives of both parts are to compare the effects of their respective treatments on cardiovascular death, major illness, health costs, and health-related quality of life. Additional objectives of the high blood pressure part are to compare the effects of the alternative treatments on death from all causes combined and on major hypertension-related illness such as left ventricular hypertrophy and renal dysfunction. Additional objectives of the cholesterol-lowering part are to assess the long-term safety of pravastatin in men and women aged 55 years and above

* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

(especially with regard to death from non-cardiovascular causes), the effect of cholesterol-lowering on cancer incidence and mortality, and the effect of lipid-lowering on combined fatal CHD plus non-fatal myocardial infarction, especially in key subgroups. The first patient entered into ALLHAT will be followed for 8.5 years, and the last patient randomized will be followed for five years, for a mean follow-up time of 6 years.

Data for determining eligibility for the antihypertensive trial will come largely from chart review, other than evaluation of blood pressure criteria. A blood chemistry battery, including serum lipids, and simply anthropometry at baseline will allow limited examination of subgroups based on metabolic profile, and a resting ECG will be obtained.

The study will consist of a vanguard phase and a full-scale trial phase. Six hundred patients will be entered into the vanguard phase; approximately 40,000 patients will be enrolled in the full-scale trial. Due to the higher prevalence and greater severity of hypertension in African-Americans, as well as the lack of clinical trial data in this group, at least 55% of the study sample will be from this ethnic group.

Maintenance of Racial Composition of ALLHAT:

Potential ALLHAT study investigators will be asked to indicate the approximate proportion of African-American patients they expect to recruit into the study. Clinical sites will be selected to produce an overall study population of at least 55% African-Americans and will be monitored by the Clinical Trials Center throughout the study to assure that their performance matches their expectations. If the overall proportion of African-Americans appears to be falling significantly short of 55%, the Steering Committee may implement remedial measures such as temporarily freezing recruitment of non-African-American patients at some or all existing clinical sites or adding new clinical sites to correct the shortfall.

This Manual of Operations describes in detail the eligibility and exclusion criteria, procedures for baseline and follow-up visits, the treatment protocol for both study components (antihypertensive and cholesterol-lowering), side effects, study endpoints, drug handling, and administrative procedures. It also provides guidelines on other procedures such as obtaining informed consent, blood pressure measurement, ECG acquisition, laboratory procedures, lifestyle intervention, compliance, and quality control.

Sections on the cholesterol-lowering part are marked by a solid bar in the right margin.

CHAPTER 1
ALLHAT QUICK REFERENCE GUIDE

1.1 How to Use this Guide

This Guide is intended to provide an overview of the **ALLHAT** study procedures and to serve as a quick reference in actual conduct of the study. It provides enough detail to inform the nurse or physician on basic operations. For more complete information, references are made to more detailed sections of the Manual of Operations (MOO) in small type (e.g., See MOO page 2-2). This Guide is not intended to replace those sections of the MOO, which must be referred to for certain procedures, particularly more detailed procedures, such as obtaining informed consent or managing side effects of drugs. However, as long as the clinician is somewhat familiar with **ALLHAT** (and as the clinician becomes more familiar with **ALLHAT** with experience), need to refer to the detailed sections of the MOO should be limited.

On page 1-2 there is a one-page overview of the study. Each bullet on this page is expanded upon in the body of the Guide.

FORMS

are indicated throughout the Guide in boxes.

Visits are referred to in italics.

Quick Reference Guide Appendices:

- A. **ALLHAT** Study Organization with names, functions, and phone numbers of persons responsible for the study.
- B. List of **ALLHAT** forms with an explanation of the purpose of each form.
- C. Summary of visit steps.
- D. Visit flowchart.

How to improve this Guide: If you feel there is additional information that would be handy to have included in this Guide, please contact your Regional Coordinator.

ALLHAT Quick Reference Guide

WHO IS ELIGIBLE FOR ALLHAT?

- Men and women age 55 and older with hypertension are eligible.
- Eligibility is based on the average of two seated blood pressures taken at each of two visits, current treatment for hypertension (whether they are currently treated or not), and the presence of at least one other condition that increases the risk for cardiovascular disease.
- Patients who are eligible for the antihypertensive trial should additionally be considered for the lipid-lowering trial.

The following sections are included in this Guide, with references to other sections of the ALLHAT Manual of Operations:

HOW DO I ENROLL PATIENTS INTO ALLHAT?

- Determine eligibility for antihypertensive trial.
- Obtain informed consent for antihypertensive trial.
- Prepare patient for randomization.
- Randomize patient into antihypertensive trial.
- Determine eligibility for lipid-lowering trial.
 - Obtain informed consent for lipid-lowering trial.
 - Randomize patient into lipid-lowering trial.

WHAT IS INVOLVED AFTER ENROLLMENT?

- Follow the participant with visits at 1 month, 3 months, 6 months, 9 months and 12 months, and then every 4 months during Years 2 through 6.
 - Perform routine clinical measurements.
 - Monitor blood pressure and drug therapy.
- Monitor participant for and report outcomes.

WHAT IF I HAVE QUESTIONS?

- Contact your Principal Investigator, Regional Coordinator, or other study organizers. (See **ALLHAT** Study Organization on page 1-13 of this Guide.)

• **Determine eligibility for the antihypertensive trial**

Potential participants may be identified by chart review and/or during a routine office visit (Visit 1)

Inclusion Criteria

FORM AL01

1. Age: 55 years or older (at the time of randomization).
2. Current treatment for hypertension and current blood pressure - based on each of 2 blood pressure **determinations** taken at least one day apart, **with each determination being an average of 2 measurements:**

Treated for at least 2 months AND currently on antihypertensive drugs AND blood pressure within this range: SBP ≤160 mmHg and DBP ≤100 mmHg at Visit 1, AND SBP ≤ 180 mmHg and DBP ≤ 110 mmHg at Visit 2. (Note: There is no lower blood pressure limit.)

OR

Not on antihypertensive drugs **or** on drugs for less than 2 months AND blood pressure within this range: SBP ≥140 mmHg OR DBP ≥90 mmHg AND SBP ≤180 mmHg and DBP ≤100 mmHg at Visit 1 and Visit 2. These participants must be diagnosed as hypertensive according to guidelines in the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V).

Blood Pressure Eligibility Criteria

Status at Visit 1 and Visit 2		Lower Limit ¹ (mmHg)		Upper Limit ² (mmHg)	
		SBP	DBP	SBP	DBP
On 1-2 Drugs Used for Hypertension at Least 2 Months	Visit 1	---	---	160	100
	Visit 2	---	---	180	110
On Drugs For Less Than 2 Months or Currently Untreated	Visit 1 & Visit 2	140	90	180	110
¹ SBP or DBP lower limit must be met at Visit 1 and Visit 2 ² SBP and DBP upper limit must be met at Visit 1 and Visit 2					

See MOO Appendix B for details of how to measure blood pressure. See MOO 2-13 and 2-15 for information on classification based on blood pressure and antihypertensive therapy.

Notes:

These criteria must be met at each of **two** separate visits at least one day apart. *(Visits 1 and 2)*

Since ALLHAT intends to recruit patients with mild or moderate hypertension, patients on antihypertensive treatment whose blood pressure can be controlled on one or two different classes of antihypertensive drugs are eligible for ALLHAT. Combination drugs that include more than one class of drug (e.g., a diuretic and a beta-blocker) should be counted as two drugs. Patients taking three or more antihypertensive medications in subtherapeutic doses or in ineffective combinations may still be considered. See MOO page 2-7.

If the patient has been on antihypertensive medication for less than 2 months and his/her blood pressure is too low for inclusion, enrollment may be considered after withdrawal (partial or complete) from their existing drug regimen. (See "Prepare participant for randomization," page 5 of this Guide.)

3. Presence of at least one of the following conditions (which place the participant at high risk for cardiovascular disease):
 - a. Myocardial infarction (age-indeterminate or at least 6 months old)
 - b. Stroke (age-indeterminate or at least 6 months old)
 - c. History of revascularization procedure (angioplasty, bypass surgery [coronary; peripheral vascular; carotid; vertebrobasilar], aortic aneurysm repair, or other revascularization procedures, such as atherectomy and stents).
 - d. Major ST segment depression or T wave elevation on any ECG in the past two years.
 - e. Other documented atherosclerotic cardiovascular disease (for example, 50% or more occlusion by angiography or Doppler, transient ischemic attack, intermittent claudication, or ankle/arm ratio less than 0.9).
 - f. Type II diabetes mellitus (plasma glucose higher than 140 mg/dl [7.77 mmol/L] (fasting) or higher than 200 mg/dl [11.1 mmol/L] (non-fasting) in the past 2 years and/or currently treated with insulin or oral hypoglycemic agents
 - g. HDL cholesterol less than 35 mg/dl (0.91 mmol/l) on any 2 or more determinations within past 5 years
 - h. Left ventricular hypertrophy on any ECG within the past two years
 - i. Combined wall thickness 25 mm or more on any echocardiogram in the past two years.

j. Current cigarette smoking.

See MOO beginning page 2-8 for further explanation of these criteria.

Exclusion Criteria

1. Symptomatic MI or stroke within 6 months
2. Hospitalized or treated for congestive heart failure and/or ejection fraction less than 35%, if known
3. Symptomatic angina pectoris within past 6 months. (Note: If the patient has had no chest pain within 6 months even if on medication for angina, this exclusion does not apply.)
4. Known renal insufficiency (serum creatinine 2 mg/dl [152.6 μ mol/l] or more).
5. Participants requiring diuretics, calcium antagonists, ACE inhibitors, or alpha adrenergic blockers for reasons other than hypertension. (Note: If the participant can be safely switched from these to other medications, this exclusion does not apply.)
6. Sensitivity or contraindications to any of the Step 1 (blinded) study medications.
See MOO page 2-7 and 2-8 for list of drugs and types of sensitivity and contraindications.
7. Factors suggesting low likelihood of compliance with protocol, such as dementia, alcohol or drug abuse, plans to move or travel, or history of unreliability in keeping appointments or taking medications.
8. Diseases likely to cause death within 6 years.
9. Systolic pressure >180 mmHg (more than 180 mmHg) or diastolic pressure >110 mmHg (more than 110 mmHg) on two separate determinations while tapering antihypertensive medications.

See MOO pages beginning 2-5 for further explanation of these criteria.

• Prepare patient for randomization

1. If patient is on more than the minimum recommended dosages of beta-blockers, clonidine, or methyldopa, medications should be tapered before stopping these agents. Other antihypertensive agents, except for diuretics as noted below, should be continued until Visit 2. See MOO page 2. Note: Post-myocardial infarction participants receiving beta-blockers or nitrates for prophylaxis **need not** discontinue therapy.
2. If the patient is on diuretics and/or potassium supplements and is being considered for randomization, tell them not to take their medication on the day of Visit 2.
3. Patients who are on drugs less than two months at Visit 1 and

whose blood pressure is below the lower limit entry criteria (140/90 mmHg) may be re-evaluated after withdrawal (partial or complete) from their existing regimen. **Unless the participant is on antihypertensive medication for reasons other than to control hypertension, all antihypertensive medications should be stopped at the time of randomization into ALLHAT.**

4. Participants should come in fasting (at least 9-12 hours) for Visit 2.

See M00 page 2-1.

- **Obtain informed consent for antihypertensive trial**

(Visit 2)

1. Explain the requirements of informed consent by reviewing the approved consent form with the patient.
2. Ensure that the patient is fully informed, has adequate time to weigh the pros and cons of participation, has the opportunity to discuss participation with family or friends, is competent to give informed consent, is provided information about participation in privacy, is not pressured into participating, and is given a copy of the informed consent form after it is signed.
3. If any change in medication is required before Visit 2, the informed consent must be signed at Visit 1.

See M00 Appendix A for details of obtaining informed consent.

- **Randomize participant into antihypertensive trial**

FORM AL01

1. Telephone the Clinical Trials Center and review form (AL01) to assess eligibility (1-800-690-7870 between 7 am and 5 pm Central Time Monday through Friday). *Please have the first three pages of the AL01 available before calling the CTC.*
2. Receive blinded assignment to study medications (1 of 4 drugs: chlorthalidone, amlodipine, lisinopril, or doxazosin) by bottle number.
3. Issue starting doses of Step 1 (blinded) drug to participant (initial dose [Dose 0] for 1 week, then Dose 1 for 4 weeks). Bottles will be labeled by bottle number and dosage. Participants will be assigned to a bottle number at randomization, which will not change throughout the study. The first dose of study medication should be taken the day after randomization. Medicine should be taken in the morning. In a medical emergency, identity of the blinded study drug can be requested by calling:

Clinical Trials Center (CTC): (713) 500-9500 or 1-800-690-7870

during normal business hours
Hermann Hospital Pharmacy: (713) 704-2078 outside normal
business hours

If possible, call your Regional Study Coordinator prior to
requesting that the study drug be unblinded.

See MOO page 6-4.

4. Obtain routine laboratory studies: ECG (unless you have an original done in last year) and laboratory panel ALL01 (potassium, glucose, creatinine, and lipid profile [total cholesterol, triglycerides, HDL and calculated LDL]). Send specimen to the Central Laboratory for the laboratory measurements. See MOO Appendix D. Send ECG to ECG Coding Center. See MOO Appendix C. If the sample cannot be obtained while the participant is fasting, the blood draw may be delayed a few days, or the blood may be drawn non-fasting, at the discretion of the clinic investigator.
5. Provide lifestyle advice for blood pressure and lipid reduction (based on reports available from the NHLB Information Center).
Give participant a copy of "Eat Right to Help Lower Your High Blood Pressure." See Appendix E for details of counseling.
6. Schedule participant to return for study Visit 3 in window provided by the CTC for dose titration. (Participants may be scheduled to return sooner, but ALLHAT data will not be collected.) (Visit 3)
7. Reimbursements are made for each participant randomized with correct AL01 completed and submitted to the CTC. See MOO page 7-11.

See pages 2-3 and 2-14 for details of randomization.

• **Determine eligibility for lipid-lowering trial**

FORM AL02

Inclusion Criteria

1. Eligible and enrolled in antihypertensive trial.
2. LDL cholesterol 120-189 mg/dl (3.11-4.90 mmol/L) in participants without CHD or 100-129 mg/dl (2.59 - 3.34 mmol/L) with known CHD. CHD includes prior myocardial infarction (including silent MI), angina, primary cardiac arrest, angiographically defined coronary stenosis more than 50%, reversible perfusion defects on cardiac scintigraphy, or prior coronary revascularization procedures.
3. Triglycerides less than 350 mg/dl (3.96 mmol/L) at Visit 2.

See MOO pages 2-17 and 2-20 for further explanation of inclusion criteria.

If the lipid randomization will take place more than 120 days from the blood draw for eligibility determination, please redraw the blood at the next visit and re-evaluate lipid eligibility (request laboratory panel ALL10).

Exclusion Criteria

1. Current use (within 2 months of eligibility blood draw) of prescribed lipid-lowering agents (one year for probucol), including resins, lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), or niacin in doses 500 mg/day or more.
2. Contraindications to HMG CoA reductase inhibitors (significant hepatic or renal disease, previous organ transplantation requiring immunosuppressive therapy, or known allergy or intolerance).
3. Known secondary cause of hyperlipidemia, such as nephrotic syndrome or untreated hypothyroidism.
4. ALT more than 100 u/L (2 times the upper limit of normal).

See MOO pages 2-17 and 2-20 for further explanation of exclusion criteria.

• Obtain informed consent for lipid-lowering trial *(Visit 3)*

See "Obtain informed consent for antihypertensive trial" on page 5 of this Guide.

See MOO Appendix A.

• Randomize participant into lipid-lowering trial

- a. Telephone the Clinical Trials Center and review form (AL02) to assess eligibility (1-800-690-7870 between 7 am and 5 pm Central Time Monday through Friday). Have the AL01 and completed AL02 available prior to calling the CTC. Participant will be assigned to either pravastatin or usual care. Those assigned to pravastatin should be given a supply of pravastatin and instructed to take a daily dose of 40 mg each evening at bedtime.
- b. Discuss the National Cholesterol Education Program (NCEP) diet based on "Eat Right to Lower Your High Blood Cholesterol." see Appendix E.
- c. Obtain fasting lipid profile (laboratory panel ALL02). (See "Perform routine clinical measurements" on page 10 of this Guide.) The Clinical Trials Center will send a revised visit schedule for additional laboratory analyses. See MOO page 2-19.
- d. Schedule follow-up appointment for the next required ALLHAT visit according to the participant's visit schedule.

See MOO page 2-3.

• Follow the participant

(Visits 4-28)

Monitor blood pressure and drug therapy

FORM AL03

For all participants:

1. Schedule ALLHAT visits at 1 month, 3 months, 6 months, 9 months, 12 months and then every 4 months. Participants may need to be seen more frequently if otherwise medically indicated or until a stable regimen for blood pressure control is achieved, but ALLHAT data will not be collected. See MOO Chapter 3.
2. Monitor blood pressure and titrate medication to achieve goal blood pressure of <140 mmHg (less than 140 mmHg) systolic and <90 mmHg (less than 90 mmHg) diastolic. See MOO page 3-1.
 - a. Begin with the lowest dose (Dose 0) of the Step 1 (blinded) drug. Increase doses of the Step 1 (blinded) drug as needed to achieve goal blood pressure. There are three dosage forms for each drug: Dose 0 (for Week 1), Dose 1, and Dose 2/3. Dose 3 is always double Dose 2, and is achieved by increasing intake from one to two capsules per day (taking both together in the morning). See MOO page 3-1 (Table 3.1).
 - b. Consider the addition of Step 2 and Step 3 open-label ALLHAT medications if goal blood pressure is not achieved. Step 2 open-label drugs include reserpine (0.05, 0.1, 0.2 mg qd), clonidine (0.1, 0.2, 0.3 mg bid), and atenolol (25, 50, 100 mg qd). The Step 3 open-label drug is hydralazine (25, 50, 100 mg bid). Choice of these agents is entirely at the discretion of the treating physician, though hydralazine should be reserved for use after reserpine, clonidine and atenolol have failed to control the blood pressure to the ALLHAT treatment goal. See MOO page 3-3 and Table 3-2.
 - c. Provide potassium supplementation (open-label slow-release 8 meq tablets, 5-12 per day) for participants with low potassium (less than 3.5 mmol/l). See MOO page 4-2. Potassium will be measured at Visit 3 and thereafter according to the visit schedule procedures, but only reported to the physician if less than 3.5 mmol/l or more than 5.5 mmol/l, or if there is an increase of 1.0 mmol/l or more to a level above 5.0 mmol/l; more frequent monitoring of potassium levels should be handled locally. See MOO page 4-2 or page 11 of this Guide.

If the level is 3.2-3.4 mmol/l, then it should be rechecked locally at the next scheduled visit. If the level is less than 3.2 mmol/l or more than 5.5 mmol/l, participants should be recalled immediately to have their potassium rechecked locally. If the level is still less than 3.5 mmol/l, oral potassium should be prescribed. Clinical discretion should be used in treating a serum potassium level of 5.5 mmol/l or in determining action to be taken for increases of 1.0 mmol/l or more.
3. Assess and optimize adherence.
 - a. Perform pill counts or cylinder measurements at each visit.

- b. Question the participant about adherence.
- c. Establish a good rapport with participants.
- d. Maintain a positive attitude.
- e. Help participants adjust to medication changes.
- f. Don't immediately stop medications for mild side effects.
Consult your Regional Study Coordinator before discontinuing the Step 1 (blinded) study drug.
- g. If medications are stopped, get participants back on as soon as possible. See MOO page 3-2 for restarting medications.

See MOO Appendix F for additional information about adherence, and for suggestions for avoiding missed visits.

4. Major side effects and serious adverse experiences (SAEs).

- a. Major side effects include allergy (purpura, asthma, generalized rash), syncope, severe dermatitis, angioedema, neutropenia, and necrotizing vasculitis. These side effects require that the medications be discontinued. See MOO page 4-1.
- b. Report any serious adverse experiences believed to be due to study drug to the Clinical Trials Center. SAEs are experiences that the investigator believes may be caused by the Step 1 (blinded) drug. SAEs include death, life threatening events, events resulting in permanent disability, hospitalizations or prolongation of hospital stays, cancers, or drug overdoses. FORM AL13
- c. For participants on pravastatin, major side effects also include hepatitis and muscle pain associated with elevated creatine kinase (CPK) levels. See MOO page 4-1.
- d. Hypokalemia and hyperkalemia are potentially serious side effects. The Central Laboratory will notify the clinical site promptly of any serum potassium value below 3.5 mmol/l or above 5.5 mmol/l, or if there is an increase of 1.0 mmol/l or more. See MOO page 4-2.

For further information, see pages beginning 4-1.

- 5. There are special procedures for handling permanent transfers to other geographic areas, housebound participants, refusals and losses to follow-up. See MOO pages 7-3 and 7-4.

In addition, for participants in the lipid-lowering trial:

- 6. You will receive a revised version of the patient's ALLHAT visit schedule. NOTE: The visit dates will remain the same as for the antihypertensive trial, but some of the routine lab work will be different. See next section in Guide, "Perform routine clinical measurements."

7. Assess and optimize adherence with lipid-lowering medications.
See 3 above.

• Perform routine clinical measurements

Visit	Months of Follow-up	All participants	Lipid-lowering trial only	
			Pravastatin	Usual Care
2	0	K, glucose, creatinine, ALT, fasting lipids, ECG (from chart, if available)		
3	1	K, creatinine	fasting lipids	fasting lipids
4	3		TC, ALT	
5	6		ALT	
6	9		ALT	
7	12	K, creatinine	ALT, total cholesterol, fasting lipids*	
8	16			
9	20		ALT	
10	24	K, glucose, creatinine, total cholesterol, ECG	fasting lipids*	fasting lipids*
11	28		ALT	
12	32			
13	36		ALT, TC LP*	LP*
14	40			
15	44		ALT	
16	48	K, glucose, creatinine, total cholesterol, ECG		
17	52		ALT	
18	56			
19	60		ALT, total cholesterol, fasting lipids*	fasting lipids*
20	64			
21	68		ALT	
22	72	K, glucose, creatinine, total cholesterol, ECG		
23	76		ALT	
24	80			
25	84		ALT, total cholesterol, fasting lipids*	fasting lipids*
26	88			
27	92		ALT	
28	96	K, glucose, creatinine, total cholesterol, ECG		

ALT=serum alanine aminotransferase

*For pravastatin participants, obtain LP on a 10% subset. For Usual Care participants, obtain LP on a 5% subset. The Clinical Trials Center will determine which participants should have the fasting lipid profile.

For ECG measurement, see Appendix C.

• **Monitor participant for and report outcomes**

1. Following are the study events of interest in ALLHAT:

Death from any cause
Hospitalized myocardial infarction
Hospitalized stroke
Hospitalized, procedure or treated for any of the following:

Congestive heart failure
Angina pectoris
Peripheral arterial disease
Cancer (a new diagnosis; not non-melanoma skin cancer)
Accident or attempted suicide
Kidney transplant or start of chronic dialysis

2. Complete checklist for study events at each visit.

FORM AL03

3. For fatal events, obtain death certificate.

4. For hospitalized events (fatal or nonfatal), obtain copies of hospital discharge summary.

5. The AL04 must be submitted to the Clinical Trials Center after deaths, hospitalizations as described above, procedures, MIs, strokes to flag potential study events.

FORM AL04

6. For a 10% random sample, the Clinical Trials Center will request more detailed information, such as copies of ECGs and cardiac enzyme results.

See MOO Chapter 5.

Quick Reference Guide Appendix A - ALLHAT Study Organization:

The Clinical Trials Center periodically circulates a list of key personnel, including NHLBI ALLHAT staff, CTC staff, and Regional Physician and Study Coordinators.

Call your Regional Coordinator if you have a question regarding;

1. The IRB and OPRR process.
2. The **ALLHAT** protocol.
3. Participant eligibility.
4. Participant recruitment.
5. The clinical management (hypertension, lipids) of the participant.
6. Collection of data for the **ALLHAT** study.
7. Problems with participant compliance.
8. Any protocol violation or perceived need for a protocol violation.
- 9. Any non-emergent need to unblind the study data.**
10. The anticipated need to stop antihypertensive or cholesterol study medications.
11. The need to use open-label diuretics, calcium antagonists, ACE inhibitors, or alpha blockers.
12. Inability to achieve blood pressure or cholesterol control.
13. Potential adverse drug reactions, especially if the study medications are suspected.

Call the Clinical Trials Center (CTC) in Houston regarding:

1. Randomization of a participant.
2. All questions regarding monies/reimbursement for **ALLHAT** (VA sites should call the Region 1 office).
3. Corrections of **ALLHAT** forms.
4. Documentation of study events.

Send all IRB approvals, forms, and paperwork in general to the CTC.

If you have questions regarding supplies/results for laboratory, ECG, study drug, call:

Study Drug Distribution: John Pelosi, M.S., Director
Ogden BioServices Corporation
Phone: (301) 309-2426
Fax: (301) 251-1863

ECG Recording & Mailing: Carmen O'Donnell
Minnesota ECG Center
Phone: (612) 626-9677
Fax: (612) 626-9444

Central Laboratory: Jean Bucksa, Laboratory Manager
(Supplies, results) University of Minnesota Hospital and Clinic
Phone: (612) 626-3645
Fax: (612) 625-6994

For unblinding of study medication, call:

Clinical Trials Center (CTC):

(713) 500-9500 or (800) 690-7870 during normal business hours

Herman Hospital Pharmacy:

(713) 704-2078 outside normal business hours

Call your Regional Coordinator first, if possible!

Other useful numbers:

Program Office -- NHLBI, Bethesda, MD: Gerald Payne, M.D., Project Officer, (301) 435-0424; Jeffrey Cutler, M.D., Project Director, (301) 435-0413; David Gordon, M.D., Ph.D., (301) 435-0564; Debra Egan, M.S., M.P.H., (301) 435-0399. Funding, coordination.

Clinical Trials Center -- University of Texas, Houston, TX: Barry Davis, M.D., Ph.D., Deputy Director, (713) 500-9515; Sara Pressel, Project Manager, (713) 500-9520. Coordination of operations, subcontracts, randomization, data collection, and analysis.

Steering Committee -- Curt Furberg, M.D., Chairman, (910) 716-3730; Jackson Wright, Jr., M.D., Ph.D., Co-Chairman, (216) 368-4408. Protocol development, operations monitoring, publications and ancillary studies.

Quick Reference Guide Appendix B - Forms

Form #	Description	Color bar
AL01	ALLHAT Antihypertensive Trial Eligibility Worksheet	
Pages 1-2	Chart Review & Visit 1	Dark blue
Pages 3-4	Visit 2 & Randomization	Light blue
AL02	ALLHAT Lipid-Lowering Trial Eligibility & Randomization Form	Red
AL03	Follow-up Visit Form - all post-randomization visits	Orange
AL04	Event Reporting Form - after deaths, hospitalized MIs, hospitalized strokes, some hospitalizations and procedures (Refer to MOO Chapter 5)	Gray
AL05A	Shipping Form for Baseline ECGs	Dark green
AL05B	Shipping Form for Follow-up ECGs	Light green
AL06	Report of Study Drug Disclosure - unblinding As of 12/95, the AL06's are complete by the CTC and mailed to the sites.	Dark purple
AL07	Report of Refusal or Loss to Follow-Up	Black
AL08	Forms Shipping Log	Brown
AL09	Correction Required	None
AL10	Drug Re-Order Form	Light purple
AL12	ALLHAT Event Quality Control Selection and Documentation - generated by computer at the CTC and faxed to the clinic site	None
AL13	Significant Adverse Events Report	Pink
AL14	Study Forms Request	Yellow
AL15	Patient Transfer Form	Teal

Quick Reference Guide Appendix C - Summary of Visits

VISIT ONE

Eligibility (Inclusion/Exclusion)

Assess exclusion and inclusion criteria -- if eligible, proceed

Blood Pressures

Measure 2 right arm blood pressures (unless known history of high left arm pressures) - *Average* must meet blood pressure eligibility
Use same arm at each visit

Obtain Consent

Obtain informed consent if patient is on a diuretic or meds that require tapering. May obtain others at Visit 2.

Case Report Forms

Complete AL01 pages 1 and 2 (Visit 1 form)

Schedule

Patient should return to clinic fasting in 1 day to 12 weeks for Visit 2 (randomization)

Remind

Instruct patient to take last dose of current antihypertensive day of Visit 2 (randomization).
Patients on diuretics need to discontinue diuretics the day before Visit 2.

Document the Visit

In the patient's medical chart, document all information including inclusion criteria in the progress notes.

VISIT TWO

Blood Pressures

Measure 2 blood pressures - Their average must meet blood pressure criteria, or patient may return to clinic for repeat measurements

Consent

Consent must be obtained at this visit if participant meets blood pressure eligibility and did not sign consent at Visit 1

Call CTC for Randomization

Obtain participant's identification number, bottle number assignment, and visit window dates for Visit 3 from CTC

Lab

Obtain fasting blood specimen (baseline lab panel ALL01)
If participant not fasting, may return in a day or two for fasting lab, or draw non-fasting

Baseline ECG

Must obtain ECG if original tracing not available within past year

Case Report Forms

Complete AL01 pages 3 and 4 (Visit 2)

Blinded Study Medication

Label and dispense Step 1 (blinded) medication with appropriate bottle number - Dose 0 and Dose 1 bottle
(Remember more than 1 participant can be randomized to the same bottle number)

Participants will take the FIRST DOSE of medication (Dose 0) the day after Visit 2

Schedule

Schedule the patient to return to clinic for Visit 3 in the visit window

Discuss

Provide lifestyle modification advice for blood pressure reduction
Dispense "Eat Right to Lower Your High Blood Pressure" pamphlet

Remind

Participant should come fasting for Visit 3 if possibly eligible for lipid-lowering trial randomization
Participant should bring bottles to each clinic visit

Document the Visit

In the patient's medical chart, document all information including inclusion criteria in the progress notes.

VISIT THREE

*(If eligible for lipid randomization)**

Blood Pressures

Measure 2 blood pressures; adjust medication to achieve ALLHAT BP goal
Issue appropriate drug bottles

Consent

Obtain consent for lipid-lowering trial

Call CTC for Randomization

Obtain participant's lipid-lowering treatment assignment from CTC

Labs

Obtain fasting blood specimen
Check lab panel ALL02 and ALL03 on requisition

Case Report Forms

Complete AL02 (lipid randomization form) and AL03 (follow-up form)

Schedule

Participant should return to clinic in 2 months for Visit 4 (refer to participant's visit schedule)

Discuss

Provide participant with lifestyle advice for cholesterol reduction based on the NCEP diet
Dispense "Eat Right to Lower Your High Blood Cholesterol" pamphlet

Reinforce

Lifestyle advice based on "Eat Right to Help Lower Your High Blood Pressure"

Remind

Participant should bring medication bottles to each clinic visit

Document the Visit

In the patient's medical chart, document all information including inclusion criteria in the progress notes.

**Remember:* If lipid-lowering trial randomization is done at a later visit that is more than 120 days from the antihypertensive randomization, please draw a blood specimen for re-determination of lipid eligibility. Check lab panel ALL10 on the laboratory requisition slip. Use these new results for determination of eligibility for the lipid-lowering trial.

VISIT THREE

(If not eligible for lipid randomization)

Blood Pressures

Measure 2 blood pressures; adjust medication to achieve ALLHAT BP goal
Issue appropriate drug bottles

Lab

Obtain blood specimen

Check lab panel ALL03 on requisition

Case Report Forms

Complete AL03 (follow-up form)

Schedule

Participant should return to clinic in 2 months for Visit 4 (refer to participant's visit schedule)

Remind

Participant should bring medication bottles to each clinic visit

Reinforce

Lifestyle advice based on "Eat Right to Help Lower Your High Blood Pressure"

Document the Visit

In the patient's medical chart, document all information including inclusion criteria in the progress notes.

VISITS FOUR AND BEYOND

Blood Pressures

Measure 2 blood pressures; adjust medication dose to achieve ALLHAT BP goal.
Issue appropriate drug bottles.

Case Report Forms

Complete AL03

Procedures

Refer to participant's visit schedule and perform procedures as required.

Schedule

Participant should return to clinic every 3 months for the first year, then every 4 months thereafter (refer to participant's visit schedule)

Remind

Participants should bring bottles to each visit

Document the Visit

In the patient's medical chart, document all information including inclusion criteria in the progress notes.

During the trial, participants may need to be seen more frequently than required if otherwise medically indicated or until a stable regimen for blood pressure control is achieved. However, ALLHAT data will not be collected at these "extra visits." The number of these visits will be captured on the AL03 form, page 1, question #4.

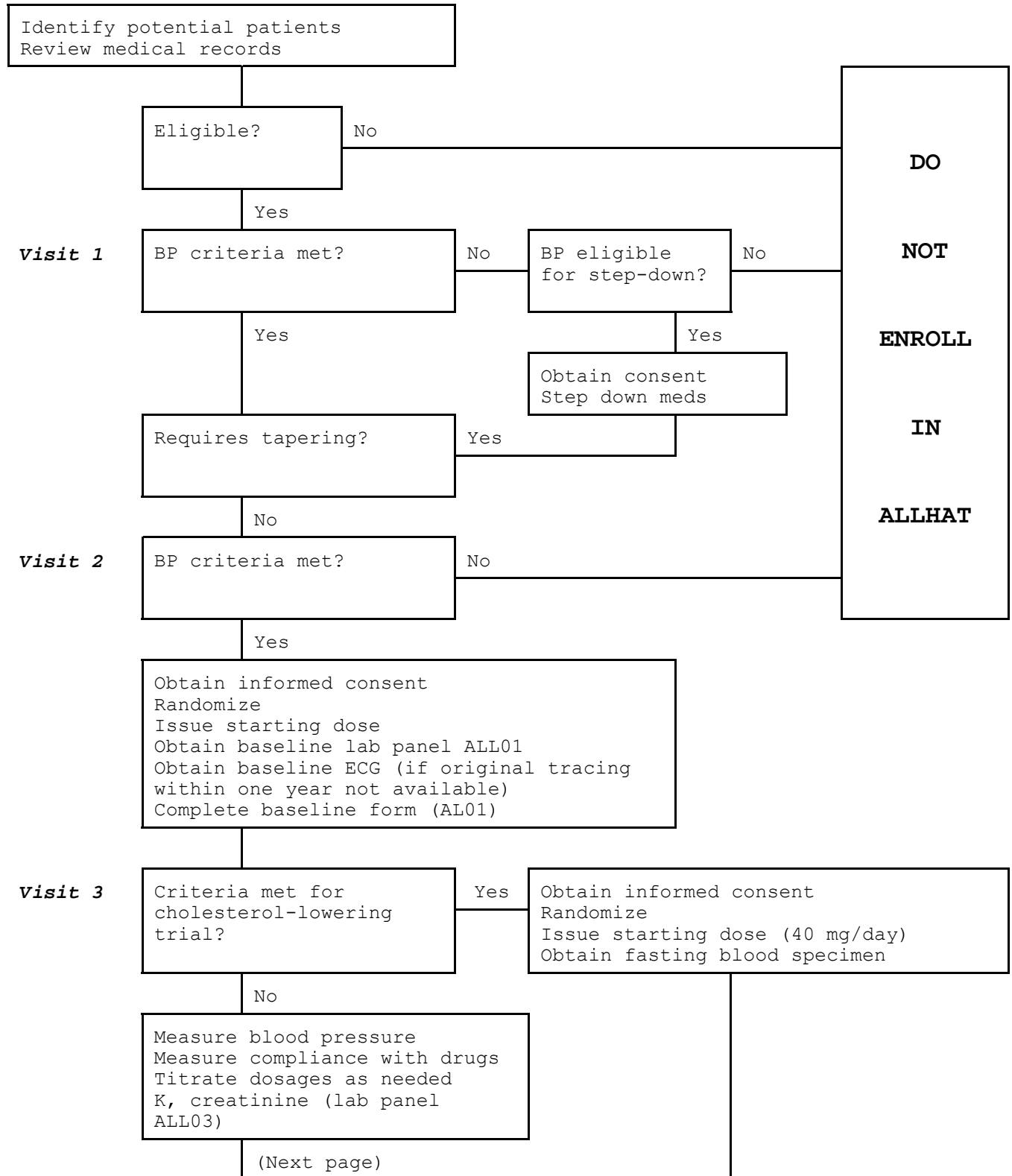
REMEMBER

All original ALLHAT case report forms should be mailed to the CTC with a shipping log (AL08) included. Keep a copy of the forms in the participant's record.

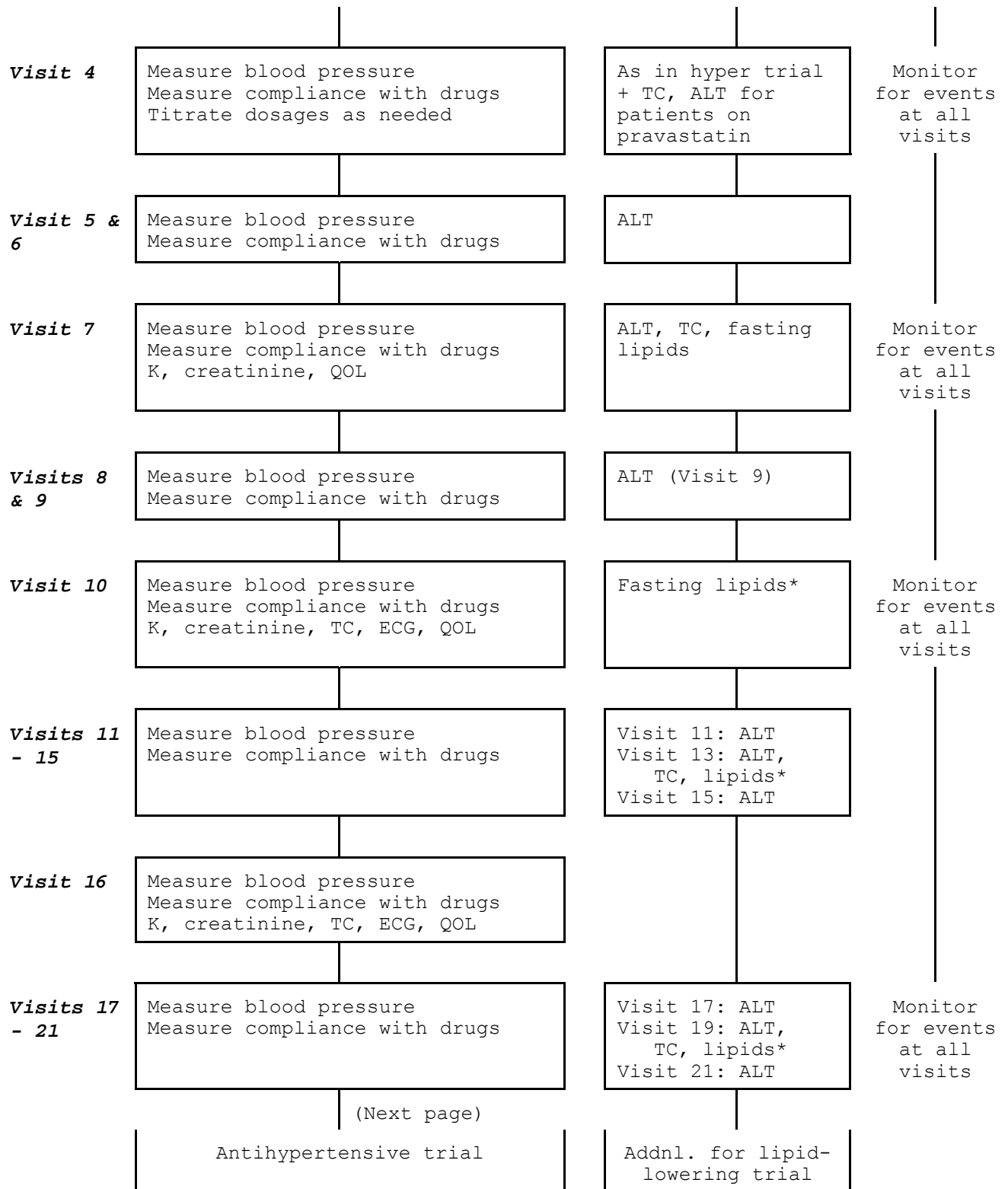
Payment will not be issued for the ALLHAT visit until the forms are received and necessary corrections are made.

Reimbursement is only made for one visit per visit window.

Quick Reference Guide Appendix D - ALLHAT Recruitment and Clinic Visit Flow Chart



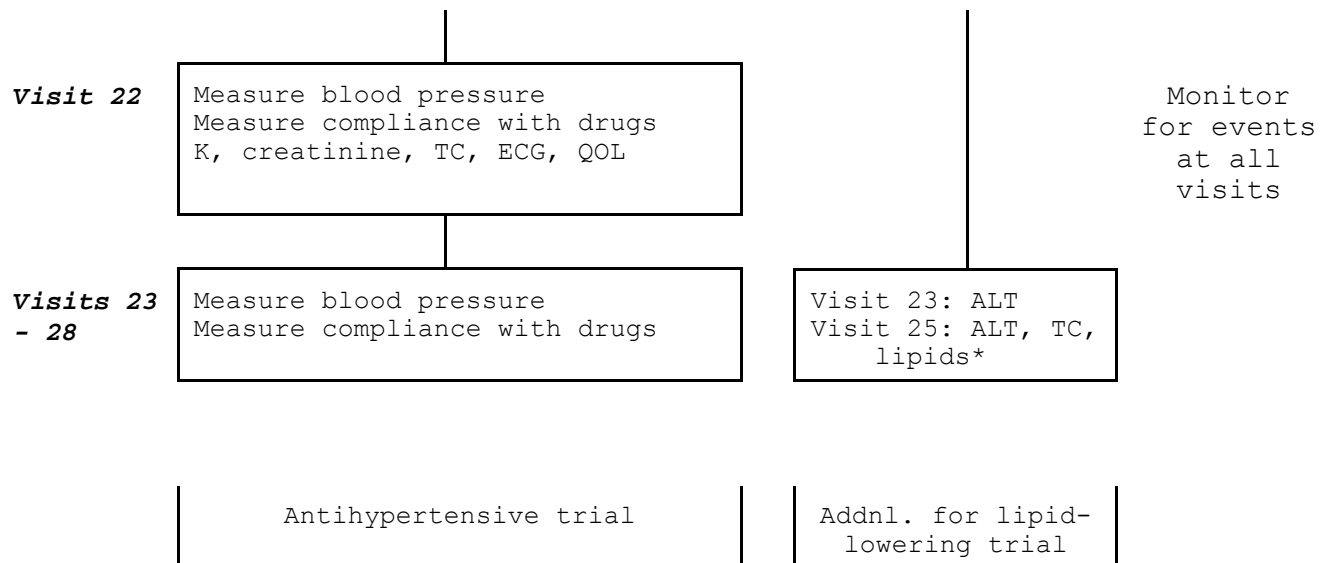
ALLHAT Recruitment and Clinic Flow Chart - continued



*10% subset for pravastatin patients, 5% subset for Usual Care patients

ALT=serum alanine transferase, TC=total cholesterol, QOL=quality of life

ALLHAT Recruitment and Clinic Flow Chart - continued



*10% subset for pravastatin patients, 5% subset for Usual Care patients
ALT=serum alanine transferase, TC=total cholesterol, QOL=quality of life

CHAPTER 2 RECRUITMENT AND RANDOMIZATION

2.1 Description of Visits

2.1.1 Visit 1

The objective of Visit 1 is to assess eligibility for and interest in ALLHAT. It is anticipated that the majority of treated hypertensives will have been identified by chart review, and that much of the pertinent information (age, risk factor status, number of antihypertensive drugs, etc.) will already be known. Any documentation not attainable by chart review to determine patient's eligibility will be considered part of the patient's routine medical management and will not be specifically reimbursed by the study.

Visit 1 will include assessing blood pressure eligibility and answering the patient's questions about the study. If tapering pre-study antihypertensive drugs, informed consent must be obtained at Visit 1. Otherwise, informed consent may be obtained at Visit 2.

Patients initially not taking antihypertensive drugs or taking drug(s) requiring little or no tapering may be randomized soon after Visit 1, while other patients may require a longer tapering process before they can complete Visit 2. More prolonged taperings (more than two months) are discouraged (though not prohibited). Many patients who cannot quickly be withdrawn from their pre-study regimens may also be more difficult to maintain on a simple regimen during the trial.

2.1.2 The patient brochure and informed consent

A detailed patient brochure has been provided. It describes in easy-to-understand language the purpose of ALLHAT, what is expected of the patient, what the patient can expect from you, the side effects of the study drugs, and other details. The informed consent forms for the antihypertensive and lipid-lowering trials are shorter, and summarize the most important things about ALLHAT.

You should carefully review the booklet and the informed consent with patients who are eligible and considering participation in ALLHAT. Patients who are not currently on antihypertensive medications, or who do not require tapering of current antihypertensive medications, should still have this information provided to them at this Visit, even though it is not necessary for them to sign the informed consent for the antihypertensive trial until Visit 2 (prior to randomization). Patients considering participation in the lipid-lowering trial need not sign the informed consent for that portion of the trial until Visit 3.

Additional detail on the informed consent process, and copies of the patient booklet and both sample informed consent forms may be found in Appendix A.

2.1.3 Visits to Taper Pre-Study Antihypertensive Medications

Not all patients on antihypertensive medications will require tapering visits. The necessity of these visits, and their number and frequency is up to the investigator. In general, the following categories of antihypertensive drugs can usually be stopped without tapering the dose:

1. Diuretics: The patient should be informed to contact the physician if he/she develops marked edema and/or significant increase in dyspnea (shortness of breath, either at night or on exertion).
2. Reserpine.
3. Angiotensin converting enzyme (ACE) inhibitors.
4. Calcium channel blockers.
5. Vasodilators (e.g., hydralazine)
6. Alpha₁-blockers (e.g., prazosin).

If a patient's antihypertensive medications can be safely switched without tapering, the patient may move directly to Visit 2. Visit 2 may take place as soon as one day after Visit 1 (if no tapering), or one day after tapering is completed.

The following categories need to be tapered if the patient is taking more than the usual starting doses:

1. Central agonists (e.g., oral clonidine or methyldopa) - taper over 1-2 weeks.
2. Beta-adrenergic blockers (e.g., propranolol or atenolol) - taper over 2 weeks.

There may be occasional circumstances where, in the physician's judgment, closer monitoring or a longer period of tapering is preferred. Extra care should be taken in tapering antihypertensive drugs in those patients with cardiovascular disease. ***Patients requiring beta-blockers for prophylaxis post-MI or for another non-hypertension reason (e.g., migraine headaches) need not discontinue therapy.***

Patients should be told to come in fasting (at least 12 hours optimum, or 9 hours minimum) for Visit 2. Patients on a diuretic (or potassium supplements, if any) should not take their medication on the day of Visit 2.

Patients whose blood pressure exceeds 180 mmHg systolic or 110 mmHg diastolic during tapering should return within 3-7 days for a repeat blood pressure measurement. If the blood pressure is still above 180/110, the patient should not be randomized into the antihypertensive trial.

Data from tapering visits will not be collected at the Clinical Trials Center.

2.1.4 Visit 2 (Randomization to Antihypertensive Trial)

Patients who have met all ALLHAT eligibility criteria and have signed their consent form may be randomized to one of the four Step 1 (blinded) study drugs at Visit 2. This visit will take

place between 1 day and 12 weeks after Visit 1.

The patient's medication status at Visit 1 and his or her average blood pressure at Visit 2 are used in determining final blood pressure eligibility for ALLHAT. If the patient's blood pressure does not fall into the eligible range at this visit, the patient may be brought back for an extra visit or two to recheck the blood pressure level for eligibility. ***Visit 1 and Visit 2 need not necessarily be consecutive visits.***

If the patient is being randomized to the antihypertensive trial, the investigator or nurse will telephone the Clinical Trials Center (1-800-690-7870) regarding each patient who meets all eligibility requirements at Visit 2, including a signed consent form. The Clinical Trials Center will review the exclusion and eligibility criteria and assign that participant a study identification number and a bottle number corresponding to chlorthalidone, amlodipine, lisinopril, or doxazosin. The treatment assignment will be blinded from both the practitioner and participant. A resting ECG, serum glucose, serum potassium and creatinine, ALT, and lipid profile (preferable fasting -- 12 hours optimum, 9 hours minimum) should be obtained at this visit for all trials who are randomized. *If the trial has not fasted prior to the blood draw, the blood draw may be delayed a day or two so that a fasting sample may be obtained. If, in your judgment, it is not possible to draw a fasting blood sample within a day or two, draw the blood non-fasting.*

Each randomized participant will be issued a one-week supply of his/her starting dose (Dose 0) and a 30-day supply of Dose 1 of the assigned Step 1 (blinded) medication and will be instructed to return for the first dosage titration (Visit 3), two to six weeks later. **The first dose of study medication should be taken the day after randomization.**

All randomized participants will be given appropriate hygienic advice (sodium and alcohol restriction, smoking cessation, exercise, caloric restriction if overweight) with reinforcement as needed during the trial. This advice is contained in the booklet "Eating to Help Lower High Blood Pressure," and is summarized in Appendix E. All randomized participants will receive a copy of this booklet.

2.1.5 Randomization into the lipid-lowering trial at Visit 3

In order to participate in the lipid-lowering trial of ALLHAT, participants must be *eligible and enrolled* in the antihypertensive trial. Participants with LDL-C between 120 and 189 mg/dl (between 100 and 129 mg/dl for trials with known CHD) and triglycerides less than or equal to 350 mg/dl at Visit 2 will be informed of their eligibility for the lipid-lowering trial and told to come in fasting for Visit 3. If they sign the Informed Consent to participate in this ALLHAT trial at Visit 3, the investigator will telephone the Clinical Trials Center and review the eligibility and exclusion criteria for the lipid-lowering trial. If the participant is eligible, the Clinical Trials Center will assign that participant to receive either pravastatin or usual care. Each participant randomized to receive pravastatin will be issued an appropriate supply of 20 mg tablets and instructed to take ***two*** each evening (a daily dose of 40 mg/day). (Alternatively, one 40 mg tablet each evening may be prescribed.) Participants assigned to usual care as well as those assigned to pravastatin will be advised to follow the NCEP Step I diet. A fasting lipoprotein profile will be

obtained at this visit as a baseline for each randomized participant in this trial.

NOTE: Nearly all of the participants in the cholesterol-lowering trial will begin the study with LDL-cholesterol levels moderately exceeding the NCEP-recommended levels for patients with multiple risk factors. For such patients, the NCEP guidelines recommend a therapeutic diet and that drugs be considered for patients who are unable to lower their LDL-cholesterol to within 30 mg/dl of the goal level. In ALLHAT, we will compare the outcome when a powerful LDL-cholesterol-lowering drug is provided at the outset to that when only dietary therapy is employed.

The upper LDL-cholesterol exclusion cutoffs (130 and above for those with clinical CHD; 190 and above for those without clinical CHD) were chosen so that current clinical practice would not mandate the use of cholesterol-lowering drugs in the "usual care" group. ***However, it is possible that the physician may believe strongly that some patients who are eligible for this trial component require cholesterol-lowering drugs. Such patients should not be randomized to this component of ALLHAT.***

2.2 The ALLHAT Antihypertensive Trial Eligibility Worksheet (AL01)

The first two pages of the ALLHAT Antihypertensive Trial Eligibility Worksheet (AL01) serves to report the exclusion and inclusion criteria and patient information to the Clinical Trials Center.

2.2.1 Visit 1 section of the AL01

In getting ready to review the patient's chart, write the patient's name in the space provided. The four parts of Item #1 will be verified with you at the time that the patient is randomized to the antihypertensive trial. You may leave them blank for now. Briefly, the randomization number is comprised of three parts - your three-digit center number, a three-digit trial number assigned at randomization, and another three-digit center number. The first and last center numbers will almost always be the same. If a participant is permanently transferred to another ALLHAT Clinical Center, the first three digits will change, but the last three will remain the same. If your clinic has more than one site, we will assign you a site code before the trial begins, and verify this with you at randomization. Site codes are A, B, C, etc., and are not assigned in any particular order. They are, however, extremely important in reimbursing you for certain study visits. Each participant is also assigned an acrostic. This is a combination of the first three letters of their last name, the first two letters of their first name, and their middle initial. For example, the acrostic for Jackson T. Wright is WRIJAT, and the acrostic for Mary Smith (no middle initial) is SMIMA. This extra identifier is useful to the Clinical Trials Center in verifying that a form does, indeed, belong to the participant whose ID is given, and in the case of a problem with other identifying information on the form.

Please note the warning regarding the age criteria for ALLHAT. If the patient will not be 55 years of age by Visit 2 (say, within the next three months), you may want to put this chart

aside and re-evaluate this patient later.

Most of the information on exclusion and eligibility may already be in the patient's chart, and should be obtained prior to the patient's next scheduled visit. These items are not meant to be used to interview the patient! Each item should be marked "Yes" or "No" until you reach an item that would exclude the patient. There is no need to complete the entire form for ineligible patients.

Item #2 - Compliance exclusion:

For Item #2, if you suspect that a patient is demented, has a recent history of alcohol or drug abuse, has plans to move or travel extensively, or has a history of unreliability in keeping appointments or taking their prescribed drugs, they might not be the best candidate to enter into ALLHAT. If the patient has any of these problems, please check "Yes" and exclude this patient from additional evaluation for ALLHAT. ***The importance of compliance to the success of ALLHAT cannot be stressed enough. A patient may be eligible on every other criterion, and may sign an informed consent to be randomized. However, if he or she subsequently refuses to take the study medication, starts other medications, or refuses to attend the clinic for scheduled visits, the patient is essentially lost to the trial and the power of the study to address its hypotheses is diminished. It is in your patients' best interests as well as the best interest of the study that you take care in considering which of your patients might be good candidates for ALLHAT.***

Items #3 through #10 are medical exclusion criteria. Check each one carefully, marking "Yes" or "No" for each one, considering the following guidelines:

Item #3 - Symptomatic MI or stroke within the last six months:

Symptomatic MI or stroke includes all patients with signs and/or symptoms of these disorders that bring them to medical attention and lead to diagnosis. These include classic, textbook, clinical presentations as well as transient episodes of arrhythmia, LV dysfunction, or disorientation, for example, that lead to diagnosis of MI or stroke. It does not include cardiac infarction detected on routine ECG or other cardiac studies, or stroke detected on cerebral imaging performed for reasons other than suspected stroke. The reason for excluding patients with recent MI or stroke is that they may be clinically unstable and/or emotionally unsettled shortly after diagnosis of a serious event such as these and are not in the best position to make decisions about long-term commitments to a randomized trial. After their condition has stabilized they may be approached about entry to the trial if in the investigator's mind they remain a reasonable candidate for the study. *Atrial fibrillation is not an exclusion criterion.*

Item #4 - Hospitalized or treated symptomatic congestive heart failure (CHF) and/or ejection fraction < 35%, if known:

Hospitalized or treated symptomatic CHF includes patients with clear-cut signs or symptoms of left or right ventricular dysfunction that cannot be attributed to other causes. It

should not include patients with only lower extremity edema or exertional dyspnea, as these can be present in the absence of any cardiac dysfunction. Criteria to be used for classification of incident CHF are described in Chapter 5 and may be useful in identifying CHF at entry to the study. Patients with symptomatic CHF are excluded because strong evidence suggests that they would benefit from treatment with an ACE inhibitor¹, one of the four classes of blinded study agents.

Item #5 - Angina pectoris within past 6 months:

Angina pectoris includes diagnosed symptomatic angina, classically described as substernal visceral pain or heaviness provoked by exertion and relieved by rest, or any other symptomatic anginal syndromes or equivalents believed by the investigator to be due to intermittent inadequacy of coronary blood supply. These patients are excluded because they may ultimately require symptomatic treatment with calcium antagonists, one of the four classes of blinded study agents. *Patients with a history of angina but who are asymptomatic for at least six months are eligible and may be switched to beta blockers and/or nitrates for treatment of angina if they are already receiving calcium antagonists and if it is deemed safe to do so. Otherwise, these patients should be excluded.*

Item #6 - Known renal insufficiency (serum creatinine 2 mg/dl [76.3 µmol/L] or higher):

Known renal insufficiency as documented by a serum creatinine 2 mg/dl (76.3 µmol/L) or higher is an exclusion criterion because such patients have a higher mortality risk within the study period. Serum creatinine need not be checked before randomization into the study. If the creatinine drawn at the time of randomization should be found to exceed 2 mg/dl (76.3 µmol/L) these patients will be maintained in the trial, and will be treated and followed on randomized study drug according to the protocol.

*Item #7 - **Requires** thiazide-like diuretics, calcium antagonists, ACE inhibitors, or alpha adrenergic blockers for reasons other than treatment of hypertension (e.g. CHF, angina)*

Patients on one of the four classes of Step 1 (blinded) study drugs within one month of randomization, for reasons other than treatment of hypertension*, or requiring or likely to require any of these drugs for reasons other than treatment of hypertension should not be entered into the study. This includes patients with conditions such as CHF or symptomatic angina for which one of the four classes is clearly indicated. It also includes conditions for which other effective and well-tolerated therapies are available, such as benign prostatic hypertrophy. Investigators should use their judgment in such situations, recognizing that no patient should be denied a potentially beneficial treatment because they have agreed to participate in ALLHAT. Should a need for one of the classes of blinded study drugs arise after randomization, such treatment can be administered as described in the protocol, but if such a need can be anticipated before

¹ The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

randomization, the patient should not be entered into the trial.

*If a patient requires one of the four classes of Step 1 (blinded) study drugs for reasons other than hypertension, you may substitute an alternative drug (e.g., nitrates or beta-blockers for angina), if it is deemed safe to do so, in order to allow that patient to enter the trial. It is recommended that the patient be switched to the alternative drug at least one month prior to randomization to assess its effectiveness. **Informed consent is required.** If the patient cannot be safely switched to an alternative medication, the patient should not be entered into the trial.

Item #8 - Requires therapeutic doses of three or more antihypertensive drugs to achieve satisfactory blood pressure control (SBP \leq 160 mm Hg and DBP \leq 90 mm Hg):

These patients' blood pressures may not be controllable on one or two medications as prescribed in ALLHAT. Combination drugs that include more than one class of drug (e.g., a diuretic and a beta-blocker) should be counted as two drugs. Patients on subtherapeutic doses of three more medications or on three or more medications in ineffective combinations are eligible.

Item #9 - Sensitivity or contraindication to any of the first-line (Step 1, blinded) study medications:

Sensitivity and contraindications to diuretics, calcium antagonists, ACE inhibitors, or alpha adrenergic blockers as described in the following boxes:

SENSITIVITY

- *Any*: Serious prior adverse experience with or serious intolerance to one of the drugs (or classes, if potentially a class effect). Examples of serious adverse experiences which would exclude a patient from the trial if he/she had experienced one of them with a study drug or drug class would be:
 - *Chlorthalidone*: Severe dermatitis or necrotizing vasculitis.
 - *Amlodipine*: None.
 - *Lisinopril*: Angioedema, significant neutropenia or vasculitis.
 - *Doxazosin*: Syncope.

A history of one or more side effects with one of the Step 1 (blinded) study drugs or drug classes that were not life threatening or serious is not a study exclusion.

Examples of such non-exclusion side effects are muscle cramps, constipation or impotence with a diuretic; flushing, dizziness or palpitations with a dihydropyridine calcium blocker; dizziness, cough, or rash with an ACE inhibitor; or dizziness, impotence or lethargy with an alpha blocker.

CONTRAINDICATIONS

- *Chlorthalidone*: None
- *Amlodipine*: None
- *Lisinopril*: Bilateral renal arterial disease or severe stenosis in artery to a solitary kidney; history of angioedema
- *Doxazosin*: Symptomatic orthostatic hypotension from an underlying condition (e.g., autonomic neuropathy)

Item #10 - Disease, such as non-curable malignancy, likely to lead to non-cardiovascular death over the course of the study:

Patients with life-threatening diseases likely to lead to non-cardiovascular death during the study are excluded because of the negative effect that these events have on the statistical power of the study to address its primary question.

Item #11 - Participation in another clinical trial

Patients currently participating in other clinical trials should not be entered as a new patient into ALLHAT until 30 days after they have complete the other trial. A patient may be entered into ALLHAT if they are enrolled in another study which is a cross-sectional, retrospective or prospective epidemiologic (observational) study and permission is given to enter ALLHAT by the principal investigator of the other study. If the patient is randomized into ALLHAT and it is subsequently learned that he/she was already a participant in another study, he/she should not be withdrawn from ALLHAT. Use of ALLHAT medications will need to be negotiated with the investigator of the other study.

Participants in ALLHAT should be instructed not to enter another clinical study, even if it only involves taking a single dose of a drug or participation in a single procedure (e.g., in a randomized study). If an ALLHAT participant is inadvertently entered into another trial, they are still a participant in ALLHAT, should continue to follow the ALLHAT protocol, and should be withdrawn from any medications given in the other study. Please call your Regional Coordinator for any clarification. Again, the participant should not be withdrawn from ALLHAT.

Once you have completed Items #2 through #11, double-check if any of the items is marked "Yes". If any of the items is marked "Yes", then the patient is not eligible for ALLHAT.

For patients remaining eligible, go on to check the eligibility criteria in Items #12 through #20. Again, most (if not all) of this information should already be in the patient's chart. If any documentation is not attainable by chart review or not available within the time period specified below, please perform the necessary tests at Visit 1. These will not be specifically reimbursed by the study.

Item #12 - Old (> 6 months) or age-inderminate myocardial infarction or stroke:

Acute myocardial infarction or stroke may be documented in records from the patient's own chart if the event occurred while under your care. If the patient reports a previous MI or stroke under another doctor's care, you may contact the other doctor or hospital to get verbal confirmation of the event, or obtain the medical records with the patient's permission. If neither of these are possible, you should query the patient in enough detail to satisfy yourself that the patient actually had the event.

Old or age-indeterminate myocardial infarction may be documented by one of the following: Q waves on ECG; akinesis or dyskinesis on echocardiogram, MUGA, or ventriculogram; prior hospital diagnosis. If MI by ECG is questionable, but you would tell the patient that he or she might have had an MI based on the ECG, that would be sufficient for this eligibility criterion.

An old or age-indeterminate stroke may be documented by one of the following: prior hospital diagnosis, or infarct on CT or MRI scan. A spinal cord infarct would not meet inclusion criterion unless it were a complication of atherosclerosis (vs. trauma, vasculitis, etc.) It can occur with clamping of the aorta during abdominal aortic aneurysm (AAA) repair - if so, the AAA repair would be a sufficient criterion (see #15).

Item #13 - History of revascularization procedure:

Examples of revascularization procedures include: angioplasty (coronary, peripheral vascular); bypass surgery (coronary, peripheral vascular, carotid, vertebrobasilar); aortic aneurysm repair; and other revascularization procedures (e.g., atherectomy). "Clipping of a cerebral aneurysm" is probably not sufficient to meet this entry criterion, since cerebral aneurysms are not usually atherosclerotic phenomena. However, if it were related to atherosclerosis, it would be acceptable. *Presence of varicose veins, or surgery for varicose veins is also not sufficient to meet this criterion.*

Item #14 - Major ST depression or T wave inversion on any ECG within the past two years

ST depression: J-point depression at least 0.5 mm and the following ST segment flat or downsloping in any of the leads I, II, aVL, or V₁-V₆.

T-wave inversion: T-wave inverted at least 1 mm in any of leads I, II, aVL, aVF, or V₂-V₆.

ST-depression or T-wave inversion are not coded in the presence of conduction defect (QRS 0.12 sec or more).

Computer ECG interpretation is acceptable when it strongly indicates that ST-T wave changes are of ischemic origin, i.e., ST-T wave changes suggest ischemia, diffuse repolarization abnormalities suggest ischemia. Patients with minor non-specific ST-T wave findings cannot qualify for *ALLHAT* based only on this finding.

Item #15 - Any other documented atherosclerotic cardiovascular disease:

A list of what might be included as ASCVD may be found in Table 2.1. Varicose veins are not from atherosclerosis, so varicose veins would not meet this entry criterion.

Table 2.1 - Revised 12/96	
MANIFESTATIONS OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE	
1.	History of angina pectoris
2.	History of intermittent claudication, gangrene, or ischemic ulcers
3.	History of transient ischemic attack
4.	Coronary, peripheral vascular, or carotid stenosis 50% or more documented by one of the following: <ul style="list-style-type: none">- angiography- Doppler studies
5.	Ischemic heart disease documented by one of the following: <ul style="list-style-type: none">- stress thallium - reversible or fixed ischemia- dipyridamole thallium- reversible or fixed ischemia- exercise testing - ST depression ≥ 1 mm for ≥ 1 minute- reversible wall motion abnormality on stress echocardiogram- Holter monitoring - ST depression ≥ 1 mm for ≥ 1 minute
6.	Ankle-arm index less than 0.9 (example procedure to be added to Appendix D, BP measurement)
7.	Abdominal aortic aneurysm detected by ultrasonography, CT scan, or X-ray
8.	Carotid or femoral bruits

Item #16 - Type II diabetes mellitus [fasting plasma glucose 140 mg/dl (7.77 mmol/L) or higher, or nonfasting plasma glucose 200 mg/dl (11.1 mmol/L) or higher, and/or on insulin or oral hypoglycemics:

One of these criteria must have been met within the past two years.

Item #17 - HDL-cholesterol < (less than) 35 mg/dl (0.91 mmol/L)(on 2 or more determinations within past 5 years):

This criterion applies whether or not the patient is already on lipid-lowering medications of any type. A patient on a medication that raises HDL-cholesterol, without two HDL's < (less than) 35 mg/dl (0.91 mmol/L) in the past five years, would not qualify based on this particular

eligibility criterion. A high total cholesterol level does not by itself qualify the patient for ALLHAT.

Item #18 - Left ventricular hypertrophy (LVH) by ECG:

An ECG used for this determination must have been obtained within the last two years. Left ventricular hypertrophy by ECG includes any one of the following:

- R amplitude in V₅ or V₆ > 26 mm.
- R amplitude in V₅ or V₆ plus S amplitude in V₁ > 35 mm.
- R amplitude in aVL > 12 mm.
- R amplitude in Lead I > 15 mm.
- R amplitude in Leads II or III, or aVF > 20 mm.
- R amplitude in Lead I plus S amplitude in Lead III > 25 mm.
- R amplitude in aVL plus S amplitude in V₃ > 28 mm for men or > 22 mm for women
- Computerized ECG machine documented LVH

For visual LVH reading, QRS amplitudes are measured in the ***second to last complete normal beat*** of the lead.

A computerized reading indicating "borderline" or "possible" LVH should be measured for the above voltage criteria.

Item #19 - LVH by echocardiogram:

If any echocardiogram done in the past two years indicates a combined wall thickness of 25 mm or more, the patient will qualify by this criterion. "Combined wall thickness" means posterior wall plus interventricular septum.

Item #20 - Current cigarette smoker:

This criterion refers ONLY to cigarette smoking, not cigars or pipes. A patient is a current smoker if he or she smoked any cigarettes within the past 30 days. Patients who qualify by this criterion should still be encouraged to quit smoking based on the ALLHAT lifestyle advice.

Once you have completed items #12 through #20, double-check to be sure that at least one of the items is marked "Yes". If not, the patient is not eligible for ALLHAT.

Items #21-25 - Visit 1:

In Item 21, complete the date as mm/dd/yy, using leading zeros where necessary. Using the blood pressure measurement procedures as explained in Appendix B, determine the proper blood

pressure cuff size, and take two seated blood pressure readings. (*Patients should be seated for five minutes, feet flat on the floor, in an erect but comfortable position, without smoking.*) The person performing the blood pressure measurements should print their initials in #22c. The average blood pressure reading should be entered as indicated on the form. Since all readings are to the nearest even mm Hg, no fractions are allowed here.

In addition to the patient's blood pressure, their antihypertensive medication status is used in determining eligibility at Visit 1. Three categories of treatment are possible:

On 1-2 drugs \geq 2 months On drugs $<$ 2 months Currently untreated	\geq means "greater than or equal to" $<$ means "less than"
--	--

Combination drugs that include more than one class of drug (e.g., a diuretic and a beta-blocker) should be counted as two drugs. If you are uncertain of how long the patient has been on medications to lower their blood pressure, please clarify this with the patient. If the patient has been on drugs recently, but is off medications at this visit (e.g., ran out of medications), they can be considered in either medication category according to the judgement of the investigator. Mark the appropriate response in Item #23 (Antihypertensive medication status).

Using the average blood pressure and knowledge of how long they have been on antihypertensive medications, use the chart on the form to determine if the patient is in a medication category and blood pressure range that would qualify them (so far) for ALLHAT:

On 1-2 drugs \geq 2 months:		On drugs $<$ 2 months or currently untreated:	
SBP \leq 160	<input type="checkbox"/> Yes <input type="checkbox"/> No	SBP \geq 140	<input type="checkbox"/> Yes <input type="checkbox"/> No
DBP \leq 100	<input type="checkbox"/> Yes <input type="checkbox"/> No	DBP \geq 90	<input type="checkbox"/> Yes <input type="checkbox"/> No
		SBP \leq 180	<input type="checkbox"/> Yes <input type="checkbox"/> No
		DBP \leq 110	<input type="checkbox"/> Yes <input type="checkbox"/> No
Both must be " Yes " for patient to be eligible.		One of these . . .	
		. . . AND both of these must be " Yes " for patient to be eligible.	

Please carefully note the "ands" and "ors". A patient must be hypertensive based on either their systolic or diastolic pressure (or both), but cannot have either blood pressure exceed an upper limit. To clarify this (and for your practice), several examples are given below:

Medication status	Avg. SBP/DBP	Eligible?	If not, why?
On 1-2 drugs \geq 2 months	155/92	Yes	
On 1-2 drugs \geq 2 months	182/92	No	SBP too high
On drugs $<$ 2 months	144/76	Yes	
Untreated	132/88	No	Both too low

Please note the following regarding diagnosis of hypertension in patients not currently on

treatment:

Patients not currently on treatment must be diagnosed as hypertensive according to the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V) criteria. That is:	
●	Hypertension should not be diagnosed on the basis of a single measurement.
●	Initial elevations should be confirmed on at least two subsequent visits over one to several weeks (unless SBP \geq 210 mm Hg and/or DBP \geq 120 mm Hg).
●	Average levels of DBP \geq 90 mm Hg and/or SBP \geq 140 mm Hg are required for diagnosis.

If you have any questions regarding blood pressure eligibility, please do not hesitate to call your Regional Coordinator for clarification. Patients who exceed the upper blood pressure limits and who are untreated or who are on one antihypertensive medication may have their dosage increased or have an additional antihypertensive drug prescribed in order to better control their blood pressure. These patients can be reassessed at a subsequent visit to see if they meet the blood pressure eligibility criteria. For patients on antihypertensive drugs for less than 2 months whose blood pressure is below the lower limits and who are on antihypertensive medications may have the dosage of these medications reduced to see if their blood pressure rises into the qualifying range. ***In order to taper (step down) antihypertensive medications (if necessary), the informed consent form for the antihypertensive trial must be signed at Visit 1, rather than waiting until Visit 2.***

If the patient is eligible, you should carefully review the patient booklet and the informed consent for the antihypertensive trial, being careful to explain that one more visit is necessary prior to randomization.

When you complete the form for an eligible patient, review it carefully to ensure that all items on page 1 are marked as appropriate, that the patient has none of the exclusion criteria in Items #2-11, and has at least one of the medical eligibility criteria in Items #12-20 (PLEASE MARK ALL THAT APPLY), and that their medication status and average blood pressure qualify them for ALLHAT. Then initial the form in Item #24 and sign #25.

If you need any tests to make a final determination of eligibility, these should be performed as soon as possible. Make an appointment to see the patient not less than 1 day nor more than 12 weeks from Visit 1.

Patients should be told to come in fasting (at least 12 hours optimum, or 9 hours minimum) for Visit 2. Patients on a diuretic (or potassium supplements, if any) should not take their medication on the day of Visit 2.

IF A BETA BLOCKER OR CENTRAL AGONIST IS BEING TAPERED PRIOR TO VISIT 2: Patients whose blood pressure exceeds 180 mmHg systolic or 110 mmHg diastolic during tapering should return within 3-7 days for a repeat blood pressure measurement. If the blood pressure is still above 180/110 mmHg at this second visit, the patient should not be randomized into the antihypertensive trial.

2.2.2 Visit 2 section of the AL01 Information from Visit 2 is collected on pages 3 and 4 of the AL01. As described previously for page 1 of the AL01, complete the identifying information at the top of page 3.

Items #26-31 - BP eligibility and randomization:

In Item #26, complete the date as mm/dd/yy, using leading zeros where necessary. Similarly, complete the birthdate in Item #27 - note that the year has four digits here. *The patient must be at least 55 years of age at the time of randomization.* Using the blood pressure measurement procedures as explained in Appendix B, determine the proper blood pressure cuff size (#28b), the heart rate (beats in 30 seconds x 2, #28b), take two seated blood pressure readings (#28c), and determine their average. Use leading zeros where necessary. The person performing the blood pressure measurements should print their initials in #28d. All blood pressure readings should be recorded to the nearest even mmHg.

Determine the patient's blood pressure eligibility at this visit. ***Use the same medication category that you used for determining eligibility at Visit 1.*** Using the Visit 2 average blood pressure, use the chart on the form to determine if the patient is in a medication category and blood pressure range that would qualify them (so far) for ALLHAT:

<i>On 1-2 drugs ≥ 2 months:</i>	<i>On drugs < 2 months or currently untreated:</i>	
SBP ≤ 180 <input type="checkbox"/> Yes <input type="checkbox"/> No	SBP ≥ 140 <input type="checkbox"/> Yes <input type="checkbox"/> No	SBP ≤ 180 <input type="checkbox"/> Yes <input type="checkbox"/> No
DBP ≤ 110 <input type="checkbox"/> Yes <input type="checkbox"/> No	DBP ≥ 90 <input type="checkbox"/> Yes <input type="checkbox"/> No	DBP ≤ 110 <input type="checkbox"/> Yes <input type="checkbox"/> No
Both must be " Yes " for patient to be eligible.	One of these AND both of these must be " Yes " for patient to be eligible.

If the patient's blood pressure does not fall into the eligible range at this visit, the patient may be brought back for an extra visit or two to recheck the blood pressure level for eligibility. If the patient does not remain blood pressure eligible, you do not need to complete the remainder of the AL01.

For patients who remain eligible, record the patient's weight in pounds (to the nearest whole pound) using a leading zero if necessary, and their height in inches without shoes (to the nearest whole inch), in Items #29 and #30.

If you have not done so, and if the patient is eligible, you should carefully review the patient booklet and the informed consent for the antihypertensive trial at this time. The informed consent must be signed prior to randomization into the antihypertensive trial. If the patient agrees to participate and signs the consent form, mark "Yes" in Item #31 and proceed to the

randomization telephone call. Otherwise, thank the patient for considering participation in **ALLHAT** and proceed with your routine clinic visit.

Congratulations! You now have a patient who is eligible and willing to be randomized into the antihypertensive trial! **To prepare for randomization, have all four pages of the AL01 in front of you before calling the Clinical Trials Center.** Complete Item #32 (date randomized), using the usual mm/dd/yy format and using leading zeros as necessary. You may call the Clinical Trials Center at 1-800-690-7870 any time between 7:00 a.m. and 5:00 p.m. Central Time to randomize a patient. During this brief telephone call, a Clinical Trials Center staff member will verify your center name and number, your site code, and most of the information on the AL01 and give you a Step 1 (blinded) drug bottle number. Copy the Step 1 (blinded) drug bottle number into Item #33, using a leading zero as necessary.

Upon completion of the telephone call, thank the participant for volunteering to participate in ALLHAT! You are not quite done with the AL01, however. A minimum amount of additional information is requested in order to characterize the ALLHAT participants at entry to the trial, and a few "housekeeping" items are requested.

Items #33 and #34 - Social Security number and Medicare number:

The participant's Social Security number (#33) and/or Medicare number (#34) will be used to track that participant if they are lost to follow-up, and may be used to track all participants after ALLHAT ends. This is extremely important information - a simple transcription error here will make this information useless, so take care in recording these numbers. **The Medicare number must be completed for participants 65 years of age or older.** You should leave the Medicare number blank only for participants under 65 years of age. Both of these items will be updated every two years during follow-up.

Some participants age 65 or older will not have Medicare numbers, and not all participants will have Social Security numbers. In these cases, simply complete these items with 9's (i.e., 999-99-9999 for the Social Security Number) - do not leave either item blank. Do not record numbers other than Social Security and Medicare numbers; if a participant does not have a Social Security Number and/or Medicare number, please record as 999-99-9999.

Item #36a and #36b - Race and Hispanic origin:

Item #36a asks for the race of the participant. If you are unsure how to answer this question, this is one that you can ask the participant directly, using language that you are comfortable with and that the participant will comprehend. What we are seeking is how the participant would describe himself or herself. Item #36b asks if the participant (self-described) is of Hispanic origin (DK = don't know"). **Both questions must be answered!** For example, a participant may be Black and of Hispanic origin.

Items #37 - #39 - Sex, cigarette smoking, and years of education:

In Item #37 put an "X" in the appropriate box for "Male" or "Female". In Item #38 indicate whether the participant is a current smoker (in past 30 days) or past smoker (not a current

smoker, but more than 100 cigarettes in his or her lifetime), or has never smoked cigarettes. Item #38 refers only to cigarettes, not cigars or pipes. For example, a participant who previously smoked more than 100 cigarettes but in the last 30 days has smoked only a pipe would be classified as a "past smoker".

Item #39 asks for years of education starting with first grade. Code this item as "99" if this is unknown and cannot be clarified with the participant.

Items #40 and #41 - Use of other medications at baseline:

Regular use of aspirin (Item #40) may alter the participant's risk of cardiovascular events. Indicate here whether the participant is currently taking regular doses of aspirin (not non-aspirin pain relievers). Medications that contain aspirin include, but are not limited to:

Acuprin 81	Excedrin Extra-Strength
Alka-Seltzer	Fiorinal
Anacin	Gelpirin
Ascriptin	Goody's (powder)
Arthritis Pain	Lortab ASA Tablets
Regular Strength	Methocarbamol & Aspirin
Aspirin	Norgesic or Norgesic Forte
Axotal	PC-CAP propoxyphene
Azdone	hydrochloride
BC (powder)	Panasal 5/500
Bufferin	Percodan or Percodan-Demi
Arthritis Strength	Propoxyphene HCl/Aspirin
Extra Strength	Robaxisal
Bufferin	Roxiprin
Damason-P	Soma Compound
Darvon Compound-65	Supac
Easprin	Synalgos-DC
Ecotrin	Talwin
Empirin	
Equagesic Tablets	

Item #41 - Estrogen supplementation (for women only):

For women only, Item #41 requests information regarding current (within the past two weeks) use of estrogen (oral or patch). This includes any estrogen preparation which might include or be taken with other hormones. *Please leave this item blank for men!*

If you are unsure of any of the above items, please discuss the proper response with the participant.

Items #42-#46 are eligibility items for the lipid-lowering trial:

Item #42 - Evidence of CHD:

The LDL-cholesterol entry criteria for the lipid-lowering trial depend on whether the participant has existing coronary heart disease (CHD). Existing CHD includes known prior myocardial infarction (including silent MI), angina, primary cardiac arrest, angiographically defined coronary stenosis more than 50%, reversible perfusion defects on cardiac scintigraphy, or prior coronary revascularization procedures. If the participant has existing CHD, mark "Yes" for Item #42. If not, or you are not sure, mark "No". Use this question as a reference for later LDL-cholesterol eligibility criteria.

Item #43 - Current use of lipid-lowering agents:

Any person on prescribed lipid-lowering agents (resins or HMG CoA reductase inhibitors) or on at least 500 mg/day of niacin at any time during last two months, or on probucol any time during the past year, is not eligible to participate in the lipid-lowering trial. If the participant has been on such medications, mark "Yes" for Item #43. If not, then mark "No". If you are not sure, clarify with the participant. Some commonly used HMG Co-A reductase inhibitors are lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), and fluvastatin (Lescol).

Item #44 - Contraindications to HMG CoA reductase inhibitors:

Patients with contraindications to HMG CoA reductase inhibitors, such as significant hepatic or renal disease (known cirrhosis or active hepatitis, or renal insufficiency requiring protein restriction or dialysis), previous organ transplantation requiring immunosuppressive therapy, or known allergy or intolerance are not eligible. If the patient has any of these conditions, mark #44 as "Yes"; that patient is ineligible. If not, mark "No".

Item #45 - Known untreated secondary cause of hypercholesterolemia:

The last exclusion during this review is a known untreated secondary cause of hypercholesterolemia, such as nephrotic syndrome or untreated hypothyroidism. If the patient has any of these possible secondary causes for hypercholesterolemia, then mark #45 as "yes", and that participant is ineligible. If not, mark "No".

Item #46 - Willingness to enter the lipid-lowering trial:

If the patient is not excluded from the lipid-lowering trial by any of Items #43 - #45, you should discuss the possibility of participating in the lipid-lowering trial of ALLHAT. An informed consent does not need to be signed at this visit for the lipid-lowering trial, but some of the details in the patient brochure may be reviewed at this time. Final determination of eligibility for the lipid-lowering trial will be determined using the results of blood drawn at Visit 2 (laboratory panel ALL01). If an eligible patient refuses to consider enrolling in the lipid-lowering trial, mark Item #46 as "no". If the patient is willing to enroll in the lipid-lowering trial, mark "yes". If the patient is undecided, mark "not sure". If the patient is ineligible due to one of Items #43 - #45, mark "not eligible".

Patients who are potentially eligible for the lipid-lowering trial should be told to come in fasting at Visit 3.

Items #47 and #48 - Quality of life items:

The remaining two questions on this form must be asked of the participant directly. Both of these items are indicators of health-related quality of life. The first, Item #47, is relatively straightforward. Repeat the question to the participant exactly as worded, and verbally list the response categories. Record the participant's response.

The second quality of life item, Item #48, might be a little harder for the participant to understand. Use language that you think might make the questions clearer for the participant. *If the participant is having trouble thinking of a 0-100 scale, you may use a 0-10 scale for clarification, but be sure to multiply the response by 10.* If the participant just cannot answer this question, code this question as "999"; do not leave this item blank.

Dispensing Step 1 (blinded) medications and other procedures at Visit 2 for randomized participants:

At this point in the visit, the baseline 12-lead ECG should be obtained, blood should be drawn for the baseline laboratory evaluations, and the diet and lifestyle advice for blood pressure reduction should be discussed (see Appendix E). The Patient Contact Information sheet, or a similar information sheet from your center, should be completed. Give the participant their assigned 7-day and 30-day supply of the Step 1 (blinded) medication (Dose 0 and Dose 1). Be sure that the participant understands how and when to take their ALLHAT medication. (The first dose of study medication should be taken the day *after* randomization, and should be taken in the morning.)

Item #49 - Consent for DNA analysis:

This procedure has been deleted for ALLHAT. Leave this item blank or mark "No". It will not be edited by the CTC.

Items #50 - #52 - Date of next visit, initials and signature

Schedule the 1-month visit in the window provided by the CTC at randomization. Complete the actual scheduled date in mm-dd-yy format, using leading zeros where necessary. Initial and sign the form in the spaces provided.

Finishing up!

You should now retrieve the set of labels that corresponds to the three-digit individual participant ID (identification) number given to you by the Clinical Trials Center. (These labels are discussed in detail in Chapter 7.) You should complete the participant's acrostic as given to you by the CTC at randomization. Separate the original (white) and NCR (yellow) copies of the AL01 (all four pages), and immediately staple the white copy and staple the yellow copy in the upper left hand corners. Use the ID labels on each page of the white copy. Do not cover the

randomization date on page 1! Use a label on the front of the yellow copy (this is your copy). The *Baseline ECG* label should be affixed to the back of a single-channel recording, and on the front of a three-channel recording. More ID labels will be generated for this participant by the Clinical Trials Center, and you should receive these in a week or two.

You're done!

2.2.3 ECG and Central Laboratory

Participants randomized to the hypertension trial should have a baseline ECG and should have blood drawn for analysis at the *ALLHAT* Central Laboratory. If the participant has had an ECG in your clinic *within the past year*, a new ECG does not need to be recorded. If you choose to use an existing ECG, send the original (not a copy) to the ECG Coding Center as described in Appendix C. Blood should be drawn for analysis (panel ALL01) at the Central Laboratory as described in Appendix D. *Note: If the participant has not fasted prior to the blood draw, the participant may still be randomized into the antihypertensive trial. If, in your judgment, it is not possible to draw a fasting blood sample within a day or two, draw the blood non-fasting at Visit 2. Nonfasting LDL-cholesterol and triglyceride values may be used to determine eligibility for the lipid-lowering trial.*

2.2.4 Visit schedule and participant identification and medication labels

When a participant is randomized into the antihypertensive trial, a visit schedule will be generated by the Clinical Trials Center indicating the required study visits, the visit windows for each visit (earliest date and latest date), and procedures expected at those visits. The participant's assigned Step 1 (blinded) medication bottle number will be listed. In addition, a set of identification labels will be printed listing the Center name, site code, the participant's ID number and acrostic. Labels will also be printed for the laboratory request slips and blood specimens and to affix to the ALLHAT medication bottles. The visit schedules and labels are discussed in Chapter 7.

2.3 AL02 (Lipid-lowering Trial Eligibility and Randomization Form)

In order to participate in the lipid-lowering trial of ALLHAT, participants must be eligible and enrolled in the antihypertensive trial.

Print the participant's name at the top of the form, or use a pre-printed ID label generated by the Clinical Trials Center.

Item #1 - Date of randomization to the lipid-lowering trial:

Item #1, the date of randomization to the lipid-lowering trial, should be left blank until the participant is actually randomized into the lipid-lowering trial.

Several of the eligibility items have already been determined at Visit 1 (AL01 Items #43-#46). These are summarized on the AL02 as a reminder of the criteria that would exclude the participant from the lipid-lowering trial.

2.3.1 Visit 2 Section of the AL02

Items #2 - #4: Laboratory values from the Visit 2 blood draw:

The final determination of eligibility for the lipid-lowering trial is determined by the results of the lipid profile drawn at Visit 2 (laboratory panel ALL01). When the results are received from the Central Laboratory, complete the Visit 2 section of the AL02 with the LDL-cholesterol (Item #2) and triglycerides (Item #3), taking care to note if the values fall into the eligible range. If the participant's LDL-cholesterol and triglycerides fall within the eligible range given on the form (depending on whether the participant has existing CHD), and the ALT (Item #4) is less than 100 IU/L (2 times the upper limit of normal), then the participant is eligible for the lipid-lowering trial. If the ALT is more than 100 IU/L, the participant should be recalled to the office for blood work only to recheck this value. If the ALT from the Central Laboratory is still 100 IU/L or more, the participant should be excluded from the lipid-lowering trial.

2.3.2 Completing the AL02 at Randomization to Lipid-Lowering Trial

Items #5-#8 - Lipid-lowering consent and randomization:

If the participant is eligible and willing to participate in the lipid-lowering trial, and signs the lipid-lowering trial informed consent form, you will be performing a randomization similar to the antihypertensive trial randomization. In Item #5, indicate whether or not the participant has signed the lipid-lowering trial informed consent form. If not, the participant cannot be randomized to the lipid-lowering trial. **In preparation for randomizing participants who are eligible and willing and have signed the consent form, have the AL01 and AL02 in front of you before calling the Clinical Trials Center.** You may call the Clinical Trials Center at 1-800-690-7870 any time between 7:00 a.m. and 5:00 p.m. Central Time Monday through Friday to randomize a participant. During this brief telephone call, a Clinical Trials Center staff member will verify your center name and number, your site code, and some of the information from the AL01 and AL02, and assign the participant to pravastatin or usual care. Indicate the treatment assignment in Item #6. The caller should initial the form in Item #7 and sign #8.

Upon completion of the telephone call, thank the participant for volunteering to participate in the lipid-lowering trial!

If the participant was randomized to pravastatin, retrieve a bottle of pravastatin and be sure that the participant understands how and when to take the medication. The first dose of medication should be taken at bedtime on the same day as randomization. **The starting dose of pravastatin is 40 mg/day (two pills), taken at bedtime.** Alternatively, 40 mg tablets may be used (one per day, taken at bedtime).

The NCEP Step 1 diet should be discussed at this time (see Appendix E), and blood should be drawn for a second determination of baseline lipid values (laboratory panel ALL02). All participants should receive a copy of the booklet "Eating to Help Your High Blood Cholesterol".

Label the form using labels generated by the Clinical Trials Center that correspond to the three-digit individual participant ID number given to you by the Clinical Trials Center at

randomization to the antihypertensive trial. By the time of Visit 3, you should have the labels that are pre-printed with the participant's name, ID number and acrostic. (These labels are discussed in detail in Chapter 7.) You should affix these to the place indicated on the AL02 and separate the copies.

You're done with the AL02!

2.3.3 Revised schedule for laboratory analyses

Participants randomized into the lipid-lowering trial will require additional laboratory analyses at specified follow-up visits, depending on which treatment group they were assigned to and whether they were selected to be among the subsample of participants who receive extra lipid profile evaluations at specified visits. A revised visit schedule will be generated at the Clinical Trials Center and will list these required procedures and their assigned treatment group. You should retain the original visit schedule for your records, but begin using the revised visit schedule to avoid missing required additional laboratory procedures.

Although total cholesterol will be used to monitor the response of most participants to pravastatin versus usual care, triglyceride and HDL and LDL cholesterol levels will also be measured along with total cholesterol for small randomly chosen cohorts of the pravastatin (10%) and usual care (5%) groups.

2.3.4 Randomizing participants to the lipid-lowering trial after Visit 3

Participants may be randomized into the lipid-lowering trial at any time. For example, the investigator or the participant may prefer to wait until Visit 4 or Visit 5 to consider participating in this additional trial. In such cases, the participant should be randomized *within 120 days of the date of the lipid value used to determine eligibility*. If randomization within 120 days is not possible, then blood should be redrawn and a new lipid panel (laboratory panel ALL10) should be requested from the ALLHAT Central Laboratory (not a local laboratory), in order to re-verify eligibility.



PARTICIPANT CONTACT INFORMATION SHEET

First name: _____ Middle initial: ___ Last name: _____

Street address: _____

City: _____ State: _____ Zip code: _____

Telephone: (____) _____ Birthdate: _____

Social Security number: _____

Medicare number: _____ State of birth: _____

Father's last name: _____

Spouse's first name: _____ Middle initial: ___ Last name: _____

Street address: _____

City: _____ State: _____ Zip code: _____

Telephone: (____) _____

Employer, if applicable: _____

Address: _____

City: _____ State: _____ Zip code: _____

Telephone: (____) _____

Names and addresses of two relatives or friends who **do not** live with you, and who would know where you might be contacted:

First name: _____ Middle initial: ___ Last name: _____

Street address: _____

City: _____ State: _____ Zip code: _____

Telephone: (____) _____

First name: _____ Middle initial: ___ Last name: _____

Street address: _____

City: _____ State: _____ Zip code: _____

Telephone: (____) _____

ALLHAT ANTIHYPERTENSIVE TRIAL ELIGIBILITY WORKSHEET- VERSION 3

Information from Chart Review and Visit 1

Name: _____ 1.a. ID #: _____ - _____ - _____ b. Site code: ____ c. Acrostic: _____ Place ID label here after randomization.	1.d. Date randomized (mm-dd-yy): ____ - ____ - ____
--	--

Warning: Patients must be at least 55 years of age at the time of randomization!

Information from Chart Review or Local Determinations

Exclusion criteria for the antihypertensive trial (patient cannot have any of the following):	<u>Yes</u>	<u>No</u>
2. Factors suggesting a low likelihood of compliance with protocol (e.g., dementia, history of alcohol or drug abuse within past six months, plans to move or travel extensively, or history of unreliability in keeping appointments or taking prescribed drugs)	<input type="checkbox"/> 1	<input type="checkbox"/> 2
3. Symptomatic myocardial infarction or stroke within past six months	<input type="checkbox"/> 1	<input type="checkbox"/> 2
4. Symptomatic congestive heart failure and/or ejection fraction < 35%, if known	<input type="checkbox"/> 1	<input type="checkbox"/> 2
5. Angina pectoris (chest pain) within past 6 months	<input type="checkbox"/> 1	<input type="checkbox"/> 2
6. Known renal insufficiency (serum creatinine ≥ 2 mg/dl)	<input type="checkbox"/> 1	<input type="checkbox"/> 2
7. Requires diuretics, calcium antagonists, ACE inhibitors, or alpha adrenergic blockers for reasons other than treatment of hypertension (e.g, CHF, angina)	<input type="checkbox"/> 1	<input type="checkbox"/> 2
8. Requires therapeutic doses of three or more antihypertensive drugs to achieve satisfactory blood pressure control (SBP ≤ 160 mm Hg and DBP ≤ 90 mm Hg)	<input type="checkbox"/> 1	<input type="checkbox"/> 2
9. Sensitivity or contraindication to any of the first-line study medications	<input type="checkbox"/> 1	<input type="checkbox"/> 2
10. Disease, such as non-curable malignancy, likely to lead to non-cardiovascular death over the course of the study	<input type="checkbox"/> 1	<input type="checkbox"/> 2
11. Participation in another clinical trial (observational studies are allowed)	<input type="checkbox"/> 1	<input type="checkbox"/> 2

If ANY of Items 2 through 11 are answered "Yes" then STOP - patient is ineligible.

<u>Eligibility criteria for antihypertensive trial (patient must have one or more of the following):</u>	<u>Yes</u>	<u>No</u>
12. Old (>6 months) or age-indeterminate myocardial infarction or stroke	<input type="checkbox"/> 1	<input type="checkbox"/> 2
13. History of CABG or coronary angioplasty or other revascularization procedure	<input type="checkbox"/> 1	<input type="checkbox"/> 2
14. Major ST segment depression or T wave inversion on any ECG in the past two years	<input type="checkbox"/> 1	<input type="checkbox"/> 2
15. Other documented atherosclerotic cardiovascular disease	<input type="checkbox"/> 1	<input type="checkbox"/> 2
16. Type II diabetes mellitus [plasma glucose > 140 mg/dl (fasting) or > 200 mg/dl (non-fasting) and/or on insulin or oral hypoglycemic agents in the past two years].....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
17. HDL-cholesterol <35 mg/dl (on any 2 determinations within past 5 years).....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
18. Left ventricular hypertrophy (LVH) on any ECG in the past two years.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
19. Combined wall thickness of ≥ 25 mm on any echocardiogram in the past two years	<input type="checkbox"/> 1	<input type="checkbox"/> 2
20. Current cigarette smoker	<input type="checkbox"/> 1	<input type="checkbox"/> 2

If NONE of items 12 through 20 are answered "Yes" then STOP - patient is ineligible.

Visit 1 Information

21. Visit 1 date (mm-dd-yy)..... - - - - -

22. a. Blood pressure cuff size (arm circumference limits in parentheses) Pediatric (16.0 - 22.5 cm) 1
 Regular adult (22.6 - 30.0 cm) 2
 Large arm (30.1 - 37.5 cm) 3
 Thigh (37.6 - 43.7 cm) 4

b. Visit 1 seated blood pressure readings (mm Hg) /

Patient should be seated for at least five minutes without smoking, feet flat on the floor, in an erect but comfortable position.

Average: /

c. Initials of person performing blood pressure measurements - - - -

23. Antihypertensive medication status On 1-2 drugs \geq 2 months 1
 On drugs $<$ 2 months 2

On 1-2 drugs \geq 2 months:		On drugs $<$ 2 months or currently untreated:			
SBP \leq 160	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	SBP \geq 140	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	SBP \leq 180	<input type="checkbox"/> Yes---- <input type="checkbox"/> No
DBP \leq 100	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	DBP \geq 90	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	DBP \leq 110	<input type="checkbox"/> Yes---- <input type="checkbox"/> No
Both must be "Yes" for patient to be eligible.		One of these and both of these must be "Yes" for patient to be eligible.	

24. Initials of person completing form..... - - - -

25. Signature of person completing form.....

- ☞ Perform physical examination, ECG, local laboratory analyses, etc., as necessary for eligibility determination.
- ☞ Schedule Visit 2 at least 1 day and not later than 12 weeks from Visit 1, depending on antihypertensive drug tapering requirements. Advise patient of need to fast prior to Visit 2, and that diuretics and potassium supplements should not be taken on the day of Visit 2.

Note: Patients requiring tapering of current antihypertensive medications between Visit 1 and Visit 2, whose blood pressure exceeds 180 mmHg SBP or 110 mmHg DBP at a step-down visit should return within a few days for a repeat blood pressure measurement. If the blood pressure is still above 180/110 mmHg, the patient should not be randomized into the antihypertensive trial.

Place ID label here

Patient name: _____

ALLHAT ANTIHYPERTENSIVE TRIAL RANDOMIZATION VISIT (VISIT 2) - VERSION 3

Name: _____ ID #: _____ Site code: _____ Acrostic: _____ Place ID label here after randomization.	26. Visit 2 date (mm-dd-yy) ____ - ____ - ____ 27. Birthdate _____ (mm-dd-yyyy)
---	---

28. a. Blood pressure cuff size Pediatric (16.0 - 22.5 cm) 1
 Regular adult (22.6 - 30.0 cm) 2
 Large arm (30.1 - 37.5 cm) 3
 Thigh (37.6 - 43.7 cm) 4
- b. Heart rate (beats/min = 30-second count x 2) _____
- c. Visit 2 seated blood pressure readings (mm Hg) _____ / _____
 _____ / _____
 Average: _____ / _____
- Patient should be seated for at least five minutes without smoking, feet flat on the floor, in an erect but comfortable position.*

On 1-2 drugs ≥ 2 months at Visit 1:		On drugs < 2 months or untreated at Visit 1:			
SBP ≤ 180	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	SBP ≥ 140	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	SBP ≤ 180	<input type="checkbox"/> Yes---- <input type="checkbox"/> No
DBP ≤ 110	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	DBP ≥ 90	<input type="checkbox"/> Yes---- <input type="checkbox"/> No	DBP ≤ 110	<input type="checkbox"/> Yes---- <input type="checkbox"/> No
Both must be "Yes" for patient to be eligible.		One of these and both of these must be "Yes" for patient to be eligible.	

- d. Initials of person performing blood pressure measurements _____
29. Weight (lbs) _____
30. Height (inches) _____
31. Consent for antihypertensive trial randomization signed?..... Yes 1
 STOP, patient is not eligible ☹ No, refused 2

- Antihypertensive trial randomization:** Call 1-800-690-7870 from 7:00 a.m to 6:00 p.m. Central time Monday - Friday.
32. Date randomized (mm-dd-yy) ____ - ____ - ____
33. Antihypertensive drug bottle number _____
34. Social Security number: ____ - ____ - ____
35. Medicare number (**required** for patients ≥ 65 years of age): ____ - ____ - ____
36. a. Race: 1 White b. Is the patient of Hispanic origin? 1 Yes
 2 Black **(must be answered!)** 2 No
 3 Amer Indian/Alaskan native 3 DK
 4 Asian/Pacific Islander
 5 Other, specify _____
37. Sex: 1 Male 38. Cigarette smoking: 1 Current smoker
 2 Female 2 Past smoker
 3 Never smoked
39. Years of education, starting with first grade (code 99 if not known) _____
40. Is patient currently taking aspirin regularly? Yes 1
 No 2
 DK 3

41. **For women only:** Is patient currently prescribed an estrogen supplement?..... Oral 1
Patch 2
No 3
DK 4

	<u>Yes</u>	<u>No</u>
42. Does patient have evidence of CHD (known prior MI, angina, primary cardiac arrest, coronary stenosis > 50%, reversible perfusion defect, prior coronary revascularization procedure)?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
Exclusions for lipid-lowering trial (patient cannot meet any of the following criteria):		
43. Current use of prescribed lipid-lowering agents or ≥ 500 mg/day of non-prescription niacin, or use of probucol within the past year.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
44. Contraindications to HMG CoA reductase inhibitors (significant hepatic or renal disease, previous organ transplantation requiring immunosuppressive therapy, or known allergy or intolerance)	<input type="checkbox"/> 1	<input type="checkbox"/> 2
45. Known untreated secondary cause of hypercholesterolemia, such as nephrotic syndrome or untreated hypothyroidism.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
46. Is the patient willing to enroll in the cholesterol-lowering component?.....	Yes <input type="checkbox"/> 1	No <input type="checkbox"/> 2
	Not sure <input type="checkbox"/> 3	Not eligible <input type="checkbox"/> 4

47. In general, would you say your health is: Excellent 1
Very good 2
Good 3
Fair 4
Poor 5
No answer/unknown 6
48. If you were to rate your current health on a scale of 0 to 100, with 100 being perfect health and 0 being death, what number would you rate yourself today? (Unknown=999)
49. Has the patient signed the consent allowing DNA analysis of the baseline blood? Yes 1
No 2
50. Date of next visit (mm-dd-yy)
51. Initials of person completing this form:
52. Signature of person completing this form

Other evaluations at this visit:

- Electrocardiogram (with routing slip AL05A) - if an ECG has been done within the past year, it may be submitted as the baseline ECG. Be sure to use the latest ECG available. Use the preprinted baseline ECG label provided by the Clinical Trials Center.
- Central laboratory evaluations - baseline profile (check profile **ALL01** on the laboratory request slip)
- Lifestyle advice for blood pressure reduction
- Remind patients eligible for the cholesterol-lowering trial to fast prior to Visit 3.
- Dispense one bottle of Dose 0 and one bottle of Dose 1 of assigned bottle number.
- Please staple all 4 pages of the AL01 together prior to sending this form to the Clinical Trials Center.

Place patient label here

Patient name: _____

ALLHAT LIPID-LOWERING TRIAL ELIGIBILITY AND RANDOMIZATION FORM - VERSION 2

Place ID label here

Patient name: _____

1. Date randomized to lipid-lowering trial (mm-dd-yy): ____ - ____ - ____

Review of Previous Information (see AL01 Items #42-#46)

Only patients **not on** any lipid-lowering medication or large doses of non-prescription niacin (≥ 500 mg/day) in the last two months are eligible for the lipid-lowering trial. Patients previously on probucol must be off that drug for at least one year.

Patients with contraindication to HMG CoA reductase inhibitors (significant hepatic or renal disease, previous organ transplantation requiring immunosuppressive therapy, or known allergy or intolerance) are **not** eligible.

Patients with known untreated secondary cause of hypercholesterolemia, such as nephrotic syndrome or untreated hypothyroidism are **not** eligible.

Information from Visit 2

2. LDL cholesterol at Visit 2, from central laboratory..... mg/dl

LDL cholesterol must be between 120-189 mg/dl (100-129 mg/dl for patients with known CHD).

3. Triglycerides at Visit 2, from central laboratory mg/dl

Triglycerides must be less than 350 mg/dl.

4. Confirmed ALT value from central laboratory IU/L

Patients with Visit 2 ALT > 100 IU/L (2 times upper limit of normal) should have blood redrawn for confirmation of ALT by the central laboratory. Patients with ALT confirmed as > 100 from the central laboratory are not eligible.

To randomize into lipid-lowering trial: Call 1-800-690-7870 between 7:00 a.m. and 6:00 p.m. Central time Monday through Friday.

5. Lipid-lowering trial informed consent signed? Yes 1
STOP, patient is not eligible No, refused 2

6. Patient is assigned to Pravastatin 1
Usual Care 2

7. Initials of person completing this form:

8. Signature of person completing this form.....

☞ Initiate NCEP Step 1 diet & draw blood for panel ALL02

Place patient label here

Patient name: _____

CHAPTER 3 TREATMENT PROTOCOLS AND FOLLOW-UP VISITS

3.1 Antihypertensive treatment protocol

Drugs from four different classes of antihypertensive agents will be used as Step 1 (blinded) treatments. The four medications are (1) the diuretic chlorthalidone, (2) the calcium channel blocker amlodipine, (3) the ACE inhibitor lisinopril, and (4) the alpha adrenergic blocker doxazosin. All participants will receive standard lifestyle advice; e.g., weight control, increased physical activity, reduction of salt intake, smoking cessation and limited use of alcohol.

3.1.1 Blood pressure goal

The blood pressure goal is less than (<) 90 mmHg diastolic and less than (<) 140 mmHg systolic. Treatment should be intensified for patients with BP levels of 160 mm Hg systolic or higher and/or 100 mm Hg diastolic or higher. If the patient is already on a three-drug regimen, SBP of 140-159 mm Hg is probably acceptable.

3.1.2 The Stepped Care treatment plan

All participants will be re-evaluated at 1 month (Visit 3) and at 3 months (Visit 4). If the investigator or the participant is concerned about the blood pressure level, visits may occur more often. If a dose level of the Step 1 (blinded) drug is not tolerated, the dosage level may be reduced. An attempt should be made to keep the participant on at least Dose 1 of the Step 1 (blinded) drug. If the blood pressure goals are not achieved on the maximum tolerated dose of Step 1 (blinded) drug, one or more of the open-label antihypertensive drugs (Step 2 - atenolol, clonidine or reserpine; and Step 3 - hydralazine) should be added and titrated as needed and tolerated.

After a reasonably stable medication regimen with satisfactory blood pressure control is achieved, routine clinic visits should take place at three-month intervals during the first year and at four-month intervals thereafter.

3.1.3 Step 1 medication doses

Each of the four Step 1 (blinded) drugs will be administered once daily in the morning. The following dosage levels will be available for each drug:

Table 3.1. First-line (Step 1, Blinded) Antihypertensive Drugs

Step 1 (Blinded) Agent	Initial Dose (Dose 0)	Dose 1	Dose 2	Dose 3*
Chlorthalidone	12.5 mg	12.5 mg	12.5 mg	25 mg
Amlodipine	2.5 mg	2.5 mg	5 mg	10 mg
Lisinopril	10 mg	10 mg	20 mg	40 mg
Doxazosin	1 mg	2 mg	4 mg	8 mg
*Dose 3 = Two capsules per day, in the morning, of Dose 2				

Starting the Step 1 (blinded) medication:

The day of randomization to the antihypertensive trial, the participant should be given one bottle of Dose 0 and one bottle of Dose 1 of the appropriate Step 1 (blinded) bottle code. The bottle code is the red two-digit number on the drug bottle. Instruct the participant to take one capsule per day, in the morning, from the Dose 0 bottle until those capsules are gone (7 days). Also instruct the participant to notify you if they cannot tolerate Dose 0. If Dose 0 is well tolerated, the participant should start taking one capsule per day, in the morning, from the Dose 1 bottle. A clinic visit is not required between Dose 0 and Dose 1. If Dose 0 of the Step 1 (blinded) drug is not tolerated, it should be discontinued.

Increasing the dose of the Step 1 (blinded) medication:

If the participant's systolic blood pressure is 140 mm Hg or more, or the diastolic blood pressure is 90 mm Hg or more at any ALLHAT visit, then the Step 1 (blinded) medication should be increased using the dosing schedule shown on page 3-1. If the participant is already on three or more antihypertensive medications, SBP of 140-159 mm Hg is probably acceptable. Further adjustments or additions to the regimen are at the discretion of the investigator.

What to do if an incorrect bottle number is dispensed:

Dispensing an incorrect bottle number to a patient is a serious problem for the study (patient and any events must be credited to the officially assigned medication), and may be a very awkward problem for the clinic to correct. ***The best solution is prevention!*** Every ALLHAT patient's assigned study bottle number is printed on their individual ALLHAT labels and on their visit schedule. Also, in your monthly report from the CTC, you will see a list of all of your patients with their correct bottle number assignments. You should check at least one of these sources every time you dispense a new bottle of study medications to your ALLHAT patients.

If you do dispense the wrong bottle number to a patient, this must be corrected as soon as possible. The CTC cannot change the assigned bottle number, and the study drug cannot be unblinded for this reason.

There are several options for retrieving the wrong bottle and dispensing the correct bottle:

Call the patient immediately and schedule a visit as soon as possible to dispense the correct bottle number. From a study standpoint, this is preferred.

If an interim visit to the clinic is impossible, dispense the correct bottle number at the next scheduled visit. If the patient returns unused medication of the wrong bottle number, do not redispense them to the patient!

The correct medication should be started as if the patient were a new randomization (i.e., Dose 0 for 7 days, then Dose 1, and then titrate the dosage up as needed).

If you encounter a situation in which you think it will be particularly difficult to switch to the correct bottle number, or if you have any questions regarding switching to the correct bottle number, please call your Regional Coordinator.

Restarting the Step 1 (blinded) medication:

If the Step 1 (blinded) medication has been discontinued for any reason other than side effects, consideration should be given to restarting the medication as soon as possible.

If the Step 1 (blinded) medication has been discontinued because of possible side effects, consideration should be given to restarting the medication when the symptom clears, or after a month, if the symptom is not a known serious adverse effect of one of the Step 1 (blinded) study drugs. If the symptom recurs and is believed to be related to the Step 1 (blinded) drug, the drug should be discontinued and one of the open-label Step 2 or Step 3 antihypertensive drugs should

be initiated. Consideration should be given to subsequently adding the Step 1 (blinded) study drug, as side effects from one drug are often ameliorated by another drug (e.g., a beta-blocker may prevent side effects of an alpha blocker).

For participants who have discontinued their Step 1 (blinded) medication for three or more days, the following procedure should be employed:

Patients on dose 1 should simply resume taking their daily dose 1 capsule.

Patients on dose 2 should be given a four-day supply of dose 1 capsules. Take the capsules from a 44-count dose 1 bottle in your inventory. Either discard the remaining 40 capsules or, if a pharmacist is dispensing the medication, dispense the four dose 1 capsules in a new container and save the remaining 40 capsules for future use. The participant should be instructed to take one capsule a day from the dose 1 container and then resume taking their daily dose 2 capsule.

Participants on dose 3 should be given a four-day supply of dose 1 as described in item 2 above, and should be instructed to take one capsule per day for four days. Then, they should be instructed to take one capsule a day for four days from the dose 2/3 bottle, and then resume taking two capsules per day (Dose 3) thereafter.

Restart Procedure for Patients With Known History of Temporary Postural Side Effects to Their Assigned Step 1 Medication

1. Patients on Dose 1 should be given a four-day supply of dose 0 capsules. The dose 0 capsules should be dispensed in the existing dose 0 bottle, from which the clinic staff should remove 3 capsules. The patient should be instructed to take one dose 0 capsule a day for four days and to resume taking their daily dose 1 capsule on the fifth day.
2. Patients on dose 2 should be given a four-day supply of dose 0 capsules and a four-day supply of dose 1 capsules. The dose 0 capsules should be dispensed in the existing dose 0 bottle, from which the clinic staff should remove 3 capsules. Similarly, the four dose 1 capsules should be dispensed in an existing 44-count dose 1 bottle from among the inventory of bottles with the patient's assigned bottle number. The clinic staff should either discard the unused 40 capsules or, when a pharmacist is dispensing drugs, the four dose 1 capsules may be dispensed in a new container and the remaining 40 capsules may be saved and stored in the pharmacy. The patient should be instructed to take one dose 0 capsule a day for four days, then take one capsule a day from the dose 1 bottle for four days, then begin taking one of their regular dose 2 capsules each day.
3. Patients on dose 3 should be given a four-day supply of dose 0 and dose 1 capsules as described in Item 2 above. They should be instructed to take one of these capsules a day for eight days. They should be instructed to then take one capsule a day for four days from their current supply of dose 2/3 medication and then to resume taking two capsules a day thereafter.

If no dose 0 bottle is available with the participant's assigned bottle code, you may elect to begin retitration with dose 1. When possible, a dose 0 bottle should be obtained from the ALLHAT Drug Distribution Center (DDC) prior to the patient's clinic visit. The DDC will ship drug bottles to you overnight by Federal Express.

Re-starting medications in post-MI participants: A one-month wait post-event is sufficient prior to re-starting ALLHAT medications.

3.1.4 Second-line and third-line ALLHAT medications

For participants who are unable to attain satisfactory blood pressure control on the maximum dose of their Step 1 (blinded) medication that they can tolerate, a choice of the following Step 2 and Step 3 drugs and doses will be provided in open-label form for addition to (not substitution for) the Step 1 (blinded) drug:

Table 3.2. Step 2 and Step 3 (Open Label) Antihypertensive Drugs

Step 2 and Step 3 Medications	Dose 1 (2 tablet)	Dose 2 (1 tablet)	Dose 3 (2 tablets)
Reserpine	0.05 qd or 0.1qod	0.1 qd	0.2 qd
Clonidine (oral)	0.1 bid	0.2 bid	0.3 bid (12 tablets)
Atenolol	25 qd	50 qd	100 qd
Hydralazine (Step 3)	25 bid	50 bid	100 bid

The choice of Step 2 and Step 3 medications will be at the discretion of the study investigator/ physician. Although in special cases, investigators may choose to prescribe antihypertensive drugs other than those provided by the study, diuretics, calcium antagonists, ACE inhibitors, and alpha adrenergic blockers should be avoided unless maximum tolerated doses of a 3-step (3 study drugs) regimen have been tried. Only in those circumstances, or when another clinical indication besides uncontrollable hypertension (e.g., severe angina or congestive heart failure) mandates a drug of one of these classes, may such a drug be used.

Below is a sample ALLHAT Dosing Schedule (Step 1, Step 2 and Step 3 medications):

Randomization

Step 1 Give Dose 0 bottle (7 caps) - 1 pill each morning until gone
And Dose 1 Bottle (44 caps) - start this when Dose 0 is gone

Titration for participants above goal: Goal BP is <140/<90

- | | |
|-----------------------------------|---|
| Increase to Step 1, Dose 2 | Give Dose 2/3 bottle and circle the 2. Patient takes 1 pill each morning. |
| Increase to Step 1, Dose 3 | Give Dose 2/3 bottle and circle the 3. Patient takes 2 pills each morning. |
| (continued on next page) | |
| Add Step 2, Dose 1 | Patient continues on Step 1, Dose 3 med and also give patient Step 2 open-label med - either atenolol, clonidine or reserpine Dose 1. See schedule above for dosing levels. |
| Increase to Step 2, Dose 2 | Patient continues on Step 1, Dose 3 med and increase open label Step 2 med to Dose 2 level. See schedule above for dosing levels. |

Increase to Step 2, Dose 3	Patient continues on Step 1, Dose 3 med and increase Step 2 open-label med to Dose 3 level. See schedule above for dosing levels.
Add Step 3	Add hydralazine, Dose 1 level and increase up to Dose 3 as needed. See schedule above for dosing levels.

Prescribing diuretics, calcium-channel blockers, ACE inhibitors and alpha blockers:

For participants who will remain on the Step 1 (blinded) drug, if a drug from the same class as any of the Step 1 (blinded) drugs - diuretics, calcium channel blockers, ACE inhibitors, or alpha blockers - must be used, the doses of added open-label drugs from one of the Step 1 classes should not exceed 2 the maximum recommended doses in the Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) (see Table 3.3, copied from the JNC VI report, for the maximum recommended doses of antihypertensive medications). There are exceptions to this limitation:

- a. If there is a compelling indication for one of the blinded classes to be added, then dose levels may need to be higher than 2 the JNC maximum. For example, the full doses of ACE inhibitors associated with improved survival in congestive heart failure should not be avoided.
- b. In rare situations, larger doses of one or more of the blinded classes of drugs will be necessary or desirable to control blood pressure or another condition adequately.

Whenever open-label therapy with one of the blinded classes of drugs is used, it should be an individual decision whether to reduce the dose level of the blinded drug. Many times the addition will be well tolerated, but if excessive hypotension, disturbing symptoms, or clinical concerns develop, the dose can be reduced to a lower level. However, every attempt should be made to continue or restart at least Dose 1 of the Step 1 (blinded) ALLHAT medication.

In most such cases, it will not be necessary to unmask the participant or the investigator as to the identity of the participant's assigned Step 1 (blinded) medication.

3.2 Lipid-lowering protocol

The lipid lowering trial of ALLHAT will employ a simple, randomized, unblinded comparison of the HMG CoA reductase inhibitor pravastatin versus usual care in a subset of participants participating in the antihypertensive trial. Upon randomization into the study, all participants in this ALLHAT trial will receive instruction in the Step I diet recommended by the NCEP (see Appendix E). Randomization to this trial will usually take place at the Visit 3, although it may take place at a later visit (refer to Chapter 2 section).

Nearly all of the participants in the lipid-lowering trial will begin the study with LDL-cholesterol levels moderately exceeding the NCEP-recommended levels for participants with multiple risk factors. For such participants, the NCEP guidelines recommend a therapeutic diet and that drugs be considered for participants who are unable to lower their LDL-cholesterol to within 30 mg/dl of the goal level. In ALLHAT, we will compare the outcome when a powerful LDL-cholesterol-lowering drug is provided at the outset to that when only dietary therapy is employed.

The upper LDL-cholesterol exclusion cutoffs (130 and above for those with clinical CHD; 190 and above for those without clinical CHD) were chosen so that current clinical practice

would not mandate the use of cholesterol-lowering drugs in the "usual care" group. *However, it is possible that the physician may believe strongly that some participants who are eligible for this trial require cholesterol-lowering drugs. Such participants should not be randomized to this trial of ALLHAT.*

3.2.1 Lipid-lowering treatment goals

Participants with fasting LDL cholesterol (LDL) between 120 and 189 mg/dl (between 100 and 129 mg/dl for participants with known CHD) and fasting triglycerides (TG) 350 mg/dl or lower at Visit 2 are eligible for the lipid-lowering trial. Participants potentially eligible for this trial should have been reminded to fast prior to the lipid randomization visit. If they sign the Informed Consent to participate in this ALLHAT trial at Visit 3, the investigator will telephone the Clinical Trials Center and review the eligibility and exclusion criteria. The participants will be randomized to receive either pravastatin or usual care. A fasting lipoprotein profile (lipid panel ALL02) will be obtained at this visit as a baseline for each randomized participant in this trial. The Clinical Trials Center will use the average total (TC) and LDL-cholesterol levels from Visit 2 and the lipid randomization visit to calculate a target TC level corresponding to a 25% decrease in LDL-cholesterol, according to the following formula:

$$\text{Target TC} = \text{TC} - (0.25 \times \text{LDL})$$

Although total cholesterol will be used to monitor the response of most participants to pravastatin versus usual care, fasting triglyceride and HDL and LDL cholesterol levels will also be measured along with total cholesterol for small randomly chosen cohorts of the pravastatin (10%) and usual care (5%) groups. An LDL cholesterol target level will be provided by the Clinical Trials Center for participants belonging to these cohorts.

3.2.2 Treatment of participants assigned to pravastatin

The starting dose of pravastatin is 40 mg/day (two 20-mg tablets or one 40-mg tablet), taken in the evening. Participants assigned to pravastatin also receive instruction in the Step 1 diet recommended by the NCEP (see Appendix E).

The Drug Distribution Center (DDC) will keep a small supply of 10 mg and 20 mg pravastatin tablets for participants who cannot tolerate the 40 mg dose. If these are needed, they may be obtained by calling the DDC at (301) 309-2426 or faxing an AL10 (Drug Order Form) to (301) 251-1863.

3.2.3 Treatment of participants assigned to usual care

Participants assigned to "usual care" will receive instruction in the Step 1 diet recommended by the NCEP (see Appendix E). "Usual care" is not intended to include pharmacologic treatment except as described below.

3.2.4 Exceptions to the assigned treatment plan

There may be some participants whose clinical situation changes after they are randomized to "usual care" and the physician is no longer comfortable withholding cholesterol-lowering drugs. For example, the LDL level may rise above 190 mg/dl, or a participant with LDL cholesterol between 130 and 189 mg/dl may develop CHD. In such circumstances, the physician may introduce whatever cholesterol-lowering agents he or she deems appropriate for such participants, although drugs will not be provided by the study.

A more restrictive diet and/or low-dose resin (e.g., 8 g/day of cholestyramine) may be

prescribed at the physician's discretion for participants who fail to attain a satisfactory cholesterol response despite good compliance with the maximum dose of pravastatin and the study diet; the study will not provide cholesterol-lowering drugs other than pravastatin.

If you have questions regarding adding a lipid-lowering medication, please contact your Regional Physician Coordinator.

3.3 Follow-up visits

The purposes of the ALLHAT follow-up visits include monitoring for blood pressure control, ascertainment of study events and serious adverse effects, and collection of minimal additional information at specific visits. At least annually (and preferably as changes occur), we strongly suggest that you update the Participant Contact Information Sheet (available from the Clinical Trials Center or your Regional Study Coordinator) providing current contact information for the participant. The annual visit may also be a good time to review the occurrence of reportable events over the past year.

During the first year of follow-up, ALLHAT follow-up visits are required at one-month, three months, six months, nine months and 12 months. Thereafter, ALLHAT follow-up visits are required every four months. However, participants may be seen more frequently if necessary to achieve satisfactory blood pressure control or for other reasons.

3.3.1 Form AL03 – Version 4 (7/98)

Items #1a, #1b, #1c and ID label - Identifying information:

In preparation for the visit, you should apply ID labels to the top of page 1 and the bottom of all other pages of the white copy. Use a label for page 1 of the yellow copy. Refer to the participant's visit schedule to determine procedures that might be required (e.g., ECG or labwork). Schedule those tests to coincide with the clinic visit.

In Item #1a, complete the date of the follow-up visit as mm-dd-yyyy, using leading zeros where necessary. To determine the visit number (Item #1b), look on the participant's visit schedule generated at the Clinical Trials Center, find the visit window that the visit date falls into, read across to the visit number, and enter the visit number on the form. Only one ALLHAT follow-up visit form should be completed in each visit window; you will not be reimbursed for additional forms filed with the CTC.

Item #1c indicates where the visit was done. Check one box as appropriate. In the case of a home visit, please check “clinic”.

Items #2a – 2b - Blood pressure measurement:

To complete Item #2a, use the blood pressure measurement procedures as explained in Appendix B, determine the proper blood pressure cuff size, and take two seated blood pressure readings. The participant should be seated for five minutes without smoking, feet flat on the floor, in a comfortable but erect position. The person performing the blood pressure measurements should print their initials in #2b. The average blood pressure reading should be entered as indicated on the form. All readings are recorded to the nearest even mm Hg. Please note the instruction regarding treatment of participants whose blood pressure is not controlled.

Items #3 - #5 - Interval history:

Items #3 - #5 assess interval history for possible study events since the last ALLHAT visit. (*Be sure to distinguish between the last non-ALLHAT office visit and the last ALLHAT office visit.*) In Item #3, we are interested in the number of *overnight hospital admissions* (not

emergency room visits or overnight observations when the participant was not actually admitted) since the participant's last ALLHAT visit. Do not provide the number of days the participant was in the hospital, but the total number of admissions. If the participant has had none, please complete the item as "00" - do *not* leave this item blank. Similarly, in Item #4, we are interested in the number of visits to a doctor's office or clinic since the last ALLHAT visit. This should include all interim visits to your office as well as other physicians' offices or clinics, and should include interim drug titration visits for ALLHAT. **DO NOT INCLUDE VISITS TO A CHIROPRACTOR OR ACUPUNCTURIST (UNLESS THE ACUPUNCTURIST IS A PHYSICIAN.)** Again, if the participant had no interim visits to either your office or another office, complete the item as "00" - do *not* leave this item blank.

Review Item #5 very carefully. For each possible study event listed, a response is expected - "Hospitalized", "Diagnosis only", "Treatment only", or "No". You should use your clinical judgment plus guidance provided in Chapter 5 in determining the proper response to each of these:

- 5a) acute myocardial infarction, including evolving MI with thrombolysis - do not report apparent "silent" MIs ascertained on the basis of definitive ECG changes; these will be ascertained centrally.
- 5b) stroke (not a TIA or "ministroke"),
- 5c) a new primary diagnosis of cancer (**do not report recurring overnight hospitalizations for chemotherapy or other cancer treatment, and do not report non-melanoma skin cancers or recurrent or metastatic/secondary cancers.**) – note that this is the only event for which a "diagnosis only" (e.g., out-patient biopsy) is reportable via AL04
- 5d) congestive heart failure - **acute episode only**
- 5e) angina pectoris - **acute episode only**
- 5f) lower extremity peripheral arterial disease - does not include carotid disease, renal artery disease or aortic aneurysms
- 5g) accident or attempted suicide
- 5h) kidney transplant or start of chronic dialysis
- 5i) Coronary artery bypass graft (CABG)
- 5j) Coronary PTCA (angioplasty), stent or atherectomy
- 5k) Lower extremity peripheral revascularization / bypass / angioplasty

"Acute episodes" are those that bring the patient to medical attention or cause some change or addition to their daily treatment or routine.

Take special note of all events which are enclosed in the two boxes on the form. For each of these events, the investigator will also obtain and submit a copy of the hospital discharge summary upon which the diagnosis is based. (For "diagnosis only" cancers, a pathology report is sufficient.) Form AL04 should be completed (one for each of these events; please refer to Chapter 5 for instructions).

We will not be collecting information via AL04 on non-hospitalized MI's or strokes. Both should still be checked on the AL03 as "treatment only" if treatment occurred. Do not report "silent" MI's discovered on the basis on definitive ECG changes; these will be ascertained as part of the central ECG coding of ALLHAT biennial ECGs.

Item #6 - Antihypertensive medication adherence:

Item #6 should be asked of the participant directly - "About what proportion (or percent) of your ALLHAT medications do you think that you have taken since your last visit?" You may use language that you are more comfortable with or that you think the participant may

understand - e.g., "out of a typical 5 days, how many days would you say that you take your medicine?" - a response of "4" or "5" indicates adherence of at least 80%. For participants not on the Step 1 (blinded) medication, check "not on ALLHAT Step 1 medications". If you are unable to determine this (e.g., the participant just cannot understand the question or there is some other problem), check "unable to determine".

If the participant reports taking his or her medication less than 80% of the time (less than 4 days out of a typical 5 days), remind and encourage the participant to take their medication as directed. Suggestions for enhancing medication adherence may be found in Appendix F.

Pill counts or cylinder measurements of returned capsules are no longer required.

Item #7 - Step 1 (blinded) antihypertensive prescription at this visit:

In Item #7, indicate which dose of the Step 1 (blinded) medication you are advising the participant to take at this visit -- either "Dose 1", "Dose 2", "Dose 3", or "None". Do not leave this item blank. Check only one box, please.

If Item #7 is "None", complete Items #8 and #9. Otherwise, skip to Item #10

Item #8 – Reasons for stopping or remaining off Step 1 (blinded) medication:

It is very important to determine why the participant might not be on the blinded study medication. Please check all the reasons that apply: morbid event (illness not directly caused by the Step 1 [blinded] drug), symptomatic adverse effect, other adverse effect (e.g., laboratory), blood pressure too high, blood pressure too low, refusal, other non-medical reason, other (specify). Use "X" in the appropriate boxes and mark all that apply.

Item #9 – Restarting Step 1 (blinded) study drug:

It is also important to consider if the patient is willing to have the Step 1 (blinded) study drug restarted, and if it is safe to do so. Please consider this carefully for each patient and indicate your restart plans for this patient as appropriate. Please check only one box.

Item #10 - Open-label medication prescriptions:

This question is asking about any open-label antihypertensive or lipid-lowering medication, including medications provided by ALLHAT or from another source, and regardless of reason for prescription. For example, if a participant is on atenolol for angina, please mark "atenolol" even though this is not prescribed for blood pressure.

Please refer to the four pages at the end of this chapter for a complete list of antihypertensive medications (generic and trade names). This list indicates which box to check for each medication. Sometimes two boxes are required for combination medications.

If the participant is not on any open-label medications put an "X" in the box indicating "None", and skip to Item #10. Otherwise, please mark all that apply.

Item #11 - Adherence to study pravastatin:

For participants not in the lipid-lowering part of ALLHAT and for participants assigned to Usual Care, and for participants assigned to pravastatin but not advised to take the ALLHAT pravastatin at the last visit, check "Not on ALLHAT pravastatin" for Item #11. For participants advised to take ALLHAT pravastatin, Item #11 should be asked of the participant directly - "About what proportion (or percent) of your ALLHAT pravastatin do you think that you have taken since your last visit?" You may use language that you are more comfortable with or that you think the participant may understand - e.g., "out of a typical 5 days, how many days would

you say that you take your cholesterol-lowering medicine?" - a response of 4" or 5" indicated at least 80% adherence. If you are unable to determine this (e.g., the participant just cannot understand the question or there is some other problem), check "unable to determine".

If the participant reports taking his or her ALLHAT pravastatin less than 80% of the time (less than 4 days of a typical 5 days), remind and encourage the participant to take his or her medication as directed.

Pill counts or cylinder measurements of returned tablets are no longer required.

Item #12 - ALLHAT pravastatin prescribed this visit:

In Item #12, record the dose of pravastatin prescribed this visit by indicating 10 mg, 20 mg, 40 mg or "None". Mark an "X" in the appropriate box. If the patient is not in the lipid-lowering part of ALLHAT, or is assigned to Usual Care, check "Not applicable" for #12. Remember that the protocol dose of pravastatin is 40 mg/day, taken at bedtime.

If Item #12 is "None", complete Items #13 and #14. Otherwise, skip to the next section.

Item #13 – Reasons for stopping or continuing off pravastatin:

It is very important to determine why participants assigned to pravastatin might not be on the medication. If the participant will be advised to take the pravastatin, mark "not applicable" and skip to the next item. If not, you should check all the reasons that apply: morbid event (illness not directly related to pravastatin), symptomatic adverse effect, other adverse effect (e.g., laboratory), refusal, other non-medical reason, other (specify). Use "X" in the appropriate boxes.

Item #14 – Restarting pravastatin:

It is also important to consider if the patient is willing to have the pravastatin restarted, and if it is safe to do so. Please consider this carefully for each patient and indicate your restart plans for this patient as appropriate. Please check only one box.

Items #15-21 - Items asked at Year 2, Year 4, and Year 6:

Several questions are asked of participants only at visits at 2 years, 4 years and 6 years (refer to the participant's visit schedule). These repeat the quality of life questions from baseline (Items #15 and #16), smoking (#17), aspirin (#18) and estrogen (#19). Also, we are asking for an update to the Social Security number (#20) and Medicare number (#21). If this visit is not an even-numbered annual visit, simply skip this section.

Items #15 and #16 - Quality of life:

Items #15 and #16 are questions that must be asked of the participant. Both of these items are indicators of quality of life. The first, Item #15, is relatively straightforward. Repeat the question to the participant exactly as worded, and verbally list the response categories. Record the participant's response. If the participant is really unsure, refuses to respond, or if you cannot otherwise ascertain the proper response, check "No answer/unknown".

The second quality of life item, Item #16, might be a little harder for the participant to understand. Use language that you think might make the question clearer for the participant. *If the participant is having trouble thinking of a 0-100 scale, you may use a 0-10 scale for clarification, but be sure to multiply the response by 10.* If the participant just cannot answer this question, code this question as "999".

Item #17 - Cigarette smoking:

In Item #17 indicate whether the participant is a current smoker (in past 30 days) or past smoker (not a current smoker, but more than 100 cigarettes in his or her lifetime), or has never smoked cigarettes. Item #15 refers only to cigarettes, not cigars or pipes. For example, a participant who previously smoked more than 100 cigarettes but in the last 30 days has smoked only a pipe would be classified as a "past smoker".

Item #18 - Regular use of aspirin:

Regular use of aspirin (Item #18) may alter the participant's risk of cardiovascular events. Indicate here whether the participant is currently taking regular doses of aspirin (not non-aspirin pain relievers). Medications that contain aspirin have been discussed on page 2-17.

Item #19 - Current use of estrogen supplements:

For women only, Item #19 requests information regarding current use of estrogen. This includes any estrogen preparation which might include or be taken with other hormones. Again, clarify with the participant if you are not clear on the proper response to this question. *Do not answer this item if the participant is male!*

Items #20 and #21 - Social Security and Medicare Numbers:

The participant's Social Security number (#20) and/or Medicare number (#21) will be used to track that participant if they are lost to follow-up, and may be used to track all participants after ALLHAT ends. This is extremely important information - a simple transcription error here will make this information useless, so take care in recording these numbers. **The Medicare number must be completed for participants 65 years of age or older.** You should leave the Medicare number blank only for participants under 65 years of age. Both of these items will be updated every two years during follow-up.

Some participants age 65 or older will not have Medicare numbers, and not all participants will have Social Security numbers. In these cases, simply complete these items with 9's (i.e., 999-99-9999 for the Social Security Number) - do not leave either item blank. Do not record numbers other than Social Security and Medicare numbers; if a participant does not have a Social Security Number and/or Medicare number, please record as 999-99-9999.

If you are unsure of any of the above items, please discuss the proper response with the participant.

Randomization to the lipid-lowering trial:

If the participant is eligible and willing to be randomized into the lipid-lowering trial, it should be done at this time if it has not been done already. This randomization has been previously described. If the participant is randomized to the lipid-lowering study at this visit, draw blood for laboratory panel ALL02.

Dispensing medication, and other procedures at this visit:

Check the participant's visit schedule to determine if labwork (designated as ALL01, ALL02, etc. on the visit schedule) or an ECG is required at this visit. If so, these should be performed at this time. Update the participant's contact information, if necessary (at least

annually). Be sure that the participant has enough medication sufficient to last until their next scheduled ALLHAT visit.

Any study medication (Step 1, Step 2, Step 3 and/or pravastatin) dispensed to the participant must be noted in the progress note (source documentation) and in the ALLHAT Drug Accountability Record.

Finishing up!

The person completing the form should initial Item #22, and sign Item #23. You should now retrieve the set of labels that corresponds to the participant's ID number. (These labels are discussed in detail in Chapter 7.) Separate the original (white) and NCR (yellow) copies of the AL03 (all four pages), and immediately staple the white copy and staple the yellow copy in the upper left hand corners. Use the ID labels on each sheet of the white copy in the boxes provided. Use an ID label on the front of the yellow copy (this is your copy). If an ECG is performed, the proper ECG label should be affixed to the back of a single-channel recording, and on the front of a three-channel recording. Be sure to use a laboratory label for the requisition form and the tube. Additional detail on ECG recording and laboratory procedures may be found in Appendices C and D.

You're done!

TABLE 3.3
ANTIHYPERTENSIVE AGENTS

(Copied from the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure)

ORAL ANTIHYPERTENSIVE DRUGS*			
Drug	Trade Name	Usual Dose Range, Total mg/day* (Frequency per Day)	Selected Side Effects and Comments*
Diuretics (partial list)			
Short-term: increases cholesterol and glucose levels; biochemical abnormalities: decreases potassium, sodium, and magnesium levels, increases uric acid and calcium levels; rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia			
Chlorthalidone (G)†	Hygroton	12.5-50 (1)	
Hydrochlorothiazide (G)	Hydrodiuril, Microzide,	12.5-50 (1)	
	Esidrix		
Indapamide	Lozol	1.25-5 (1)	(Less or no hypercholesterolemia)
Metolazone	Mykrox	0.5-1.0 (1)	
	Zaroxolyn	2.5-10 (1)	
<i>Loop diuretics</i>			
Bumetanide (G)	Bumex	0.5-4 (2-3)	(Short duration of action, no hypercalcemia)
Ethacrynic acid	Edecrin	25-100 (2-3)	(Only nonsulfonamide diuretic, ototoxicity)
Furosemide (G)	Lasix	40-240 (2-3)	(Short duration of action, no hypercalcemia)
Torsemide	Demadex	5-100 (1-2)	
<i>Potassium-sparing agents</i>			
Amiloride hydrochloride (G)	Midamor	5-10 (1)	Hyperkalemia
Spironolactone (G)	Aldactone	25-100 (1)	(Gynecomastia)
Triamterene (G)	Dyrenium	25-100 (1)	
Adrenergic inhibitors			
<i>Peripheral agents</i>			
Guanadrel	Hylorel	10-75 (2)	(Postural hypotension, diarrhea)
Guanethidine monosulfate	Ismelin	10-150 (1)	(Postural hypotension, diarrhea)
Reserpine (G)**	Serpasil	0.05-0.25 (1)	(Nasal congestion, sedation, depression, activation of peptic ulcer)
<i>Central alpha-agonists</i>			
Clonidine hydrochloride (G)	Catapres	0.2-1.2 (2-3)	Sedation, dry mouth, bradycardia, withdrawal hypertension (More withdrawal)
Guanabenz acetate (G)	Wytensin	8-32 (2)	
Guanfacine hydrochloride (G)	Tenex	1-3 (1)	(Less withdrawal)
Methyldopa (G)	Aldomet	500-3,000 (2)	(Hepatic and "autoimmune" disorders)
<i>Alpha-blockers</i>			
Doxazosin mesylate	Cardura	1-16 (1)	Postural hypotension
Prazosin hydrochloride (G)	Minipress	2-30 (2-3)	
Terazosin hydrochloride	Hytrin	1-20 (1)	
<i>Beta-blockers</i>			
Bronchospasm, bradycardia, heart failure, may mask insulin-induced hypoglycemia; less serious: impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity)			
Acebutolol§‡	Sectral	200-800 (1)	
Atenolol (G)§	Tenormin	25-100 (1-2)	
Betaxolol§	Kerlone	5-20 (1)	
Bisoprolol fumarate§	Zebeta	2.5-10 (1)	
Carteolol hydrochloride‡	Cartrol	2.5-10 (1)	
Metoprolol tartrate (G)§	Lopressor	50-300 (2)	
Metoprolol succinate§	Toprol-XL	50-300 (1)	
Nadolol (G)	Corgard	40-320 (1)	
Penbutolol sulfate‡	Levatol	10-20 (1)	
Pindolol (G)‡	Visken	10-60 (2)	
Propranolol hydrochloride (G)	Inderal	40-480 (2)	
	Inderal LA	40-480 (1)	
Timolol maleate (G)	Blocadren	20-60 (2)	
<i>Combined alpha- and beta-blockers</i>			
Carvedilol	Coreg	12.5-50 (2)	
Labetalol hydrochloride (G)	Normodyne, Trandate	200-1,200 (2)	
Direct vasodilators			
Hydralazine hydrochloride (G)	Apresoline	50-300 (2)	Headaches, fluid retention, tachycardia (Lupus syndrome)
Minoxidil (G)	Loniten	5-100 (1)	(Hirsutism)

ORAL ANTIHYPERTENSIVE DRUGS* (continued)

Drug	Trade Name	Usual Dose Range, Total mg/day* (Frequency per Day)	Selected Side Effects and Comments*
Calcium antagonists			
<i>Nondihydropyridines</i>			
Diltiazem hydrochloride	Cardizem SR 120-360 (2) Cardizem CD, Dilacor XR, Tiazac 120-360 (1)		Conduction defects, worsening of systolic dysfunction, gingival hyperplasia (Nausea, headache)
Mibefradil dihydrochloride (T-channel calcium antagonist)	Posicor 50-100 (1)		(No worsening of systolic dysfunction; contraindicated with terfenadine [Seldane], astemizole [Hismanal], and cisapride [Propulsid]) (Constipation)
Verapamil hydrochloride	Isoptin SR, Calan SR 90-480 (2) Verelan, Covera HS 120-480 (1)		
<i>Dihydropyridines</i>			
Amlodipine besylate	Norvasc 2.5-10 (1)		Edema of the ankle, flushing, headache, gingival hypertrophy
Felodipine	Plendil 2.5-20 (1)		
Isradipine	DynaCirc 5-20 (2) DynaCirc CR 5-20 (1)		
Nicardipine	Cardene SR 60-90 (2)		
Nifedipine	Procardia XL, Adalat CC 30-120 (1)		
Nisoldipine	Sular 20-60 (1)		
ACE inhibitors			
Benazepril hydrochloride	Lotensin 5-40 (1-2)		Common: cough; rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia
Captopril (G)	Capoten 25-150 (2-3)		
Enalapril maleate	Vasotec 5-40 (1-2)		
Fosinopril sodium	Monopril 10-40 (1-2)		
Lisinopril	Prinivil, Zestril 5-40 (1)		
Moexipril	Univasc 7.5-15 (1-2)		
Quinapril hydrochloride	Accupril 5-80 (1-2)		
Ramipril	Altace 1.25-20 (1-2)		
Trandolapril	Mavik 1-4 (1)		
Angiotensin II receptor blockers			
Losartan potassium	Cozaar 25-100 (1-2)		Angioedema (very rare), hyperkalemia
Valsartan	Diovan 80-320 (1)		
Irbesartan	Avapro 150-300 (1)		

* These dosages may vary from those listed in the Physicians' Desk Reference (51st edition), which may be consulted for additional information. The listing of side effects is not all-inclusive, and side effects are for the class of drugs except where noted for individual drugs (in parentheses); clinicians are urged to refer to the package insert for a more detailed listing.

† (G) indicates generic available.

‡ Has intrinsic sympathomimetic activity.

§ Cardioselective.

**Also acts centrally.

TABLE 3.3 (Continued)
ANTIHYPERTENSIVE AGENTS

COMBINATION DRUGS FOR HYPERTENSION	
Drug	Trade Name
Beta-adrenergic blockers and diuretics	
Atenolol, 50 or 100 mg/chlorthalidone, 25 mg	Tenoretic
Bisoprolol fumarate, 2.5, 5, or 10 mg/hydrochlorothiazide, 6.25 mg	Ziac*
Metoprolol tartrate, 50 or 100 mg/hydrochlorothiazide, 25 or 50 mg	Lopressor HCT
Nadolol, 40 or 80 mg/bendroflumethiazide, 5 mg	Corzide
Propranolol hydrochloride, 40 or 80 mg/hydrochlorothiazide, 25 mg	Inderide
Propranolol hydrochloride (extended release), 80, 120, or 160 mg/hydrochlorothiazide, 50 mg	Inderide LA
Timolol maleate, 10 mg/hydrochlorothiazide, 25 mg	Timolide
ACE inhibitors and diuretics	
Benazepril hydrochloride, 5, 10, or 20 mg/hydrochlorothiazide, 6.25, 12.5, or 25 mg	Lotensin HCT
Captopril, 25 or 50 mg/hydrochlorothiazide, 15 or 25 mg	Capozide*
Enalapril maleate, 5 or 10 mg/hydrochlorothiazide, 12.5 or 25 mg	Vaseretic
Lisinopril, 10 or 20 mg/hydrochlorothiazide, 12.5 or 25 mg	Prinzide, Zestoretic
Angiotensin II receptor antagonists and diuretics	
Losartan potassium, 50 mg/hydrochlorothiazide, 12.5 mg	Hyzaar
Calcium antagonists and ACE inhibitors	
Amlodipine besylate, 2.5 or 5 mg/benazepril hydrochloride, 10 or 20 mg	Lotrel
Diltiazem hydrochloride, 180 mg/enalapril maleate, 5 mg	Teczem
Verapamil hydrochloride (extended release), 180 or 240 mg/trandolapril, 1, 2, or 4 mg	Tarka
Felodipine, 5 mg/enalapril maleate, 5 mg	Lexxel
Other combinations	
Triamterene, 37.5, 50, or 75 mg/hydrochlorothiazide, 25 or 50 mg	Dyazide, Maxide
Spironolactone, 25 or 50 mg/hydrochlorothiazide, 25 or 50 mg	Aldactazide
Amiloride hydrochloride, 5 mg/hydrochlorothiazide, 50 mg	Moduretic
Guanethidine monosulfate, 10 mg/hydrochlorothiazide, 25 mg	Esimil
Hydralazine hydrochloride, 25, 50, or 100 mg/hydrochlorothiazide, 25 or 50 mg	Apresazide
Methyldopa, 250 or 500 mg/hydrochlorothiazide, 15, 25, 30, or 50 mg	Aldoril
Reserpine, 0.125 mg/hydrochlorothiazide, 25 or 50 mg	Hydropres
Reserpine, 0.10 mg/hydralazine hydrochloride, 25 mg/hydrochlorothiazide, 15 mg	Ser-Ap-Es
Clonidine hydrochloride, 0.1, 0.2, or 0.3 mg/chlorthalidone, 15 mg	Combipres
Methyldopa, 250 mg/chlorothiazide, 150 or 250 mg	Aldochlor
Reserpine, 0.125 or 0.25 mg/chlorthalidone, 25 or 50 mg	Demi-Regroton
Reserpine, 0.125 or 0.25 mg/chlorothiazide, 250 or 500 mg	Diupres
Prazosin hydrochloride, 1, 2, or 5 mg/polythiazide, 0.5 mg	Minizide

*Approved for initial therapy.

ALLHAT FOLLOW-UP VISIT FORM - VERSION 4

Place ID label here

Patient name: _____

- 1.a. Today's date (mm-dd-yyyy): ____ - ____ - ____
- b. Visit # (range 03 - 28): ____
- c. Type of visit (check one): Clinic visit 1
 Telephone visit 2
 Postcard information 3

2. a. Seated blood pressure readings (mmHg) (use 999 for telephone visits and postcard information) ____ / ____

Patient should be seated for five minutes without smoking, feet flat on the floor, in an erect but comfortable position. Be sure to use the correct cuff size: pediatric (16.0-22.5 cm), regular arm (22.6 - 30.0 cm), large arm (30.1 - 37.5 cm), thigh (37.6 - 43.7 cm). See Manual of Operations, Appendix B, for further instructions.
Blood pressure goals are <90 mmHg diastolic and <140 mmHg systolic.

____ / ____
 Average: ____ / ____

- b. Initials of person performing blood pressure measurements (use 999 for telephone visits and postcard information) ____

Interval History:

3. Number of overnight hospitalizations since the patient's last ALLHAT visit (none = 00, unknown = 99) ____
4. Number of visits to any doctor's office or clinic since the patient's last ALLHAT visit (none = 00, unknown = 99). ____
 (Includes interim visits to **ALLHAT** clinic for blood pressure measurements and/or drug titration.)
5. Since the last visit, has the participant experienced any new occurrence of the following:
 (Please check one box for each of the items #5a-k.)

	<u>Hospitalized</u>	<u>Only</u>	<u>Only</u>	<u>No</u>
a. Acute myocardial infarction (including evolving MI with thrombolysis).....	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Stroke (not TIA or "ministroke")	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Cancer (a new primary diagnosis; excluding non-melanoma skin cancer)	<input type="checkbox"/> 1	<input type="checkbox"/> 4	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d. Congestive heart failure.....	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
e. Angina pectoris (actual episode of chest pain)	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
f. Lower extremity peripheral arterial disease	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
g. Accident or attempted suicide	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3

Any of the following procedures?

	<u>Yes</u>	<u>No</u>
h. Kidney transplant or start of chronic dialysis.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
i. Coronary artery bypass graft (CABG).....	<input type="checkbox"/> 1	<input type="checkbox"/> 2
j. Coronary PTCA (angioplasty), stent or atherectomy	<input type="checkbox"/> 1	<input type="checkbox"/> 2
k. Lower extremity peripheral revascularization/bypass/angioplasty.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2

Complete an Event Reporting Form (AL04) for all boxed events in Items 5a-k.

6. Considering the Step 1 (blinded) ALLHAT antihypertensive medication, what percent of ALLHAT antihypertensive medication does the patient report having taken since the last visit? Less than 80% 1
 80% or more 2
 Not on ALLHAT Step 1 (blinded) medication 3
 Unable to determine 4

Encourage patients taking less than 80% of their medications to take their medications regularly as prescribed.

7. What dose of the ALLHAT Step 1 (blinded) antihypertensive medication is the patient Dose 1 1
 being advised to take until the next visit? Dose 2 2
 Dose 3 3
 None 4

If Item #7 is "None", complete Items #8 and #9. Otherwise, skip to Item #10.

8. If the patient will not be taking the Step 1 (blinded) antihypertensive study drug, please give reasons *(check all that apply)*.
- a. Morbid event 1
 - b. Symptomatic adverse effect 1
 - c. Other adverse effect (e.g., abnormal blood test) 1
 - d. Blood pressure too high 1
 - e. Blood pressure too low 1
 - f. Refusal 1
 - g. Other non-medical reason 1
 - h. Other (specify) _____ 1
9. When will you be restarting Step 1 (blinded) study drug?
- a. Will restart at the next visit 1
 - b. Can't tell at this time 2
 - c. No plan to restart 3

10. Which of the following medications a. None (go to #11) 1
is the patient being advised to take until the next visit? *(check all that apply)* b. Diuretic 1-2 times per week 1

This refers to any open-label antihypertensive or lipid-lowering medication, including medications provided by ALLHAT or from another source, **and regardless of reason for prescription.**

- Diuretic 3 or more times per week 1
- Calcium channel blocker 1
- ACE inhibitor 1
- Alpha blocker 1
 - Atenolol 1
 - Clonidine 1
 - Reserpine 1
 - Hydralazine 1
- Other antihypertensive medication, regardless of indication (specify) _____ 1
 - HMG CoA reductase inhibitor (including ALLHAT pravastatin) 1
 - Other lipid-lowering medication (including niacin, resins and probucol) 1
 - Potassium chloride or other potassium supplement 1

11. What percent of ALLHAT pravastatin tablets does the patient report Not on ALLHAT pravastatin 3
having taken since the last visit? Less than 80% 1
80% or more 2
Unable to determine 4

If the patient is not in the lipid-lowering part of ALLHAT, or is assigned to Usual Care, or is assigned to pravastatin but not advised to take the ALLHAT pravastatin at the last visit, check "Not on ALLHAT pravastatin" for #11.

Encourage patients taking less than 80% of their medications to take their medications regularly as prescribed.

12. What dose of the ALLHAT pravastatin is the patient being advised to take until the next visit?..... Not applicable 5
10 mg 1
20 mg 2
40 mg 3
None 4

If the patient is not in the lipid-lowering part of ALLHAT, or is assigned to Usual Care, check "Not applicable" for #12.

Reminder: ALLHAT protocol starting dose is 40 mg/day.

Place ID label here

Patient name: _____

If Item #12 is "None", complete Items #13 and #14. Otherwise, skip to next section.

13. If the patient will not be taking the ALLHAT pravastatin, give reasons (check all that apply).

- a. Morbid event 1
- b. Symptomatic adverse effect 1
- c. Other adverse effect (e.g., abnormal blood test) 1
- d. Refusal 1
- e. Other non-medical reason 1
- f. Other (specify) _____ 1

14. When will you be restarting pravastatin?

- a. Will restart at the next visit 1
- b. Can't tell at this time 2
- c. No plan to restart 3

Ask the following questions of the participant at 2 years, 4 years and 6 years, and record a 12-lead ECG (refer to patient's visit schedule):

15. In general, would you say your health is: Excellent 1
Very good 2
Good 3
Fair 4
Poor 5
No answer/unknown 6

16. If you were to rate your current health on a scale of 0 to 100, with 100 being perfect health and 0 being death, what number would you rate yourself today? (Unknown = 999) _____

17. Have you ever smoked cigarettes? Current smoker (past 30 days) 1
Past smoker (100+ cigarettes) 2
Never smoked 3
Unknown 4

18. Are you currently taking aspirin regularly? Yes 1
(Including aspirin-containing products; see Manual of Operations Chapter 2 for a list) No 2
Don't know 3

19. **For women only:** Are you currently prescribed an estrogen supplement? Yes 1
No 2
Don't know 3

From clinic records (complete with 9's if not available):

20. Social Security number. _____ - _____ - _____

21. Medicare number (required for patients ≥65 years of age). _____ - _____ - _____

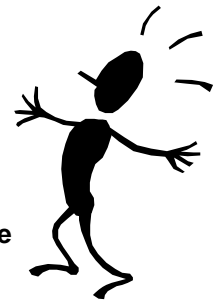
22. Initials of person completing this form:

23. Signature of person completing this form.....

<i>Place ID label here</i>	<p>Check patient's visit schedule for labwork and ECGs to be done at this visit.</p> <p>Be sure that the patient has enough ALLHAT medication to last until their next visit. Check the bottle label to be sure that the correct bottle number is dispensed.</p> <p>Be sure that the patient contact information is up to date, at least annually.</p> <p>Schedule the patient's next ALLHAT visit according to their visit schedule.</p>
Patient name: _____	



Hypertensive and Lipid Lowering Drugs (for Question 10 of AL03 forms)



With so many drugs on the market, answering question 10 on the AL03 can be quite confusing. The list below will guide you in answering this question. Please note that the letter preceding the classification corresponds to the answer choices in question 10.

Drug Name	Category
Accupril	e. ACE inhibitor
acebutolol	k. Other (Beta blocker)
Aceon	e. ACE inhibitor
acetazolamide	b. or c. Diuretic
Adalat	d. Calcium channel blocker
Alazine	j. Hydralazine (Vasodilator)
Aldaclor	b. or c. Diuretic and k. Other (Centrally acting adrenergic)
Aldactazide	b. or c. Diuretic
Aldactone	b. or c. Diuretic
Aldomet	k. Other (Centrally acting adrenergic)
Aldoril	b. or c. Diuretic and k. Other (Centrally acting adrenergic)
Altace	e. ACE inhibitor
amiloride	b. or c. Diuretic
amlodipine	d. Calcium channel blocker
Anhydron	b. or c. Diuretic
Apresazide	b. or c. Diuretic and j. Hydralazine (Vasodilator)
Apresoline	j. Hydralazine (Vasodilator)
atenolol	g. Atenolol (Beta blocker)
atorvastatin	l. HMG CoA reductase inhibitors
Atromid-S	m. Other lipid-lowering medication
Avapro	k. Other (Angiotensin II receptor antagonist)
Baycol	l. HMG CoA reductase inhibitors
benazepril	e. ACE inhibitor
bendroflumethiazide	b. or c. Diuretic
benzthiazide	b. or c. Diuretic
bepridil	d. Calcium channel blocker
Betapace	k. Other (Beta blocker)
betaxolol	k. Other (Beta blocker)
bisoprolol	k. Other (Beta blocker)

Drug Name	Category
Blocadren	k. Other (Beta blocker)
bumetanide	b. or c. Diuretic
Bumex	b. or c. Diuretic
Calan	d. Calcium channel blocker
Capoten	e. ACE inhibitor
Capozide	e. ACE inhibitor and b. or c. Diuretic
captopril	e. ACE inhibitor
Cardene	d. Calcium channel blocker
Cardiazem	d. Calcium channel blocker
Cardura	f. Alpha blocker
carteolol	k. Other (Beta blocker)
Cartrol	k. Other (Beta blocker)
carvedilol	f. Alpha blocker and k. Other (Beta blocker)
Catapres	h. Clonidine (Centrally acting adrenergic)
cerivastatin	l. HMG CoA reductase inhibitors
chlorothiazide	b. or c. Diuretic
chlorthalidone	b. or c. Diuretic
cholestyramine	m. Other lipid-lowering medication
Cholybar	m. Other lipid-lowering medication
cilazapril	e. ACE inhibitor
clofibrate	m. Other lipid-lowering medication
clonidine	h. Clonidine (Centrally acting adrenergic)
Colestid	m. Other lipid-lowering medication
cholestipol	m. Other lipid-lowering medication
Combipres	h. Clonidine and k. Other (Centrally acting adrenergic)
Coreg	f. Alpha blocker and k. Other (Beta blocker)
Corgard	k. Other (Beta blocker)
Corzide	b. or c. Diuretic and k. Other (Beta blocker)
Covera HS	d. Calcium channel blocker

Drug Name	Category
Cozaar	k. Other (Angiotensin II receptor antagonist)
cyclothiazide	b. or c. Diuretic
Demadex	b. or c. Diuretic
Demi-Regroton	i. Reserpine and b. or c. Diuretic
Diachlor	b. or c. Diuretic
Diamox	b. or c. Diuretic
diazoxide	k. Other (Vasodilator)
Dibenzyline	f. Alpha blocker
Dilacor	d. Calcium channel blocker
diltiazem	d. Calcium channel blocker
Diovan	k. Other (Angiotensin II receptor antagonist)
Diucardin	b. or c. Diuretic
Diulo	b. or c. Diuretic
Diupres	i. Reserpine and b. or c. Diuretic
Diurigen	b. or c. Diuretic
Diuril	b. or c. Diuretic
doxazosin	f. Alpha blocker
Dralzine	j. Hydralazine (Vasodilator)
Dyazide	b. or c. Diuretic
DynaCirc	d. Calcium channel blocker
Dyrenium	b. or c. Diuretic
Edecrin	b. or c. Diuretic
enalapril	e. ACE inhibitor
Enduron	b. or c. Diuretic
Esidrix	b. or c. Diuretic
Esimil	b. or c. Diuretic and k. Other (Peripheral acting adrenergic)
ethacrynic acid	b. or c. Diuretic
Exna	b. or c. Diuretic
felodipine	d. Calcium channel blocker
Flomax	f. Alpha blocker
fluvastatin	l. HMG CoA reductase inhibitors
fosinopril	e. ACE inhibitor
furosemide	b. or c. Diuretic
gemfibrozil	m. Other lipid-lowering medication

Drug Name	Category
guanabenz	k. Other (Centrally acting adrenergic)
guanadrel	k. Other (Peripheral acting adrenergic)
guanethidine	k. Other (Peripheral acting adrenergic)
guanfacine	k. Other (Centrally acting adrenergic)
hydralazine	j. Hydralazine (Vasodilator)
hydrochlorothiazide	b. or c. Diuretic
Hydrodiuril	b. or c. Diuretic
hydroflumethiazide	b. or c. Diuretic
Hydromox	b. or c. Diuretic
Hydropres	i. Reserpine and b. or c. Diuretic
Hygroton	b. or c. Diuretic
Hylorel	k. Other (Peripheral acting adrenergic)
Hytrin	f. Alpha blocker
Hyzaar	b. or c. Diuretic and k. Other (Angiotensin II receptor antagonist)
indapamide	b. or c. Diuretic
Inderal	k. Other (Beta blocker)
Inderide	b. or c. Diuretic and k. Other (Beta blocker)
Inhibace	e. ACE inhibitor
irbesartan	k. Other (Angiotensin II receptor antagonist)
Ismelin	k. Other (Peripheral acting adrenergic)
Isoptin	d. Calcium channel blocker
isradipine	d. Calcium channel blocker
Kerlone	k. Other (Beta blocker)
labetalol	f. Alpha blocker and k. Other (Beta blocker)
Lasix	b. or c. Diuretic
Lescol	l. HMG CoA reductase inhibitors
Levator	k. Other (Beta blocker)
Lexxel	e. ACE inhibitor and d. Calcium channel blocker
Lipitor	l. HMG CoA reductase inhibitors
lisinopril	e. ACE inhibitor
Loniten	k. Other (Vasodilator)
Lopid	m. Other lipid-lowering medication
Lopressor	k. Other (Beta blocker)
Lopressor HCT	b. or c. Diuretic and k. Other (Beta blocker)

Drug Name	Category
Lorelco	m. Other lipid-lowering medication
losartan potassium	k. Other (Angiotensin II receptor antagonist)
Lotensin	e. ACE inhibitor
Lotensin HCT	e. ACE inhibitor and b. or c. Diuretic
Lotrel	e. ACE inhibitor and d. Calcium channel blocker
lovastatin	l. HMG CoA reductase inhibitors
Lozol	b. or c. Diuretic
Mavik	e. ACE inhibitor
Maxzide	b. or c. Diuretic
methyclothiazide	b. or c. Diuretic
methyldopa	k. Other (Centrally acting adrenergic)
metolazone	b. or c. Diuretic
metoprolol	k. Other (Beta blocker)
Mevacor	l. HMG CoA reductase inhibitors
Microzide	b. or c. Diuretic
Mictrin	b. or c. Diuretic
Midamor	b. or c. Diuretic
Minipress	f. Alpha blocker
Minizide	f. Alpha blocker and b. or c. Diuretic
Minodyl	k. Other (Vasodilator)
minoxidil	k. Other (Vasodilator)
Moduretic	b. or c. Diuretic
moexipril	e. ACE inhibitor
Monopril	e. ACE inhibitor
Mykrox	b. or c. Diuretic
nadolol	k. Other (Beta blocker)
Naqua	b. or c. Diuretic
Naturetin	b. or c. Diuretic
Niac	m. Other lipid-lowering medication
Niacels	m. Other lipid-lowering medication
niacin	m. Other lipid-lowering medication
Niacor	m. Other lipid-lowering medication
nicardipine	d. Calcium channel blocker
Nico-400	m. Other lipid-lowering medication
Nicobid	m. Other lipid-lowering medication
Nicolar	m. Other lipid-lowering medication

Drug Name	Category
Nicotinex	m. Other lipid-lowering medication
nifedipine	d. Calcium channel blocker
nimodipine	d. Calcium channel blocker
Nimotop	d. Calcium channel blocker
nisoldipine	d. Calcium channel blocker
Normodyne	k. Other (Beta blocker)
Norvasc	d. Calcium channel blocker
Oretic	b. or c. Diuretic
papaverine	k. Other (Vasodilator)
Pavabid	k. Other (Vasodilator)
penbutolol	k. Other (Beta blocker)
perindopril	e. ACE inhibitor
phenoxvbenzamine	f. Alpha blocker
pindolol	k. Other (Beta blocker)
Plendil	d. Calcium channel blocker
polythiazide	b. or c. Diuretic
pravastatin	l. HMG CoA reductase inhibitors
Pravachol	l. HMG CoA reductase inhibitors
prazosin	f. Alpha blocker
Prinivil	e. ACE inhibitor
Prinzide	e. ACE inhibitor and b. or c. Diuretic
probucol	m. Other lipid-lowering medication
Procardia	d. Calcium channel blocker
propranolol	k. Other (Beta blocker)
Questran	m. Other lipid-lowering medication
quinapril	e. ACE inhibitor
quinethazone	b. or c. Diuretic
ramipril	e. ACE inhibitor
rauwolfia root	k. Other (Peripheral acting adrenergic)
Renese	b. or c. Diuretic
reserpine	i. Reserpine (Peripheral acting adrenergic)
Rolzine	j. Hydralazine (Vasodilator)
Saluron	b. or c. Diuretic
Sectral	k. Other (Beta blocker)
Ser-Ap-Es	i. Reserpine and j. Hydralazine and b. or c. Diuretic
Serpalan	i. Reserpine (Peripheral acting adrenergic)

Drug Name	Category
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Drug Name	Category
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Serpasil	k. Other (Peripheral acting adrenergic)
simvastatin	l. HMG CoA reductase inhibitors
sotalol	k. Other (Beta blocker)
Span	m. Other lipid-lowering medication
spironolactone	b. or c. Diuretic
Sular	d. Calcium channel blocker
Tarka	e. ACE inhibitor and d. Calcium channel blocker
Teczem	e. ACE inhibitor and d. Calcium channel blocker
Tega-Span	m. Other lipid-lowering medication
Tenex	k. Other (Centrally acting adrenergic)
Tenoretic	g. Atenolol (Beta blocker) and b. or c. Diuretic
Tenormin	g. Atenolol (Beta blocker)
terazosin	f. Alpha blocker
Thalitone	b. or c. Diuretic
Thiuretic	b. or c. Diuretic
Tiazac	d. Calcium channel blocker
Timolide	b. or c. Diuretic and k. Other (Beta blocker)
timolol	k. Other (Beta blocker)
Toprol	k. Other (Beta blocker)
torseamide	b. or c. Diuretic
Trandate	f. Alpha blocker and k. Other (Beta blocker)
trandolapril	e. ACE inhibitor
triamterene	b. or c. Diuretic
trichlormethiazide	b. or c. Diuretic
Univasc	e. ACE inhibitor
valsartan	k. Other (Angiotensin II receptor antagonist)
Vascor	d. Calcium channel blocker
Vaseretic	e. ACE inhibitor and b. or c. Diuretic
Vasotec	e. ACE inhibitor
verapamil	d. Calcium channel blocker
Verelan	d. Calcium channel blocker
Visken	k. Other (Beta blocker)
Wyntensin	k. Other (Centrally acting adrenergic)
Zaroxolyn	b. or c. Diuretic
Zebeta	k. Other (Beta blocker)
Zestoretic	e. ACE inhibitor and b. or c. Diuretic

Zestril	e. ACE inhibitor
Ziac	b. or c. Diuretic and k. Other (Beta blocker)
Zocor	l. HMG CoA reductase inhibitors
To follow is a list of hormone therapies to help you answer question 19 at required visits.	
conjugated equine estrogen	Hormone replacement therapy
esterified estrogens	Hormone replacement therapy
Estrace	Hormone replacement therapy
Estraderm	Hormone replacement therapy
estradiol	Hormone replacement therapy
Estratab	Hormone replacement therapy
estropipate	Hormone replacement therapy
Estrovis	Hormone replacement therapy
Menrium	Hormone replacement therapy
Ogen	Hormone replacement therapy
PMB 200	Hormone replacement therapy
PMB 400	Hormone replacement therapy
Premarin	Hormone replacement therapy
Premphas	Hormone replacement therapy
Prempro	Hormone replacement therapy
quinnestrol	Hormone replacement therapy



Developed for use in ALLHAT, an international multi-centered study funded by the National Heart, Lung and Blood Institute (NHLBI) and the Department of Veterans Affairs Cooperative Studies Program (VACSP).

CHAPTER 4

ASSESSMENT AND MANAGEMENT OF SIDE EFFECTS

4.1 Introduction to side effects

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 minimal 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. The investigator is encouraged to call the Regional Coordinator for assistance.

4.2 Assessment of symptoms

4.2.1 Allergy, syncope or severe dermatitis

Development of an allergy (such as purpura, asthma, or a generalized rash) to any of the ALLHAT medications, syncope, or severe dermatitis, 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.

4.2.2 Angioedema, neutropenia, or necrotizing vasculitis

Development of angioedema, neutropenia or necrotizing vasculitis requires that the ALLHAT medication be discontinued. Such participants will need to be withdrawn permanently from the medication.

4.2.3 Clinical hepatitis - for patients on pravastatin

Pravastatin should be discontinued in any patient who develops clinical hepatitis.

4.2.4 Muscle pain - for patients on pravastatin

If the patient reports diffuse muscle pain, or pain in two or more unrelated muscle groups, a creatine kinase (CK) should be obtained locally.

If the CK level is > 10 times the upper limit of normal, pravastatin should be discontinued immediately and the CK level reassessed. The patient should be hydrated, renal function should be assessed, and CK levels should be monitored at weekly intervals (or more frequently) until at least two consecutive levels are within three times the upper limit of normal. CK should then be monitored at six-week intervals or more frequently until at least two consecutive measurements are within the normal range.

If the CK level is between three and ten times the upper limit of normal, another measurement should be obtained immediately. If clinical symptoms and CK levels are consistent with myositis, the pravastatin should be discontinued immediately. CK levels should be monitored at weekly intervals (or more frequently) until at least two consecutive levels are within three times the upper limit of normal. CK should then be monitored at six-week intervals or more frequently until at least two consecutive measurements are within the normal range.

4.2.5 Other symptoms

Other side effects that develop are a matter for the judgment of the clinic physician who has the primary objective of assuring the safety of the participant and the secondary objective of maintaining the treatment protocol wherever possible. Consultation with the Regional Coordinator, however, is encouraged.

4.3 Blood tests

4.3.1 Hypokalemia and Hyperkalemia

Physician-investigators will routinely receive reports of all Central Laboratory determinations except serum potassium level, which will be masked after Visit 2. However, the Central Laboratory will notify the clinical site promptly of any serum potassium values below 3.5 mmol/l. If the level is between 3.2 and 3.5 mmol/l, it will be rechecked locally at the next scheduled visit. If the level is below 3.2 mmol/l or above 5.5 mmol/l, the participant should be recalled immediately to have his/her potassium level rechecked locally. Oral potassium supplementation should be prescribed for any patient whose potassium level is below 3.5 mmol/l on recheck.

The oral potassium supplementation provided by ALLHAT is a slow-release formulation in 8 meq tablets. The suggested starting dosage is 5 tablets (40 meq) once per day, which may be raised as need to 12 tablets (96 meq) per day.

The Central Laboratory will also notify the clinical site promptly of any serum potassium values above 5.5 mmol/l, or of serum potassium increases of 1.0 mmol/l or more to above 5.0 mmol/l. Clinical discretion should be used in treating a serum potassium level above 5.5 mmol/l or in determining action to be taken for increases of 1.0 mmol/l or more.

4.3.2 Serum ALT - for participants assigned to pravastatin

The Central Laboratory will routinely provide ALT and lipid values to study investigators. ALT levels exceeding three times the upper limit of normal (>150 u/L) will be flagged as "alert" values. When ALT is in the alert range, blood should be redrawn and sent to the Central Laboratory for repeat measurement. If the alert value is confirmed and is not explained by other factors, the investigator should consider stopping the study medication. The patient may subsequently be rechallenged at 10 mg/day after the ALT returns to normal or pre-treatment levels. If no further difficulties are encountered after four months at reduced dosage, the dosage may be increased to 20 mg/day and subsequently to 40 mg/day (the protocol starting

dose of pravastatin). ALLHAT investigators are also expected to reduce or, if necessary, to discontinue the study medication in the presence of other medically significant side effects that are judged to be attributable to pravastatin and to rechallenge (if judged appropriate) with a reduced dosage when the side effects subside.

4.4 Serious Adverse Experiences (SAEs) - the AL13

Most apparent side effects will not be serious. However, some apparent side effects may involve one of the following:

- Death
- Life threatening event
- Events resulting in permanent disability
- Hospitalization
- Prolongation of hospital stay
- Cancer
- Drug overdose

Any of these events that are *deemed by the investigator to be caused by the blinded study drug* must be reported to the CTC as soon as possible via the ALLHAT Adverse Experience Form, the AL13. **Only those SAE's fitting into one of the above seven categories and which the investigator feels may be caused by the blinded study drugs should be reported on this form. IF ANY INFORMATION ON THIS FORM IS LEFT BLANK OR ANSWERED INCORRECTLY, THE FORM WILL BE RETURNED TO YOU FOR CORRECTION.**

Patient identification label:

As with all ALLHAT forms, place the patient's ID label in the space provided. If you wish, you may write the patient's name in this rectangle so that their name will be transferred to the NCR copy, or you may place a label on the NCR copy.

Item #1 - Today's date:

Complete "today's date" (the date the form was completed) as mm/dd/yy, using leading zero's as necessary.

Item #2 - Outcome of adverse experience:

The adverse event will fall into one of seven categories as listed on the form in Item #2. Please check all that apply.

Item #3 - Relationship of SAE to the blinded ALLHAT medication:

Please indicate how this SAE is related to the study drug. Check one only of "definitely

due to study drug”, “possibly due to study drug”, or “not due to study drug”. IF YOU CHECK “NOT DUE TO STUDY DRUG”, PLEASE DO NOT COMPLETE THIS FORM.

Item #4 - Duration of this experience:

For each adverse experience, indicate the duration of experience in Items #4a and #4b. **Do not leave either date blank.** If the month and year are known, but you are uncertain of the day, use "15" for the day. If the event lasted only one day (i.e., "from" and "to" are the same day), put the same date in both spaces.

Item #5 - Action taken:

Indicate the action taken with respect to the study drug and with respect to symptomatic therapy. Check all that apply. If none of the responses in #5a-c are applicable, be sure to check #5d (“None of the above”).

Item #6 - Patient’s current status:

Please check all that apply in #6a-e. At least one of these must be checked.

Item #7 - Body system classification:

Again, please check all of the body systems that apply. At least one of these must be checked.

Item #8 - Description of adverse experience:

It is very important that details of the adverse experience be given in the space provided for comments. Please print clearly - your comments will be data entered at the Clinical Trials Center. If this space is left blank, or the comments do not clearly describe and name the adverse experience, the form will be returned to you for completion or clarification.

The person completing the form should initial and sign the form as usual.

The white and yellow copies of the AL13 should be sent to the CTC, and the pink copy should be kept in your clinic records.

ALLHAT ADVERSE EXPERIENCE FORM - VERSION 2, 4/96

Place ID label here	<p>Serious adverse experiences (SAES) <u>which the investigator feels may be caused by the blinded study drugs</u> must be reported to the CTC. SAES include death, life threatening events, events resulting in permanent disability, hospitalizations or prolongation of hospital stays, cancers, or drug overdoses.</p>
---------------------	---

1. Today's date (mm-dd-yy): - - - - -
2. Outcome of adverse experience (check all that apply):
 - a. Death 1
 - b. Life threatening event 1
 - c. Event resulting in permanent disability 1
 - d. Hospitalization 1
 - e. Prolongation of hospital stay 1
 - f. Cancer 1
 - g. Drug overdose 1

ATTENTION: Only those SAEs fitting into one of the 7 categories in item #2 and which the investigator feels may be caused by the blinded study drugs should be reported on this form.

3. Relationship of SAE to the blinded ALLHAT medication
 - Definitely due to study drug 1
 - Possibly due to study drug 2
 - STOP - do not file AL13** Not due to study drug 3
4. Duration of this experience:
 - a. Start date (mm-dd-yy) - - - - -
 - b. End date (mm-dd-yy) - - - - -
5. Action taken (check all that apply):
 - a. Decrease dosage 1
 - b. Symptomatic therapy 1
 - c. Study drug discontinued 1
 - d. None of the above 1
6. Patient's current status (check all that apply)
 - a. Recovered 1
 - b. Abated with decreased dose 1
 - c. Alive with sequelae 1
 - d. Under treatment for sequelae 1
 - e. Death 1
7. Body system classification (check all that apply)
 - a. Circulatory system 1
 - b. Genitourinary system 1
 - c. Musculoskeletal system 1
 - d. Nervous system & sense organs 1
 - e. Respiratory system 1
 - e. Skin & subcutaneous tissue (include angioedema here) 1
 - f. Digestive system 1
 - g. Other (specify in comments) 1
 - h. Unknown 1
8. Please describe this adverse experience (an AL13 without a description will be returned to you):

9. Initials of person completing this form:
10. Signature of **INVESTIGATOR**: _____

CHAPTER 5 STUDY EVENTS

5.1. Diagnostic categories to be recorded by the clinical center staff

- ✓ Death, with cause of death
- ✓ Hospitalized acute myocardial infarction
- ✓ Hospitalized stroke
- ✓ Congestive heart failure
- ✓ Angina pectoris
- ✓ Peripheral arterial disease (lower extremity claudication)
- ✓ Cancer, with primary site
- ✓ Nonfatal accidents and attempted suicides
- ✓ Kidney transplant
- ✓ Start of chronic kidney dialysis

5.2. Discovery of a possible event

The study investigators will be required to complete and submit a short events questionnaire to apprise the Clinical Trials Center of any study events that may have occurred. This is done as part of the routine follow-up form (AL03). For each event involving a death or hospitalization, the investigator will also obtain and submit a copy of the death certificate and/or hospital discharge summary upon which the diagnosis is based.

The underlying cause of death will be classified by the physician-investigator at the clinical site as due to:

- Coronary heart disease – definite myocardial infarction, definite CHD or possible CHD;
- Other cardiovascular disease - stroke, congestive heart failure, or other CVD;
- Cancer - with primary site;
- Kidney disease;
- Accident, suicide, or homicide;
- Other non-cardiovascular disease; or
- Unknown cause

For a random (10%) subset of hospitalized (fatal and nonfatal) myocardial infarctions and strokes, the Clinical Trials Center will request more detailed information as described below so that the in-hospital ECGs and enzyme levels (for MIs) and other records (for strokes) can be evaluated by the study events committee and the accuracy of the discharge diagnosis on the AL04 (versus the definitions in this chapter) can be assessed.

Information from the Health Care Financing Administration (HCFA) and the VA will be requested several times throughout the study to identify study events that may have occurred but which have not been reported to the CTC by the study sites. Sites will be notified of possible unreported events and documentation will be requested.

A National Death Index (NDI) Search will be performed near the end of the study to identify and document deaths that may have occurred among patients lost to follow-up. Because of the time lag inherent in the NDI, a private tracing service will also be utilized for selected participants.

5.3. Event definitions

5.3.1. Coronary Death (myocardial infarction, definite CHD, possible CHD):

Death consistent with coronary heart disease (CHD) as underlying cause on death certificate, plus any one of the following:

- 1) Pre-terminal hospitalization with myocardial infarction,
- 2) Previous angina or myocardial infarction and no known potentially lethal non-coronary disease process, and/or
- 3) Death resulting from a procedure related to coronary artery disease such as coronary bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Note: Deaths due to a non-coronary underlying cause in which the terminal event was an MI shall be ascribed to the underlying cause -- not to CHD.

Coronary death will be subclassified as:

- 1) Definite fatal MI: no known non-atherosclerotic cause and definite MI within 4 weeks of death (see definition below in section 5.3.2), or acute MI as cause of death on autopsy.
- 2) Definite fatal CHD: no known non-atherosclerotic cause and one or both of the following: chest pain within 72 hours of death or a history of chronic ischemic heart disease in the absence of valvular heart disease or non-ischemic cardiomyopathy, or
- 3) Possible fatal CHD: no known non-atherosclerotic cause, and death certificate consistent with underlying cause.

In patients without a known potentially lethal non-coronary disease process, coronary death will also be classified as rapid or non-rapid, based on whether death did or did not occur within 24 hours after the onset of symptoms (or the time at which the patient was last seen without symptoms).

5.3.2. Acute Nonfatal Myocardial Infarction

This is usually documented by hospital discharge summary, and *includes suspected myocardial infarction with thrombolytic therapy*. Procedures accompanying a possible MI may be coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), coronary stent, coronary atherectomy, thrombolytic therapy (TPA, streptokinase).

The identification and coding of definite clinical acute myocardial infarction (MI) should be based on meeting at least two of the following three generally accepted criteria, consistent with the World Health Organization criteria:

- 1) Symptoms (such as chest pain) compatible with an acute MI of at least 20 minutes duration.
- 2) ECG changes compatible with an acute MI, such as new persistent ST segment elevation of ≥ 0.1 mV or new pathologic Q waves (QRS >0.04 sec), each in two contiguous leads..
- 3) A serum biochemical marker compatible with an acute MI, such as:
 - ✓ Total CK at least twice the upper limits of normal with an MB fraction of $>5\%$ of total CK, or
 - ✓ *Troponin >2 times the upper limit of normal, or
 - ✓ LDH1/LDH2 ratio ≥ 1 .

*1/99 – Changed from “Troponin 2” to “Troponin”

Rapid onset of persistent neurologic deficit attributable to an obstruction or rupture of the

arterial system, including stroke occurring during surgery, that is not known to be secondary to brain trauma, tumor, infection, or other non-ischemic cause. The deficit must last more than 24 hours unless death supervenes or there is a demonstrable lesion compatible with acute stroke on CT or MRI scan. Procedures accompanying a possible stroke may be carotid endarterectomy or carotid angioplasty.

Non-fatal stroke (either of the following):

- 1) Unequivocal objective findings of a localizing neurologic deficit (with or without recent onset of severe headache and loss of consciousness) AND duration longer than 24 hours AND absence of other disease process causing neurologic deficit such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder, and/or
- 2) Diagnosis of stroke based on abnormality demonstrated by CT or MRI consistent with current neurologic symptoms or signs, or positive lumbar puncture (for subarachnoid hemorrhage).

Transient ischemic attacks (TIA's) or "mini-strokes" should NOT be reported as non-fatal strokes.

Fatal stroke: Death certificate listing stroke as consistent with, underlying, or immediate cause of death, plus any one or more of the following:

- 1) Preterminal hospitalization with stroke as defined above,
- 2) Previous stroke and no known potentially lethal non-cerebrovascular disease process, and/or
- 3) Stroke diagnosed as cause of death at post-mortem examination.

5.3.4. Congestive heart failure

Symptomatic CHF includes patients with clear-cut signs or symptoms of left or right ventricular dysfunction that cannot be attributed to other causes. It should not include patients with only lower extremity edema or exertional dyspnea, as these can be present in the absence of any cardiac dysfunction. Procedures that may accompany CHF include aortic balloon pump, assist devices, heart transplant.

The diagnosis of CHF 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
- ✓ S₃ 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:

- positive chronic bronchitis questionnaire
 - plus smoking history of 10 pack years or greater
 - and X-ray confirmation
- ✓ Pneumonia
 - ✓ Other severe lung disease documented by X-ray or other tests.

5.3.5. Angina pectoris

Angina pectoris includes diagnosed symptomatic angina, classically described as substernal visceral pain or heaviness provoked by exertion and relieved by rest, or any other symptomatic anginal syndromes or equivalents believed by the investigator to be due to intermittent inadequacy of coronary blood supply. Distinction should be made between hospitalized angina (with or without revascularization procedure), which is reportable via AL03 and AL04, and angina treated as an outpatient (reportable on AL03 only). Procedures that may accompany angina pectoris include CABG, PCTA, atherectomy and stent.

5.3.6. Peripheral arterial disease (PAD)

PAD means lower extremity intermittent claudication, or lower extremity arterial disease leading to procedures that may accompany possible PAD include revascularizations or angioplasty of peripheral arteries, e.g., ilio-femoral bypass. Only *hospitalized* cases of PAD should be reported on both the AL03 and AL04. Cases of PAD treated, but not hospitalized, should only be reported on the AL03. (Note 5/17/06 – amputations were included in this category).

5.3.7. Cancer

New nonfatal cancer diagnoses excluding non-melanoma skin cancers will be recorded, as well as cancer deaths, along with the primary site. We are not collecting a special report on every hospitalization for chemotherapy, or multiple hospitalizations for the same cancer. We are only seeking to describe each new case of cancer, whether or not the patient is hospitalized. If the participant was not hospitalized for a new diagnosis of cancer, a copy of the pathology report or other documentation of the diagnosis should be submitted in place of the discharge summary.

5.3.8. Nonfatal accidents and attempted suicides

Report nonfatal accidents and attempted suicides only if the patient is hospitalized.

5.3.9. Kidney transplant or start of chronic kidney dialysis

Report kidney transplanation, and report the *start of chronic* kidney dialysis.

5.4. The AL04 - ALLHAT Event Reporting Form - and supporting documentation

Events for which an AL04 (ALLHAT Event Reporting Form) should be filed are:

- Any death
- Hospitalization for acute myocardial infarction (including evolving MI with thrombolysis)
- Hospitalization for stroke (not TIA or “ministroke”)
- Cancer (a new primary diagnosis; excluding non-melanoma skin cancer)
- Hospitalization for congestive heart failure
- Hospitalization for angina pectoris (actual episode of chest pain)
- Hospitalization for lower extremity arterial disease
- Hospitalization for accident or attempted suicide

- Kidney transplant
- Start of chronic kidney dialysis
- Coronary artery bypass graft (CABG)
- Coronary PTCA (angioplasty), stent or atherectomy
- Lower extremity peripheral revascularization/bypass/angioplasty

If you submit an AL04 when one is not required, it will be returned to you.

It is important that the Clinical Trials Center be apprised of all events as they occur or as close to the time of the event as possible. The ALLHAT Event Reporting Form should be completed as sent to the Clinical Trials Center as soon as it is discovered that an event has occurred. Many times this means that the death certificate and/or discharge summary will be sent at a later date.

Patient identification label:

As with all ALLHAT forms, place the patient's ID label in the space provided. If you wish, you may write the patient's name in this rectangle so that their name will be transferred to the NCR copy, or you may place a label on the NCR copy.

Item #1 – Today's date:

Complete "today's date" (the date the form was completed) as mm/dd/yyyy, using leading zero's as necessary.

Item #2 - Date of event:

Complete Item #2, the date of event, as mm/dd/yyyy, using leading zeros where necessary. If a death occurred during a hospitalization, the date of death is considered the event date (not the admission date). If you are not sure of the exact date of the event, but you know the month and the year, complete the month and year as usual, and use "15" for the day. This date should be the date of hospitalization. If the patient was not hospitalized, the date should reflect the date of procedure or, for nonhospitalized new cancers, the date of diagnosis. The date of cancer diagnosis is usually considered the date of the diagnostic biopsy, surgery or radiology.

It is crucial that the date of event be a valid date. DO NOT COMPLETE THIS DATE WITH 99-99-9999. A form with an invalid event date cannot be entered onto the data file at the CTC. Please provide an approximate date, if an accurate date cannot be determined.

Item #3 - Death or nonfatal event:

Indicate in Item #3 if you are reporting a death or a nonfatal event. Do not mark both - use a separate AL04 for each event.

Items #4 - #9 - for deaths only:

Item #4 - Cause of death:

The investigator should examine what is known regarding the circumstances of the death, and make an evaluation regarding the cause of death in Item #4. Please keep in mind the descriptions of some of these causes, particularly MI, other CHD, and stroke, as described previously. Check only one cause of death - the underlying cause of death.

Item #5 – If MI or definite or possible CHD, did death occur within 24 hours of symptoms?:

If you checked "MI", "definite CHD" or "possible CHD" for Item #4, indicate in Item #5 whether or not the death occurred within 24 hours of symptoms. If you cannot determine this, check "DK". If the death was not due to "MI", "definite CHD" or "possible CHD" leave this item blank.

Item #6 - If cancer, give **primary** site:

If the death is due to cancer, please indicate the primary site in Item #6. If you are unsure of the primary site, check "DK". If the death is not due to cancer, leave this item blank.

Items #7a and 7b - Was patient hospitalized, or taken to a hospital during fatal event?:

Item #7a inquires whether the patient was hospitalized or taken to a hospital during the fatal event. Check "Yes", "No" or "DK". Do not leave this item blank. If the patient was hospitalized or taken to a hospital, you should obtain a copy of the discharge summary (or other description, if the participant was not actually admitted and a discharge summary is not available). Item #7b asks if the discharge summary is attached (Yes or No). If you check "No" here, please check the primary reason in Item #9 and explain in Item #14.

Item #7c – Other events during hospitalization (other than cause of death):

Often, more than one study event will occur during a hospitalization for a fatal event. For example, a participant hospitalized for an MI may die of congestive heart failure, and therapeutic procedures may have been done. We would like to know about all of those. Therefore, please mark all applicable events and procedures in Item #7c, other than the cause of death marked in Item #4.

Item #8 - Is death certificate attached?:

For all deaths, it is very important that a death certificate be obtained as soon as possible. If you are including the death certificate with this report, mark "Yes" in Item #8. If not, mark "No".

Item #9 - Primary reason for missing death certificate and/or discharge summary:

If you indicated "No" for either the discharge summary or death certificate, please give the primary reason in Item #9 (pending, family refusal, unable to locate records, other/specify). Check only the one primary reason. Explain in Item #14.

Items #10 - #13 - for nonfatal events only:

Item #10 - Type of nonfatal event:

In Item #10, specify the type of nonfatal event (check all that apply, if more than one type of event occurred during a particular hospitalization). Please refer to definitions for these events reviewed earlier in this chapter. Non-melanoma skin cancers should not be reported.

Item #11 - If cancer, give **primary** site:

If the event is a new primary cancer diagnosis (not non-melanoma skin cancer), please indicate the primary site in Item #11. If you are unsure of the primary site, check "DK". If the event is not cancer, leave this item blank.

Item #12 - Was patient hospitalized?:

Item #12a inquires whether the patient was hospitalized (admitted to a hospital). Check "Yes", "No" or "DK". Do not leave this item blank. If the patient was admitted to a hospital, you should obtain a copy of the discharge summary (or other similar description if a discharge

summary is not available). Item #12b asks if the discharge summary is attached (Yes or No). If you check "No" here, please check the primary reason in Item #13 and explain in Item #14.

Item #13 - Primary reason for missing discharge summary:

If you indicated that the discharge summary is not attached, please give the primary reason in Item #13 (pending, family refusal, unable to locate records, other/specify). Check only the one primary reason. Explain in Item #14.

Items #14 - #17 - for all events:

Comments are requested in Item #14, particularly for events where the documentation will not be available or may be delayed a long time. A good, brief description of symptoms is crucial. Also note if there are, in your judgment, unusual circumstances surrounding the event that you think might be useful for reviewers to know.

The person completing the form should clearly print their initials in Item #15, and sign at Item #16. The investigator should always review the form and supporting documentation, and sign the form in Item #17.

Reimbursements are made separately for the AL04 and the supporting documentation.

Regarding pending documentation:

This is one of the few ALLHAT forms that has an original and two copies (most forms have only one copy). Only the white copy should initially be sent to the Clinical Trials Center. If records are pending, and they are obtained later, attach the record(s) to the pink copy of the form, and send it as is to the Clinical Trials Center with your regular batch of study forms. Do not complete a new AL04 for these cases! Always keep the yellow copy of the AL04 and copies of supporting documentation for your records.

Hints for getting copies of discharge summaries, death certificates, and other event documentation:

If your office does not routinely obtain discharge summaries, death certificates or other information for your patients who have events, collection of these items will be a new challenge. To help you obtain these documents, the following may be helpful:

Release of Information (page 5-8) – To ease the collection of discharge summaries and death certificates, copy the provided Release of Information Form onto your office letterhead and have each participant sign it at his or her next scheduled visit. This form can also be mailed to a participant if they are unable to come into the clinic. If you have your own release of information form that works for you, go ahead and use it!

However, be aware that hospital medical records departments have varying requirements for the timing of the signature in relation to the event. It is a good idea to check with several departments that you frequently need records from regarding their requirements. It may be necessary to have a participant sign such a release at least once a year.

Letter to Family Regarding Death of Participant (page 5-9) – To collect a Death Certificate and any information on preceding events, send this letter to the family. Remember to enclose a self addressed stamped envelope.

Getting a Death Certificate – Getting a death certificate can be difficult. Refer to the suggestions on page 5-10 for ideas on how to obtain a Death Certificate.

(on physician's letterhead)

ALLHAT PATIENT AUTHORIZATION FOR RELEASE OF MEDICAL INFORMATION

TO: _____

RE: Patient name: _____
DOB: __ - __ - __ Social Security/SIN # _____ Hospital # _____

I give my consent to release information from my medical records as requested by Dr. _____ to be used in relation to ALLHAT (Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial) for the purpose of documenting ALLHAT study events. I understand the information obtained will be held in strict confidence. This consent is valid for the duration of the ALLHAT study.

Signature: _____ Date: _____
Witness: _____ Date: _____

Information requested relating to the dates of:

__ - __ - ____ through __ - __ - ____
m m d d y y y y m m d d y y y y

- | | |
|--|---|
| <input type="checkbox"/> Complete records | <input type="checkbox"/> Hospital discharge/death summary |
| <input type="checkbox"/> Lab/cardiac enzymes reports | <input type="checkbox"/> Surgery/consultation reports |
| <input type="checkbox"/> X-ray/CT/MRI reports | <input type="checkbox"/> ER notes |
| <input type="checkbox"/> ECG | <input type="checkbox"/> Other (_____) |

Requested by: _____
Study physician/Coordinator

Thank you for your assistance in this matter.



Date: _____

Dear _____

We were saddened to hear of _____ death. We always enjoyed seeing and talking with _____ during the clinic visits and appreciated their willingness to participate in the ALLHAT Study.

We know this is a hard time for your family, but as part of the ALLHAT study, we would like to obtain information regarding his/her condition during any hospitalization. We have enclosed a release of information form for you to sign and return in the same envelope along with a copy of the death certificate. Enclosed is a self addressed stamped envelope.

If you have any questions or concerns, please feel free to call us at _____.

Our deepest sympathy to you and your family.

Sincerely,

Enc.

Getting a Death Certificate

How to get death certificates & other event documentation

- ♥ Have participant sign a Release of Medical Records Form annually. If a medical records department requires the release to be signed after the event, have the participant sign a release at their next visit or mail it to the participant or their family with a self-addressed return envelope.
- ♥ Know the requirements of your local medical records departments.
- ♥ Inform your participant and their family that you need to be notified whenever they go into the hospital and that the attending physician should be asked to send a copy of the discharge summary to your office.
- ♥ Ask the participant to contact the hospital, obtain a copy of the medical record, and bring it to their next visit.
- ♥ Establish a good rapport with the participant's other physicians by sending them copies of ALLHAT blood work results and other reports. If you then need a copy of the participant's medical records, they may reciprocate.
- ♥ Send a copy of the signed informed consent and a memo indicating what you need to the medical records department.
- ♥ If a participant enters a long-term care facility, establish a rapport with the staff at the facility so that they may inform you of any events and send medical records.
- ♥ Request the death certificate from the participant's family. Let the participant and their family know that unfortunately this may be needed some day.
- ♥ Contact the mortuary.
- ♥ Call or go to the Office of Vital Statistics in the county where the participant died. If you have the date of death, you may be able to obtain a copy of the death certificate. There is usually a fee involved.
- ♥ If you have access to the Internet, go to www.vitalcheck.com where you can find a list of county offices and their phone numbers.
- ♥ If you are requesting a death certificate from Puerto Rico, please contact the CTC for a letter that must accompany all requests.

These suggestions can be utilized in obtaining death certificates of ALLHAT participants depending on the laws and practices of the individual states and local institutions of each clinic. If you are experiencing any difficulty, please contact your regional coordinator, or the CTC.

ALLHAT EVENT REPORTING FORM - VERSION 3

Attach hospital discharge summary and, if applicable, death certificate. For cancers diagnosed out of hospital, please attach pathology report.

Place ID label here

Patient name: _____

1. Today's date: ___ - ___ - ___
2. Date of event: ___ - ___ - ___
3. Type of event:
 - Death 1
 - Non-fatal event 2

For all deaths - Complete Items #4 - 9. Attach death certificate and, if applicable, discharge summary.

4. Cause of death (check *only one*)
 - Definite MI 1
 - Definite CHD 2
 - Possible CHD 3
 - Stroke 4
 - CHF 5
 - Other cardiovascular disease 6
 - Cancer (list primary site in Item #6) 7
 - Kidney disease 11
 - Accident, suicide, homicide 8
 - Other noncardiovascular disease 9
 - Unknown cause 10
5. If MI or definite or possible CHD, did death occur within 24 hours of symptoms?
 - Yes 1
 - No 2
 - DK 3
6. If cancer, give *primary* site
 - Lung 1
 - Colon 2
 - Breast 3
 - Prostate 4
 - Bladder 5
 - Other (specify) _____ 6
 - DK 7
7. a. Was patient hospitalized, or taken to a hospital, during fatal event?
 - Yes 1
 - No (go to #8) 2
 - DK (go to #8) 3

b. If yes, is discharge summary attached?.....

 - Yes 1
 - No 2

c. If hospitalized or taken to a hospital, what other events occurred during this hospitalization, other than the cause of death checked in #4?

 - a. None 1
 - b. Acute myocardial infarction (including evolving MI with thrombolysis) 1
 - c. Stroke (not TIA or Aministroke≡) 1
 - d. Cancer (a new primary diagnosis; excluding non-melanoma skin cancer) 1
 - e. Congestive heart failure 1
 - f. Angina pectoris (actual episode of chest pain) 1
 - g. Lower extremity arterial disease 1
 - h. Accident or attempted suicide 1
 - i. Kidney transplant 1
 - j. Start of chronic kidney dialysis 1
 - k. Coronary artery bypass graft (CABG) 1
 - l. Coronary PTCA (angioplasty), stent or atherectomy 1
 - m. Lower extremity peripheral revascularization/bypass/angioplasty 1

8. Is death certificate attached? Yes Γ 1
 No Γ 2
9. If death certificate or discharge summary is not attached, give primary reason Pending Γ 1
 Patient/family refusal Γ 2
 Unable to locate records Γ 3
 Other (specify in comments) Γ 4

For all nonfatal events, complete Items #10 - 13. Attach discharge summary.

10. Type of nonfatal event (check all that apply)
- a. Hospitalized for acute myocardial infarction (including evolving MI with thrombolysis) Γ 1
 - b. Hospitalized for stroke (not TIA or Aministroke \equiv) Γ 1
 - c. Cancer (a new primary diagnosis; excluding non-melanoma skin cancer) Γ 1
 - d. Hospitalized for congestive heart failure Γ 1
 - e. Hospitalized for angina pectoris (actual episode of chest pain) Γ 1
 - f. Hospitalized for lower extremity arterial disease Γ 1
 - g. Hospitalized for accident or attempted suicide Γ 1
 - h. Kidney transplant Γ 1
 - i. Start of chronic kidney dialysis Γ 1
 - j. Coronary artery bypass graft (CABG) Γ 1
 - k. Coronary PTCA (angioplasty), stent or atherectomy Γ 1
 - l. Lower extremity peripheral revascularization/bypass/angioplasty Γ 1

11. If cancer, give **primary** site Lung Γ 1
 Colon Γ 2
 Breast Γ 3
 Prostate Γ 4
 Bladder Γ 5
 Other (specify) _____ Γ 6
 DK Γ 7

12. a. Was patient hospitalized? Yes Γ 1
 No Γ 2
 DK Γ 3
- b. If yes, is discharge summary attached? Yes Γ 1
 No Γ 2

13. If discharge summary is not attached, give primary reason Pending Γ 1
 Patient/family refusal Γ 2
 Unable to locate records Γ 3
 Other (specify in comments) Γ 4

For all events, please describe symptoms and your assessment/diagnosis

Place ID label here

Patient name: _____

14. Comments: _____

15. Initials of person completing this form _____
16. Signature of person completing this form _____
17. Signature of investigator _____

5.5 Verification of a subsample - AL12

For a random (10%) subset of fatal and nonfatal myocardial infarctions, possible or probable CHD's and strokes, the Clinical Trials Center will request more detailed information as described below so that the in-hospital ECGs and enzyme levels (for MIs and CHDs) and other records such as neurologist consultation/exam and CT scan reports (for strokes) can be evaluated by the study events committee and the accuracy of the discharge diagnosis (versus the definitions in this chapter) can be assessed.

When the Clinical Trials Center receives an AL04 for a study event, it will be entered into the main study data base. Once a month, a special program will be run to select a sample of recently received reports of MIs, definite and possible CHD deaths, and strokes (fatal or nonfatal) for further study as described above. When an event is selected, a special 1-page report called an "ALLHAT Endpoint Quality Control Selection and Documentation" - the AL12, will be generated. This will be sent to you from the Clinical Trials Center. The report will indicate the patient ID and acrostic, the date of the report, the date of event that you indicated on the AL04, and the type of event that you reported. In addition, it will list several items of additional documentation that are being requested. These will include:

For MIs and Definite and Possible CHD Deaths	For Strokes
In-hospital ECGs (3) - the first, the last, and one in the middle Reports of enzyme values	Neurologist reports CT or MRI scan reports Lumbar puncture results

You will need to complete the middle section (Items #8 - #11) and return this to the CTC, with the requested documentation, with your regular shipment of study forms. In Item #8, check each piece of documentation that you are forwarding to the CTC. If documentation is requested but not being forwarded, please explain in Item #9 (Comments). Initial the form as usual in Item #10 and sign Item #11.

A separate reimbursement is made upon receipt of the requested documentation for these selected events.

ALLHAT ENDPOINT QUALITY CONTROL SELECTION AND DOCUMENTATION

The event listed below has been selected as part of ALLHAT's endpoint quality control documentation. Please obtain the records requested and send them with this cover sheet to the Clinical Trials Center with your regular shipment of study forms.

PLEASE KEEP A PHOTOCOPY OF THIS FORM FOR YOUR FILES.

1. Date this request generated: mm-dd-yyyy
Sequence number: #
2. Patient ID:111-222-333
3. Site code:A
4. Acrostic:PRESAL
5. Event date from AL04 (mm-dd-yyyy):04-10-98
6. Event type: a. MI death
b. Definite CHD death
c. Possible CHD death
d. Stroke death
e. Nonfatal MI
f. Nonfatal stroke X
7. The following additional documents are requested:..... a. ECGs
b. Enzymes
c. Reports of CT or MRI scans X
d. Lumbar puncture results X
e. Reports from neurologists X
f. Discharge summary X

For clinical site use: Label all additional records with patient ID, acrostic and event date

8. The following additional records are enclosed:a. None (explain) ___
b. ECGs ___
c. Enzymes ___
d. Reports of CT or MRI scans ___
e. Lumbar puncture results ___
f. Reports from neurologists ___
g. Discharge summary ___

9. Comments: _____

10. Initials of clinical site staff person completing form: _ _ _ _
11. Signature: _____

Clinical Trials Center Use Only:

12. Date additional documentation received: _ _ - _ _ - _ _ _ _
13. Date completed: _ _ - _ _ - _ _ _ _
14. Initials of CTC monitor: _ _ _ _
15. Signature of CTC monitor: _____

CHAPTER 6 DRUG HANDLING PROCEDURES

6.1 The ALLHAT Drug Distribution Center

The ALLHAT Drug Distribution Center (DDC) is located at Ogden BioServices Corporation in Rockville, Maryland. The DDC is directed by Mary Mease and co-directed by Greg Berezuk. The address of the ALLHAT DDC is:

Ogden BioServices Corporation
ALLHAT Drug Distribution Center
625-C Lofstand Lane
Rockville, MD 20850
Phone (301) 309-2426
FAX (301) 738-2478

6.2 Drug Distribution

All of the antihypertensive study medications are available in three bottle sizes- 7-count, 44-count, and 134-count bottles. The 7-count bottles are used for Step 1 Dose 0 (used for only a few days). All other antihypertensive study medications (blinded and unblinded) are available in 44-count and 134-count bottles. The 44-count bottles contain enough medication for about 30 days, plus an extra 14-day supply. The 134-count bottles should last approximately 4 months for patients taking one capsule per day, and approximately two months for patients taking 2 capsules per day.

6.2.1 *Blinded Antihypertensive Agents (Step 1 Drugs)*

The drug content of Step 1 bottles will be masked and identified only by *bottle numbers* that were assigned by the Clinical Trials Center to specific Step 1 agents. In case of emergency, the contents of a bottle may be revealed by following the unblinding procedures in Section 4.

At the time of randomization, a patient will be assigned a bottle number corresponding to a bottle code on the label of a Step 1 bottle. The participant will be assigned to this bottle number throughout the trial and should be given blinded drug bottles *only* with this number. More than one patient will be assigned to a particular bottle code.

Each of the Step 1 antihypertensive drugs has four dosages as follows:

Step 1 Agent	Initial Dose (Dose 0)	Dose 1	Dose 2	Dose 3
Chlorthalidone	12.5 mg	12.5 mg	12.5 mg	25 mg
Amlodipine	2.5 mg	2.5 mg	5 mg	10 mg
Lisinopril	10 mg	10 mg	20 mg	40 mg
Doxazosin	1 mg	2 mg	4 mg	8 mg

Dose 0: Dose 0 is the initial dose and is packaged in 7-count bottles only. One bottle of Dose 0 medication is given to the participant at the hypertension randomization visit.

Dose 1: Dose 1 is the first titration dose and is packaged in 44-count and 134-count bottles.

Dose 2/3: The same bottle is used to achieve Dose 2 and Dose 3 and is labelled Dose 2/3. Dose 2/3 is packaged in 44-count and 134-count bottles. On the bottle label, the dose is noted as "2/3" and the directions are "Take ___ capsule(s) daily. When dispensing, circle the appropriate dose (either the 2 or 3) and write in the corresponding number of capsules ("1" for dose 2 and "2" for dose 3). Dose 3 patients will need 2 bottles. Make sure the patient understands that he or she should be taking 2 capsules daily from one bottle and *not* 2 capsules daily from both bottles.

Restart packs:

If a patient discontinues the Step 1 drug for more than 3 doses, a restart pack should be used to rechallenge the patient with the study drug. This is intended to avoid (as much as possible) first-dose hypotension with doxazosin. Each restart pack bottle will contain sufficient medication for 4 doses, and the patient should be instructed to take one dose each day from the Dose 0 bottle until all the capsules have been taken (four days), following which he/she will take one dose each day from the Dose 1 bottle until all the capsules have been taken (four days), until they restart their regular study medication. The patient should be warned not to take the bottles out of order, and not to take medication from more than one bottle at a time.

See Chapter 3, page 7 for details of how to use the restart packs.

6.2.2 *Step 2 and Step 3 Antihypertensive Agents*

Clonidine 0.2 mg, reserpine 0.1 mg, atenolol 50 mg, and hydralazine 25 mg tablets will all be packaged in 44-count and 134-count bottles (see above note regarding bottle counts for vanguard study). The label will read "Take ___ tablet(s) daily" or for clonidine and hydralazine "Take ___ tablet(s) twice daily". When dispensing one of these agents, write in the corresponding number of tablets for the dose as follows:

Agent:	Number of Tablets		
	Dose 1	Dose 2	Dose 3
Reserpine	½	1	2
Clonidine	½	1	1½
Atenolol	½	1	2
Hydralazine	1	2	4

6.2.3 *Potassium Supplements*

The potassium chloride 8 meq tablets will be packaged in bottles containing 134 tablets. The bottle label will read "Take ___ tablet(s) daily." The clinical site is to fill in the blank with the appropriate number of tablets.

6.2.4 *Cholesterol-lowering Agent (Pravastatin)*

The pravastatin 10 mg and 20 mg tablets will be packaged in bottles containing 100 tablets. The 20 mg bottle label will read "Take ___ tablet(s) daily." The clinical site is to fill in the blank with the appropriate number of tablets. (Complete the blank with either a "1" for 20 mg dose or a "2" for the 40 mg dose.) The pravastatin 10 mg tablets will be stored at the DDC and distributed on an as needed basis.

6.3 **Drug Supply**

6.3.1 *Receiving Study Medication*

Each clinic has furnished the name and address of a person authorized to receive drugs. Instructions for receiving and inventory of the *ALLHAT* drug supply may be found in the Drug Accountability Notebook, provided by Ogden Bioservices, with your first shipment of study drugs.

6.3.2 *Re-Supply of Study Medication*

Routine re-ordering of drugs will be done by each clinic. Clinic staff should monitor their existing drug supply and assure that sufficient drugs are in stock to meet patient needs each week. Clinics will be re-supplied on the basis of specific orders placed by the clinic with the DDC at Ogden Bioservices Corporation. Clinics will be prompted periodically by the CTC regarding suggested inventories based on current *ALLHAT* medication prescriptions.

AN AL10 (Drug Re-Order Form) should be used to order drugs from the DDC (see page 8). Simply complete the form with the numbers of bottles needed, and fax the form to the DDC at the number indicated on the form. Alternatively, you may phone the DDC with your order.

6.4 **Drug Dispensing and Inventory**

Instructions for dispensing and inventory of the *ALLHAT* drugs may be found in the Drug Accountability Notebook, provided by Ogden Bioservices, with your first shipment of study drugs.

6.5 **Emergency Labels**

The following labels are examples of labels that will be supplied to each clinic from the CTC. The label including the statement regarding bottle contents is for use with the Step 1 medication. The other label, without this statement, is intended for use with the Step 2, Step 3, and other *ALLHAT* medications. A label must be completed and placed on each bottle of medication at the time it is dispensed.

A supply of labels for placement in dispensed drug bottles will be provided with initial study supplies and for each randomized patient. These labels have spaces for writing the dispensing date and the patient's name and *ALLHAT* ID number (the ID number is pre-printed on labels after patients are randomized). The label contains the name and telephone of the Principal Investigator or physician primarily responsible for the medical care of *ALLHAT* patients, as well as the telephone number of a central unblinding facility.

The unblinding number listed on the label provides 24-hour access to the unblinding service at Hermann Hospital Pharmacy (Houston, Texas). This number can be called in an emergency where it is necessary to reveal the contents of a blinded study medication. See

Section 6.6 for the procedures to be followed for disclosure of study medication.

<p>Date (mm-dd-yy): ____ - ____ - ____</p> <p>Patient: _____ ID: 456 - ____ - 456 William A. Jones, M.D. Anywhere Hospital & Clinical Center Anywhere, USA (123) 123-4567 Site: A</p> <p>Emergency: (713) 704-2078 (Ask for pharmacist)</p> <p>Bottle contains either chlorthalidone, amlodipine, lisinopril, or doxazosin</p>	<p>Date (mm-dd-yy): ____ - ____ - ____</p> <p>Patient: _____ ID: 456 - ____ - 456 William A. Jones, M.D. Anywhere Hospital & Clinical Center Anywhere, USA (123) 123-4567 Site: A</p>	<p>Pravastatin, 20 mg, 100 tablets Take ____ tablet(s) each evening</p> <p>Date (mm-dd-yy): ____ - ____ - ____</p> <p>Patient: _____ ID: 456 - ____ - 456 William A. Jones, M.D. Anywhere Hospital & Clinical Center Anywhere, USA (123) 123-4567 Site: A</p> <p>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</p>
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6.6 **Unblinding Study Medications**

6.6.1 *Procedures for Unblinding Study Medication*

Emergency situations may arise where it is in the best interest of the patient to identify the assigned antihypertensive treatment drug, although the unblinding of *ALLHAT* participants and their physicians should otherwise be vigorously discouraged and kept to an absolute minimum. In an emergency, the identification of a blinded study drug should be obtained from the Hermann Hospital Pharmacy by telephone by calling (713) 704-2078. All disclosures of randomized (blinded) treatment drugs must be reported on form AL06, the *ALLHAT Report of Study Drug Disclosure*.

The following principles apply to requests for unblinding. They should be carefully read and understood by all staff members likely to be involved in unblinding of study drugs.

- (1) Under usual circumstances, unblinding should be vigorously discouraged and kept to an absolute minimum.
- (2) If the *ALLHAT* physician, the participant, or other interested party is concerned about the occurrence of what might be a serious adverse drug reaction, the participant can be given optimum care by discontinuation of the study drugs without unblinding the Step 1 agent.
- (3) If the physician feels that the administration of a known antihypertensive medication is in the best interest of the patient, this can be done by simultaneously discontinuing the assigned study medication and starting the known drug without unblinding. A known drug of the same class as one of the blinded medications may be *added* to the patient's Step 1 regimen, up to ½ of the maximum recommended dose.
- (4) Except where immediate knowledge of the study drug is essential, all cases where unblinding is contemplated should be discussed in advance with the designated Regional Coordinator, the Clinical Trials Center staff, or the NHLBI *ALLHAT* Project Officers.
- (5) If unblinding is requested by someone unrelated to *ALLHAT* (e.g., an anesthesiologist or surgeon), the program physician should try to ascertain if such knowledge is essential. If in his or her judgement it is not, every reasonable effort should be made 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 temporary discontinuation of the study drug is sufficient. If it is still necessary that the patient's medication be identified, the CTC should be contacted

immediately. If the situation is an emergency and outside the CTC's normal business hours, arrangements should be made locally for someone other than the ALLHAT personnel to unblind and communicate this information to the person requesting it. The identity of a blinded study drug can be obtained 24-hours a day from the unblinding center at *Hermann Hospital Pharmacy* (Houston, Texas) by calling (713) 704-2078. Anyone becoming aware of the identity of the drug should be urged to preserve the confidentiality of this information. A *Report of Study Drug Disclosure* (AL06) must be completed when any unblinding occurs.

- (6) Unblinding of the patient and/or ALLHAT clinic personnel should be avoided whenever possible, although under some circumstances this may not be possible. If the treatment is disclosed to the patient and/or ALLHAT personnel, the patient should continue on the assigned treatment, resuming treatment as soon as possible if it was discontinued for some reason, and in any event should continue receiving every other aspect of the follow-up procedures on the same schedule as before the unblinding occurred. It is important to understand that the patient is still participating in ALLHAT even while off the assigned study medication or after unblinding has occurred. Our aim is to insure that as great an extent as possible of each randomized study group is receiving the assigned medication. All trial outcomes occurring in patients assigned at baseline to any specific treatment group will be attributed to that group, regardless of the actual treatment received or whether the participant's treatment has been revealed.

6.6.2 *Report of Study Drug Disclosure (AL06)*

The ALLHAT *Report of Study Drug Disclosure* is a very simple 1-page form to record the circumstances surrounding the unblinding of a Step 1 drug code. If you wish, you may fill in the patient's name on the line provided. (This will later be covered by a label for the original, but the name will then be on the clinic's NCR copy.) Complete the date of disclosure (Item #1) as mm/dd/yy, using leading zero's where necessary. Complete the date the form was completed (Item #2) in the same manner.

Item #3 asks for the reason(s) for the disclosure. Check all reasons that apply to this disclosure. If "Other medical reason" or "Other non-medical reason" is checked, explain in the space provided for comments (Item #6). *Disclosures of blinded Step 1 drug codes for "Other non-medical reasons" should be kept to an absolute minimum!*

Item #4 asks to whom the code was revealed. Please check all that apply. Usually, this will be a non-ALLHAT physician or a pharmacist. Only under very unusual circumstances should the code ever be revealed to the patient or to an ALLHAT staff member responsible for the patient's care. If the code is revealed to someone not in one of the four specific categories, check "Other" and specify in the space provided for comments (Item #6).

Unless the situation is emergent, your ALLHAT Regional Physician or Nurse Coordinator, the Clinical Trials Center, or the NHLBI Project Office should be contacted to discuss the possibility of revealing a drug code. Check all that apply. These ALLHAT representatives can be contacted per the Quick Reference Guide, page 12 or your study directory.

Space for comments is provided in Item #6. These comments should document the

particular circumstances leading to the request to reveal a drug code, as well as comments called for in Items #3 and #4.

As for all ALLHAT forms, the person completing the form should initial Item #7 in the space provided, and sign at Item #8.

If not already done, an identification label for the participant should be placed in the rectangle at the top of the form.

6.7 **Processing of Old and Unused Drugs**

Old and unused drugs should be returned to the DDC per the procedures outlined in the ALLHAT Drug Accountability Notebook, provided by Ogden Bioservices, with your first shipment of study drugs. The DDC will provide you with the method of shipping at a later date.

ALLHAT Bottle Code 29 0001 Dose 1
ALLHAT Bottle Code 29 0001 Dose 1
(44 Capsules)

Take 1 (one) capsule daily

Keep out of reach of children

Store at controlled room temperature (59° - 86°F)

*Antihypertensive and Lipid-Lowering Treatment
to Prevent Heart Attack Trial*

Distributed by: Ogden BioServices Corporation, Rockville, MD 20850
Caution: New Drug - Limited by Federal (USA) Law to Investigational Use.

ALLHAT Bottle Code 29 0001 Dose 2/3
ALLHAT Bottle Code 29 0001 Dose 2/3
(134 Capsules)

Take _____ capsule(s) daily

Keep out of reach of children

Store at controlled room temperature (59° - 86°F)

*Antihypertensive and Lipid-Lowering Treatment
to Prevent Heart Attack Trial*

Distributed by: Ogden BioServices Corporation, Rockville, MD 20850
Caution: New Drug - Limited by Federal (USA) Law to Investigational Use.

Reserpine 0.1mg

(134 tablets)

Take _____ tablet(s) daily

Keep out of reach of children.

Store at controlled room temperature (59° - 86°F)

*Antihypertensive and Lipid-Lowering Treatment
to Prevent Heart Attack Trial*

Distributed by: Ogden BioServices Corporation, Rockville, MD 20850
Federal law prohibits dispensing without a prescription.

Lot #XXXXXX Exp. 99/99/99

ALLHAT Drug Order Form

Clinic: _____ Site: _____ Date: _____ MM DD YY	Fax form to Drug Distribution Center @ (301) 251-1863 Alternatively, you may telephone your request to the DDC @ (301) 309-2426 .
Clinic Name: _____	
Requestor's telephone No.: (_____) _____	

Blinded Antihypertensive Agents: Enter bottle number and quantity required. If same dose and quantity are required for more than one bottle number, a single line may be used. Dose-0 and 44 ct bottles are routinely shipped to sites for randomizations as needed. Dose-0 and 44 ct bottles do not need to be stocked for follow-up, except when Dose-0 is needed for re-challenge.

Bottle Numbers (e.g., 25,36,52)	Dose-0 (7 ct)	Dose-1 (44 ct)	Dose-1 (134 ct) †	Dose-2/3 (44 ct)	Dose-2/3 (134 ct) †

† Large bottles should be dispensed to patients on maintenance therapy with 3 to 4 months between scheduled visits.

Open Label Agents

Drug Name	# of Bottles
Atenolol, 50 mg (134 ct)	
Clonidine, 0.2 mg (134 ct)	
Reserpine, 0.1 mg (134 ct)	
Hydralazine, 25 mg (134 ct)	
Potassium Supp., 8 mEq (134 ct)	
Pravastatin, 10 mg (100 ct)	
Pravastatin, 20 mg (100 ct)	
Pravastatin, 40 mg (100 ct)	

COMMENTS

Signature of person completing this form.....

FOUND ON DRUG BOTTLE

Patient Name: _____

Patient ID: _ _ | _ _ | - _ _ | _ _ | - _ _ | _ _ |

Acrostic: _ _ | _ _ | _ _ | _ _ | _ _ | _ _ |

ALLHAT REPORT OF STUDY DRUG DISCLOSURE

Date of Disclosure: ____ - ____ - ____

Military Time of Disclosure: _____

Please refer all unblinding calls during weekday hours 8am - 5pm to the ALLHAT Clinical Trials Center, 1-800-690-7870. Otherwise:

- A) Inquire whether call is for a medical emergency. If it is, go to Item C below.
- B) If it is **not** a medical emergency, ask if the caller has tried to contact the **ALLHAT** staff person listed on the drug bottle label.
 - **If caller persists** in his or her request for disclosure of the bottle contents, proceed to Item C.
 - **If caller agrees** to contact the patient's **ALLHAT** Clinic (or physician or pharmacist), nothing else need be done. Please advise the caller that **clinical center personnel cannot unblind medication.**
- C) **If it is a medical emergency** or the caller insists on knowing the bottle's content, request the following information and give the caller the name of the **ALLHAT** drug that corresponds to the **bottle code** and the actual dose which corresponds to the dose number.

1. Caller's Name: _____
2. Caller is: (Patient = 1, ALLHAT Staff = 2, Anesthesiologist/Surgeon = 3, ER Staff = 4, Unknown = 8, Other **See Comments** = 9)
3. Caller's phone number: _ _ | _ _ | - _ _ | _ _ | - _ _ | _ _ |
4. Caller's City: _ _ | _ _ | _ _ | _ _ | _ _ | _ _ | _ _ | _ _ | State: _ _ |

Note: Remind the caller to keep the information on actual contents and dose unknown to as many people as possible. If possible, they should not reveal the information to the **ALLHAT** investigator, staff, or to the patient.

5. Reason for disclosure (check all that apply)
 - a. Suspect Adverse reaction 1
 - b. Diagnostic Test and/or surgery 1
 - c. Other medical reason (specify below) 1
 - d. Other non-medical reason (specify below) 1
6. Bottle code: _ _ |
7. Dose: (Dose-0 = 0, dose-1 = 1, dose-2 = 2, dose 3 = 3, unknown = 9) _ _ |
8. Drug name given to caller: (Chlorthalidone = 1, Amlodipine = 2, Lisinopril = 3, Doxazosin = 4) _ _ |
mg/day _ | _ .

9. Comments: _____

Fax a copy of this form to the ALLHAT Clinical Trial Center as soon as possible. Questions: Call Charles E. Ford, Ph.D. or Sara Pressel.

UTSPH, 1200 Herman Pressler Ste. 801, Houston, 77003 FAX: 792-4401 PHONE: 792-4480

CHAPTER 7

ADMINISTRATIVE PROCEDURES FOR PARTICIPANT SCHEDULING


7.1 Preparing for a Visit

- a. By phone or postcard, remind the participant in advance of the upcoming appointment. He or she should also be reminded to bring all unused pills and empty bottles to the clinic, and to fast prior to the visit if necessary for laboratory tests.
- b. Retrieve the participant's medical file.
- c. Place the participant's ID label on all forms pertinent to the scheduled visit.
- d. Schedule laboratory test appointments, if necessary.
- e. Prepare for the shipment of laboratory specimens and ECGs, if necessary.
- f. Obtain the participant's potential supply of study medications for either continuing the same dosage or being stepped-up.


Copies of the ALLHAT appointment card and the postcard reminder may be found on the next page.

Reminder for the end of the visit: Use the participant's ALLHAT ID card at each visit to record the average blood pressure reading and the date and time of the next scheduled visit.

Appointment card example

 Appointment Time: _____	<i>Appointment for:</i> _____ Your next ALLHAT appointment is: DATE: _____ TIME: _____ DR: _____ PHONE: _____
---	--

Sample postcard reminder

Clinic Name _____	
Clinic Address _____	
Please bring your ALLHAT medicine to your next appointment on	
Date _____	Time _____
Fast for blood work: NO YES (but be sure to take your ALLHAT medicine)	
Call _____ at _____ with any questions or to reschedule	

7.2 Scheduling Study Visits

At the time of randomization, a visit schedule will be generated, containing a visit “window” for each required study visit, as well as procedures required by the ALLHAT protocol.

As you will note from the attached example visit schedule, each visit is expected to occur during a visit "window". The visit windows do not overlap, but no dates are excluded. *Visits should be scheduled close to the middle of the target window, if possible.*

Because ALLHAT investigators will be scheduling extra visits for drug titration and may be providing primary care to ALLHAT patients that may not be related to the ALLHAT protocol (e.g., visits for acute illnesses such as the flu or other reasons), there may be more than one visit scheduled in a visit window. The clinician should use his or her judgment in determining if a separate visit would be necessary in order to fulfill the ALLHAT protocol requirements.

If, for any reason, a visit to the clinic cannot be scheduled in a visit window, it is permissible and desirable to collect visit information by telephone or postcard (see page 7-5). Of course, blood pressure cannot be measured. Visits cannot be "made up" -- that is, two required visits cannot be scheduled in the same visit window. If the participant cannot attend the clinic in the visit window, and pertinent information cannot be gathered by telephone or postcard, then that visit will be considered as "missed".

A revised visit schedule, including additional required blood tests, is generated when participants are randomized into the lipid-lowering component.

Sample visit schedules may be found on the following two pages.

ALLHAT Visit Schedule
Medical Group of Western New York, PC

ALLHAT ID: 599-001-599 Site:A Acrostic: FIEAN
 Date randomized to Antihypertensive trial: 09-Sep-1997
 Step 1 bottle number: 20

Visit Number	Time Period	Visit Window		Actual Date	Meds Dispensed	Procedures Required
		----- From	To			
3	1mo	25-Sep-1997	23-Oct-1997			ALL03
4	3mo	24-Oct-1997	20-Jan-1998			
5	6mo	21-Jan-1998	20-Apr-1998			
6	9mo	21-Apr-1998	21-Jul-1998			
7	1 year	22-Jul-1998	09-Nov-1998			ALL03
8	1yr 4mo	10-Nov-1998	09-Mar-1999			
9	1yr 8mo	10-Mar-1999	09-Jul-1999			
10	2 year	10-Jul-1999	09-Nov-1999			ALL09, ECG
11	2yr 4mo	10-Nov-1999	09-Mar-2000			
12	2yr 8mo	10-Mar-2000	09-Jul-2000			
13	3 year	10-Jul-2000	09-Nov-2000			
14	3yr 4mo	10-Nov-2000	09-Mar-2001			
15	3yr 8mo	10-Mar-2001	09-Jul-2001			
16	4 year	10-Jul-2001	09-Nov-2001			ALL09, ECG
17	4yr 4mo	10-Nov-2001	09-Mar-2002			

Sample visit schedule – antihypertensive trial only
--

ALLHAT Visit Schedule
 REVISED 22-DEC-1998

University of Ottawa Heart Institute

ALLHAT ID: 601-037-601 Site:A Acrostic: DREWI
 Date randomized to Antihypertensive trial: 17-SEP-1997
 Step 1 bottle number: 20
 Date randomized to Lipid-lowering trial: 29-OCT-1997
 Lipid-lowering assignment: Pravastatin

Target Total Cholesterol: \leq 154 mg/dl Target LDL: \leq 77 mg/dl

Visit Number	Time Period	Visit Window		Actual Date	Meds Dispensed	Procedures Required
		From	To			
3	1mo	03-OCT-1997	31-OCT-1997			ALL02, ALL03
4	3mo	01-NOV-1997	28-JAN-1998			ALL04
5	6mo	29-JAN-1998	28-APR-1998			
6	9mo	29-APR-1998	29-JUL-1998			
7	1 year	30-JUL-1998	17-NOV-1998			ALL06
8	1yr 4mo	18-NOV-1998	17-MAR-1999			
9	1yr 8mo	18-MAR-1999	17-JUL-1999			
10	2 year	18-JUL-1999	17-NOV-1999			ALL08, ECG
11	2yr 4mo	18-NOV-1999	17-MAR-2000			
12	2yr 8mo	18-MAR-2000	17-JUL-2000			
13	3 year	18-JUL-2000	17-NOV-2000			ALL10
14	3yr 4mo	18-NOV-2000	17-MAR-2001			
15	3yr 8mo	18-MAR-2001	17-JUL-2001			
16	4 year	18-JUL-2001	17-NOV-2001			ALL08, ECG
17	4yr 4mo	18-NOV-2001	17-MAR-2002			

Sample visit schedule – participant randomized to pravastatin

7.3 “Generic” participant identification labels

“Generic” labels are provided to you to randomize about 40 patients. These labels include the clinic number and site code, and an ID number, but no acrostic. These are provided prior to randomization. (See following page). Two pages of generic labels are provided for each participant:

- ✓ 6 baseline ECG labels, 2 lab labels, 6 forms labels
- ✓ Baseline ECG labels: complete acrostic and date recorded
- ✓ Lab labels: complete acrostic and date drawn
- ✓ Forms labels: complete acrostic
- ✓ 14 forms labels

When you need additional “generic” labels to randomize participants 41 and above, please order them from the CTC using the AL14.

Three other types of “generic” labels are also provided:

- ✓ *Step 1 medication labels*: These contain the emergency unblinding number and the clinic number. Complete the participant’s ID number, date dispensed, and the participant’s name.
- ✓ *Unblinded medication labels*: These are for the atenolol, clonidine, reserpine, and hydralazine. Complete the ID, date dispensed, and the participant’s name.
- ✓ *Pravastatin labels*: Note that several are provided for each dose. Complete the participant’s ID number, the number of tablets, date dispensed, and the participant’s name.

7.4 “Patient-specific” identification labels

After a participant is randomized, you will receive their visit schedule along with a new set of labels for the first year of follow-up. The ID and acrostic are printed on these labels:

- ✓ Forms labels (several sheets)
- ✓ ECG for possible MI (quality control events)
- ✓ Lab labels - complete the visit number and date drawn
- ✓ Labels for Step 1 (blinded) medications - complete the date dispensed
- ✓ Labels for unblinded study medications - complete the date dispensed

Labels for years 2 and after are automatically provided each year. Patients randomized to pravastatin will receive patient-specific pravastatin labels with their following-year resupply.

Generic baseline ECG label

ALLHAT Sample Center

ID: 011 - 005 - 011 Site: A

Acrostic: _____
ECG for Baseline

Date recorded: ____ - ____ - ____

Generic baseline laboratory label (for tube and request sheet)

=====

ALLHAT Sample Center

ID: 011 - 005 - 011 Site: A

Acrostic: _____

Lab Visit # : 0 2

Date drawn: ____ - ____ - ____

Generic forms labels

ALLHAT Sample Center

ID: 011 - 005 - 011 Site: A

Acrostic: _____

Generic labels for Step 1 study medication

Date (mm-dd-yy): ____ - ____ - ____

Patient: _____

ID: 011 - ____ - 011

A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A

Emergency unblinding: (713) 704-2078
(ask for pharmacist)

*Bottle contains either chlorthalidone,
amlodipine, lisinopril, or doxazosin.*

Generic labels for Step 2 and Step 3 (unblinded) study meds

Date (mm-dd-yy): ____ - ____ - ____

Patient: _____

ID: 011 - ____ - 011

A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A

Generic pravastatin labels (provided for 10 mg, 20 mg, 40 mg)

Pravastatin, 40 mg, 90 tablets

Take ____ tablet(s) each evening

Date (mm-dd-yy): ____ - ____ - ____

Patient: _____

ID: 011 - ____ - 011

A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A

Antihypertensive and Lipid-Lowering
Treatment to Prevent Heart Attack Trial

Patient-specific follow-up ECG label

ALLHAT Sample Center
ID: 011 - 005 - 011 Site: A
Acrostic: SMILER
ECG for Year 2
Date recorded: - -
 mm - dd - yy

Patient-specific MI ECG label

ALLHAT Sample Center
ID: 011 - 005 - 011 Site: A
Acrostic: SMILER
ECG for possible MI
Date of event: - -
 mm - dd - yy
Date recorded: - -
 mm - dd - yy

Patient-specific follow-up laboratory label (for tube and request sheet)

ALLHAT Sample Center
ID: 011 - 005 - 011 Site: A
Acrostic: SMILER
Lab Visit # :
Date drawn: - -
 mm - dd - yy

Patient-specific forms labels

ALLHAT Sample Center
ID: 011 - 005 - 011 Site: A
Acrostic: SMILER
Drug Bottle: #20

Patient-specific labels for Step 1 meds

Date (mm-dd-yy): - -
Patient: Leon R Smith
ID: 011 - 005 - 011 SMILER #20
A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A
Emergency unblinding: (713) 704-2078
(ask for pharmacist)
*Bottle contains either chlorthalidone,
amlodipine, lisinopril, or doxazosin.*

Patient-specific labels for Step 2 and Step 3 (unblinded) study medications

Date (mm-dd-yy): - -
Patient: Leon R Smith
ID: 011 - 005 - 011 SMILER
A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A

Patient-specific pravastatin labels (10 mg, 20 mg, 40 mg)

Pravastatin, 40 mg, 90 tablets
Take tablet(s) each evening
Date (mm-dd-yy): - -
Patient: Leon R Smith
ID: 011 - 005 - 011 SMILER
A. Doctor, M.D.
ALLHAT Sample Center
Clearwater, Florida
(813) 734-6780 Site: A
Antihypertensive and Lipid-Lowering
Treatment to Prevent Heart Attack Trial

7.5 Rescheduling of Required Procedures

Always refer to the participant's visit schedule for required procedures. 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 prior to certain annual visits. In these cases, clinical judgment should be used in determining whether the entire visit should be rescheduled or whether only individual visit components should be rescheduled. The following situations should be reviewed when rescheduling seems necessary:

- (1) Results from procedures required for determination of eligibility must be available prior to randomization.
- (2) If any procedure required at randomization must be delayed, then initiation of the study drug should be temporarily delayed also. Every effort should be made to avoid delaying initiation of study drug at randomization. For instance, if a baseline lab can not be obtained at the time of randomization, study drug should be delayed until the baseline lab is drawn.
- (3) If a **follow-up ECG** (at 2 years, 4 years or 6 years) is not done in the required visit window, an ECG should still be obtained as soon as possible, up to the date of the next required ECG. Examples:

Did you miss the visit window for a 2-year ECG? Obtain that ECG as soon as possible, but any time up to the opening date of the 4-year window. (Another ECG is required in the 4-year visit window.)

Did you miss the visit window for a 4-year ECG? Obtain that ECG as soon as possible, but any time up to the opening date of the 6-year window. (Another ECG is required in the 6-year visit window.)

- (4) If a **follow-up laboratory evaluation** is not done in the required visit window, the blood should still be drawn as soon as possible, up to the date of the next biennial visit. On the labels for the tube and the Laboratory Test Request Form, use the visit number when the blood was *actually drawn*. Examples:

You forget to draw blood for the required laboratory evaluations at the 2-year visit. You should obtain the blood for this evaluation as soon as possible, but any time up to the opening date of the 4-year visit. (A repeat laboratory panel is required at the 4-year visit.)

For a participant randomized to pravastatin, you forget to draw blood for the required laboratory evaluations at the 3-year visit. You should obtain the blood for this evaluation as soon as possible, but any time up to the opening date of the 4-year visit.

7.6 Missed Visits

Every effort must be made to avoid missed visits. However, if a participant fails to come in to the clinic for a visit within the window, the Clinical Center should contact him or her by telephone. 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. Some participants may respond more favorably to a telephone call from the project physician. ***Participants should be encouraged to report at scheduled visits, even if they are not taking the ALLHAT Step 1 (blinded) study medication.***

A participant's lack of cooperation and/or decreased commitment to the study may be the result of many reasons. Some of these reasons, and their solutions, are discussed in Appendix F, Assessing Compliance, and in the Adherence Survival Kit (ASK).

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.

Document all communication with the participant. For example, missed appointment, calls made (with time and date), message left (with time and date), return call expected, reason for refusal.

- 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 or postcard visit. Otherwise, an appointment should be scheduled to occur as soon as possible.
- e) Keep local records of clinic attendance for each participant.
- 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. Some ideas that have worked well in other clinical trials included options that allowed the patient to "partially" comply rather than drop out of the trial altogether, e.g., allowing telephone visits, attending clinic only every six or eight months, agreeing to take reduced dosages of study medications instead of no study medication, etc. These essentially "make deals" and "keep your foot in the door" for future improvement in compliance by that patient.

7.7 Following Participants by Postcard

The ALLHAT postcard may be used to collect follow-up information by mail for participants who have missed, or will miss, a visit and for whom telephone contact will not be possible during the visit window. The intent of this postcard is to collect enough information for you to complete an AL03 (ALLHAT Follow-up Form). Postcard follow-up may be used in several circumstances:

- ✓ Participant misses a scheduled appointment and cannot be rescheduled in the visit window and a telephone visit is not possible. (**As a phone visit is preferred, please attempt to set up a phone appointment.**)
- ✓ Participant is going on an extended vacation (e.g., snowbirds) and will not be able to be reached by telephone during a visit window (give the participant the postcard ahead of time). (**As a phone visit is preferred, please attempt to set up a phone appointment prior to the participant leaving on an extended vacation.**) Be sure to give the participant enough study medications to last until their next expected visit to your clinic.
- ✓ Participant is currently declining to come to the clinic for visits and will not allow phone visits, or phone visits are not feasible - the postcard could be a part of negotiated partial adherence.
- ✓ A visit is missed for any other reason.

You will need to complete the participant's name (2 places), the ALLHAT ID, the date of the last visit (where it says "Since we last contacted you on _____"), the date and time of the next scheduled appointment (if any), your signature, and clinic contact information at the bottom of the card. On the reverse side (the side that appears when the participant mails the folded card to the clinic), you will need to provide the clinic's address. You should pre-affix a postage stamp if you wish. If you mail a postcard to a participant, it would probably be best to mail the postcard in an envelope with a short cover memo rather than try to address the postcard itself to the participant.

If a participant indicates that an event has occurred, you will have to contact the participant directly and get more detailed information and a signed medical records release.

Do not send the completed postcards to the CTC - just the AL03 completed with the postcard information.



WE MISSED YOU AT YOUR LAST VISIT!

Dear _____:

We missed seeing you at your last appointment. Your health is very important to us, and we want to make sure you are well. We value you as our patient and thank you for participating in the **ALLHAT** program. The information you provide about your health is very important, not only to us, but to other patients with high blood pressure. Please take a few minutes and fill out the information on this card and drop it in the mail to us.

Thank you for your cooperation, and we look forward to seeing you at your next visit.

Name: _____ ALLHAT ID: _____ - _____ - _____

Since we last contacted you on _____:

- 1. How many times have you made a visit a doctors office or clinic? _____
- 2. How many times have you been in the hospital overnight? _____
- 3. Have you been hospitalized for:

Heart attack?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know	Cancer?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
Stroke?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know	Accident?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
Heart failure?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know	Kidney dialysis?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
Chest pain?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know	Kidney transplant?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know

If you answered Yes to any of the health problems in Question 3, please tell us where you were in the hospital and the dates you were in the hospital:

- 4. Are you still taking the ALLHAT blood pressure medicine that we gave you? Yes No
- 5. What other medicines are you taking for your blood pressure or cholesterol (including the ALLHAT Pravachol)?
- 6. We may need to contact you for more information. What is your current address and telephone number, and when is the best time of day to reach you?

7. Your next scheduled appointment: _____

Thank you!

Address:

_____ Telephone: _____ - _____ ext _____

7.8 Permanent Transfer of Participant to Another Clinical Center Area

Participants who permanently move into another Clinical Center area will need a new ALLHAT physician in that area. A list of eligible ALLHAT sites in the participants new area should be obtain from the Clinical Trials Center and the procedures on the ALLHAT Participant Transfer form (AL15) should be followed. Please be sure to be clear with the patient and new site regarding financial arrangements. For example, if you have not been charging the patient for ALLHAT visits, please be sure that the new site is aware of the need to discuss financial arrangements.

The participant will not be officially transferred until the following have all occurred:

1. An ALLHAT Participant Transfer (AL15) has been received by the Clinical Trials Center from the old Clinical Center, changing the first three digits of the ID number.
2. The new site will have to confirm in writing to the CTC that the participants has been contacted and either seen, or an appointment has been established before the transfer will be “official”.
3. The CTC will then notify you that the transfer has been successfully completed.
4. If the new site *cannot* contact the participant at their new location after reasonable efforts, or the participant changes his or her mind regarding the transfer, the transfer will be “cancelled”, and you will remain responsible for telephone or postcard follow-up.
5. For completed transfers, the CTC will generate revised participant labels and a new visit schedule, indicating the new participant ID number.

If there is not an ALLHAT center to which this participant can be permanently transferred, he or she remains the responsibility of the former Clinical Center and should be followed by telephone or postcard to record any ALLHAT event data. The participant should be advised that they will no longer be taking ALLHAT medications and that they should seek routine medical care from a physician in their new location.

ALLHAT PARTICIPANT TRANSFER

Study Coordinator Transferring Participant _____ Phone _____

When you need to **PERMANENTLY** transfer an ALLHAT participant to another ALLHAT center, please follow these procedures. Check each item as it is completed.

PLEASE NOTE: If there is not an ALLHAT center to which this participant can be permanently transferred, your center should remain in contact with the participant by telephone or post card to record any ALLHAT event data. The participant should be advised that they will no longer be taking ALLHAT medications and that they should seek routine medical care from a physician in their new location.

STEP 1) Contact the CTC, at 713-500-9500, for a list of ALLHAT centers approved to accept transfers in the city/state where the ALLHAT participant will be living.

STEP 2) Together with the patient choose a clinic that will be convenient for them in their new location.

STEP 3) Contact the Principal Investigator or Study Coordinator at the ALLHAT center where you intend to transfer the participant. Verify that they are willing to accept the transfer.

A) Person Contacted: _____ Phone: _____ Date: _____

Transfer: Accepted _____ (Continue) Declined _____ (STOP, do not send AL15 to CTC)

B) If the center agrees to accept the participant, provide the participant's name, current identification number, acrostic, relocation date, and information about how to contact the patient. (Complete Page 2) PROVIDE THE NEW CENTER INFORMATION ABOUT THE PARTICIPANT'S CURRENT ALLHAT MEDICATION, INCLUDING BOTTLE CODE SO THAT THEY CAN ORDER SUFFICIENT MEDICATION FOR THE PARTICIPANT.

C) Schedule an appointment for your participant. DATE: _____ TIME: _____

STEP 4) Send copies of the participant's Visit Schedule, the last two (2) Case Report Forms (e.g. AL03), brief medical history/physical, and laboratory results (baseline & most recent) to the Study Coordinator at the participant's NEW CENTER. Please remember to submit any outstanding Case Report Forms to the CTC before the participant is transferred. If you do not, the new center will receive payment for these forms.

STEP 5) Complete the following:

Place CURRENT ID Label Here
Also place on Yellow and Pink copies

1. Today's Date: _____ - _____ - _____

2. ALLHAT Center to which the participant is transferring: _____

Site Code: _____

3. Approximate date of relocation: _____ - _____ - _____

STEP 6) Provide the PARTICIPANT the name, telephone, and location of the new center, names of the Principal Investigator, Study Coordinator, and sufficient medication to last until the participant's next ALLHAT visit. (Complete Page 2 and give the white copy of page 2 to the participant)

The CTC will change the participant's identification number on the study database and forward new participant labels and a new visit schedule to the center receiving the participant.

IMPORTANT: Please note the distribution of copies

Permanent Transfer - Information Sheet

Page 2 of the AL15

Participant Contact Information - Please print clearly

Participant Name: _____

Relocation Date: ____ - ____ - ____

Participant ID Number: _____ - _____ - _____

Bottle Code # _____

Participant Acrostic: _____

Dose (circle one) 1 2 3

Participant's Current Address & Telephone Number:

Participant's New Address & Telephone Number:

City State Zip

City State Zip

(____) _____ - _____

(____) _____ - _____

Name and address of a relative or friend who would know how to contact the participant:

Name: _____

Telephone: (____) _____ - _____

Address: _____
City State Zip

Contact Information of Center Receiving Transferring Participant

Principal Investigator: _____

Study Coordinator: _____

Practice Name: _____

Center's Address: _____

City State Zip

Center's Telephone Number: (____) _____ - _____

IMPORTANT: Please note the distribution of copies

7.9 Participants Temporarily Visiting in Another Geographical Area

In some cases, participants may routinely visit another geographical area for a few months each year (e.g., participants with winter homes in Florida). In these situations the ALLHAT Out of Town Worksheet should be followed (refer to the next two pages). The participant should be seen prior to their departure and an adequate amount of medications should be dispensed to cover the period of their expected absence.

ALLHAT PARTICIPANT OUT OF TOWN WORKSHEET

KEEP THIS FORM FOR USE WITHIN YOUR CLINIC. DO NOT SUBMIT THIS FORM TO THE CTC IN HOUSTON.

Participant Name: _____

ALLHAT Identification Number _____ - _____ - _____ Acrostic _____

When an ALLHAT participant will be out of town for 6 months or less please follow these procedures. Check off each item when completed.

_____ **STEP 1)** It is recommended that you schedule a clinic visit shortly before the participant will be leaving town to provide ALLHAT medication and a blood pressure check. For the safety of the participant, this visit should be done even if the participant was already seen within the window. Keep in mind that reimbursement is only for one visit per visit window.

_____ **STEP 2)** Determine, from the participant, the length of time he/she will be out of town.

Expected Departure Date: _____ - _____ - _____ Expected Return Date: _____ - _____ - _____

_____ **STEP 3)** Dispense sufficient ALLHAT Study medication.

Dose: _____ Bottle # _____ Number of Bottles Dispensed: _____

_____ **STEP 4)** Establish how to contact your participant while they are out of town.

Address: _____

City _____ State _____ Zip _____

Telephone: (_____) _____

Name & Telephone number of someone who can help contact the participant if needed:

_____ **STEP 5)** Review the dates of the next ALLHAT visit(s) with your participant and schedule a telephone or postcard visit(s). Remember that telephone and postcard visits are reimbursable as long as an AL03 has been completed in as much detail as possible.

1) DATE: _____ - _____ - _____ TIME: _____ AM PM

Participant's Telephone Number: (_____) _____

2) DATE: _____ - _____ - _____ TIME: _____ AM PM

Participant's Telephone Number: (_____) _____

_____ **STEP 6)** Complete the attached wallet card and give the wallet card to the participant.

The participant should keep a copy of this form and the attached wallet card with them as they travel. Should the participant have any medical problems while they are traveling they should contact a physician or emergency room.

I am participating in the ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL sponsored by the National Heart Lung and Blood Institute. **For my medical information please contact:**

Name: _____ City: _____ Phone: _____

I may be randomized to one of the following blood pressure medications:

Randomized Drug	Dose 1	Dose 2	Dose 3
Chlorthalidone - <i>Hygroton</i>	12.5 mg - 1 capsule po qd	12.5mg - 1 capsule po qd	25 mg - 2 capsules po qd
Amlodipine - <i>Norvasc</i>	2.1 mg - 1 capsule po qd	5 mg - 1 capsule po qd	10 mg - 2 capsules po qd
Lisinopril - <i>Zestril</i>	10 mg - 1 capsule po qd	20 mg - 1 capsule po qd	40 mg - 2 capsules po qd
Doxazosin - <i>Cardura</i>	2 mg - 1 capsule po qd	4 mg - 1 capsule po qd	8 mg - 2 capsules po qd

My bottle code is _____ and the dose of the medication I am taking is (*Circle one*): 1 2 3

FOR EMERGENCY MEDICATION DISCLOSURE CALL 1-800-690-7870 (8-5/M-F Central Time) OR 713-704-2078 OUTSIDE OF THESE HOURS.

Other medications I am taking include:

My medical history includes:

7.10 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 or postcard follow-up purposes.

7.11 Housebound Participants

Participants unable or unwilling to attend the clinic should nonetheless be contacted and interviewed per the required visit schedule. This interview will most likely occur by telephone or postcard, but in some cases a home visit may be possible. Of course, not every procedure can be carried out in these cases, and clinical judgment should be used in determining which procedures might be accomplished. If possible ALLHAT events are ascertained at a telephone or postcard 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 home visits are feasible for your center, priorities for home visits should be as follows: (1) keep those still on ALLHAT medications on protocol, (2) for those who have not yet had a study event, to document a possible event, (3) for documentation of secondary events, (4) annual follow-up.

7.12 Refusals

Some participants randomized into the study may not be actively participating, i.e., not taking ALLHAT medication and/or not attending the ALLHAT Clinic. This may be due to any of a number of reasons, including transportation problems, or to the participant deciding against participation. Regardless of the reason, these participants should be followed for the duration of the study, and the Clinic staff must make contact every three or four months. It may be possible to complete a visit over the telephone or by postcard. These contacts are intended to first, ascertain possible ALLHAT events, and second, to remind the participant that he or she is still an ALLHAT participant.

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.

You may have a very small number of participants who will absolutely refuse to be followed in any way - in the clinic, by telephone or by postcard. When you have done all that you reasonably can to convince the participant to stay with ALLHAT and they still are declining any sort of follow up, their wish must be honored. **At that point, an ALLHAT Report of Refusal or Lost to Follow-up (AL07) should be filed.** Try to negotiate for at least one last contact at the end of the study. Leave the door open for future participation!

7.13 Losses to Follow-Up

The Clinical Centers should also regularly update the Patient Contact Information Sheet contacts. It is recommended that this information be updated at least annually as a routine part of a clinic visit. 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	Social Service exchanges
Neighborhood merchants	School boards
Unions, professional societies	Voter registration offices
Clergymen	Public housing and relocation authorities
Utility companies	Car registration
Health and welfare agencies	
Family	

If the participant has missed two consecutive required visits, and all attempts to contact the participant have failed, then the participant may be considered as lost to follow-up, and an AL07 should be filed. Periodic attempts should still be made to locate the participant.

7.14 Documenting Refusals and Losses to Follow-up and Locating Participants Who Are Lost to Follow-up

In the case of those participants who miss clinic visits and cannot be contacted at all, 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.

An AL07 (Documentation of Refusal or Lost to Follow-Up) should be completed when: (1) a participant is refusing further contact with ALLHAT - i.e., no clinic, phone or postcard visits will be done; or (2) the participant is classified as lost to follow-up as described above.

For a participant who is lost to follow-up, be sure to review Item #5 on the AL07 as well as those sources described above, and attempt all possibilities in an effort to locate the participant. It is essential that we know the whereabouts of all participants!

7.15 ALLHAT Report of Refusal or Loss to Follow-up - the AL07

Once a participant has been classified as a "refusal" or "loss to follow-up", an AL07 must be filed to document that classification. Place the participant's ID label in the space provided. If you wish, you may write the participant's name in this space prior to affixing the ID label, so that the name appears on the NCR copy (or you may use a label on the NCR copy).

In Item #1, put the date that the form is completed, using mm/dd/yy format and using leading zeros as necessary. Indicate in Item #2 whether this form documents a refusal or loss to follow-up (check only one).

Refusals - complete Items #3, #4, and #6. This category *only* includes patients who are refusing to allow any further information to be collected for ALLHAT. This category does *not* include patients who decide not to take the study medication or who are still or can be followed routinely in the clinic or by home visit, phone or postcard – do not complete an AL07 for these patients. If an AL07 is appropriate for this patient, remember that the patient can come back into ALLHAT any time in the future with either clinic visits or telephone visits.

Items #3, #4 and #6 document a refusal. *Do not complete this section for a patient who is classified as lost to follow-up.* Item #3 is a reminder to NOT complete the AL07 for participants who are agreeable to being followed by telephone or by postcard. Indicate the primary reason for the refusal (check only one) in Item #4. Be sure to detail the circumstances of the refusal in Item #6. A form without sufficient detail in Item #6 will be returned to you for more information.

Lost to follow-up - complete Items #5 and #6. This category includes patients who have moved with no forwarding address; who cannot be contacted through relatives, neighbors or other contacts; and who have missed their last two consecutive visits. Periodic attempts should still be made to locate the patient. Please see ALLHAT Manual of Operations Section 7.13 and the AL07 for ideas for locating patients who are lost to follow-up. If an AL07 is appropriate for this patient, remember that patients who are lost to follow-up now can come back to ALLHAT in the future!

Items #5 and #6 document a participant who is lost to follow-up. As mentioned above, there are many ways to attempt to find a person who is lost to follow-up. Indicate every attempt type in Items #5a-i, and document the circumstances in Item #6 (Comments). A form without sufficient detail in Item #6 will be returned to you for more information.

The person completing the form should initial Item #7 and sign where indicated in Item #8.

ALLHAT REPORT OF REFUSAL OR LOSS TO FOLLOW-UP – Version 2 – 10/98

This form is to be used to document: (1) patients who **refuse** to allow any further information to be collected for ALLHAT; and (2) final attempts to contact patients who have missed two consecutive follow-up visits with all attempts to contact unsuccessful (**lost to follow-up**).

<p align="center"><i>Place ID label here</i></p> <p>Patient name: _____</p>	<p>1. Date form completed: ___ - ___ - ___</p> <p>2. This form documents (check one): Refusal <input type="checkbox"/> 1 Lost to follow-up <input type="checkbox"/> 2</p>
---	--

Refusals - complete Items #3, #4, and #6. This category *only* includes patients who are refusing to allow any further information to be collected for ALLHAT. This category does *not* include patients who decide not to take the study medication or who are still or can be followed routinely in the clinic or by home visit, phone or postcard – do not complete an AL07 for these patients. If an AL07 is appropriate for this patient, remember that the patient can come back into ALLHAT any time in the future with either clinics visits or telephone visits.

3. Will patient allow follow-up in the clinic or at home Yes (**STOP – DO NOT COMPLETE AL07**) 1
or by phone or post-card? No 2
4. Primary reason for refusal (check one): Problem with study medication 1
Intervening illness 2
Advice of another physician 3
Other (explain in #6) 4

Lost to follow-up - complete Items #5 and #6. This category includes patients who have moved with no forwarding address; who cannot be contacted through relatives, neighbors or other contacts; and who have missed their last two consecutive visits. Periodic attempts should still be made to locate the patient. Please see ALLHAT Manual of Operations for other ideas for locating patients who are lost to follow-up. If an AL07 is appropriate for this patient, remember that patients who are lost to follow-up now can come back to ALLHAT in the future!

5. Check all attempts to locate participant: a. Telephone 1
b. Regular mail 1
c. Certified mail, return receipt requested 1
d. Contacting patient's other physicians 1
e. Contacting patient's family members 1
f. Other known contacts 1
g. Contacting place of employment 1
h. Contacting insurance companies 1
i. Other (explain in #6) 1

Comments – Complete this section for all patients. AL07's which do not have a completed comments section (#6) will be returned to you for further information. A CTC representative may contact you for further details.

6. _____

7. Initials of person completing this form..... _____
8. Signature of person completing this form _____

7.16 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 treatment groups being studied. The following are general procedures to be followed in filling out study forms:

a. **PRINT IN BOLD CAPITAL LETTERS.** 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, and use leading zeros as necessary.

Example: December 1, 1994, is recorded as: _1__2_ - _1__4_ - _1__9__9__9_
mm dd yyyy

2) 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 15 for the unknown information; e.g., "sometime during September of 1996" would be recorded as:

_0__9_ - _1__5_ - _1__9__9__6_
mm dd yyyy

c. 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 check (✓) or other mark, as they are more difficult to find. Example:

Yes

(2) Spaces for numerical recordings (e.g., blood pressures and dates):

a) Use leading zeros as necessary; e.g., _0__8__4_

b) If the value is unknown, the item should be coded with 9s.

d. ID labels -- Every page of each form, including copies retained at your clinic) should have the patient's ID label, in case pages of forms should become separated.

Standard ALLHAT 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.

7.17 Data Transmission

Transmission of data is currently not available in the ALLHAT Study. All data must be submitted on hardcopy forms.

7.17.1 Transfer of Hardcopy Forms to the Coordinating Center

Most ALLHAT forms are two-copy NCR forms. Completed 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 (not clipped or left loose). Originals should always be sent to the CTC.

ALLHAT Forms Shipping Log (AL08):

Originals of completed forms should be sent to the CTC **weekly** via First Class Mail. An ALLHAT Forms Shipping Log (AL08) should be included with every shipment, listing the ALLHAT ID number, acrostic and number of forms of each type. Endpoint documentation should be included as appropriate and should be clearly labeled with the patient's ID and acrostic on each page. ECG's should be included, and appropriate labels should be used.

Fill in your clinical center name, your center number and site code (for example, 001A), and complete the mailing date in mm/dd/yy format, using leading zeros as necessary.

You can use the participant labels in the space provided. For each participant, list how many AL01s, AL02s, etc, you are including in this shipment of forms. You do not need to list the dates of the forms. If you are including event documentation, such as the death certificate or discharge summary indicate the number of each that you are including. (Every sheet of event documentation should include a participant ID label.)

You will periodically receive edit notices or requests for data changes from the CTC. You do not need to list the edits on the AL08, as the edits have their own batch sheet.

This form is an NCR form, so that you will have a copy for your records. You have several choices for your copy: you can write the identifying information on the original so that it appears on your yellow copy, you can use the participant ID labels on your copy also, or you can photocopy the original form for your records.

You may use the AL08 to ship forms for up to five participants. If records for more than five participants are included, use more than one AL08, and indicate the number of AL08's for the shipment in the space that says "This shipping log contains ___ pages."

<p>PLEASE SEND ALL COMPLETED FORMS IN WEEKLY. FORMS RECEIVED AT THE CTC BY THE PUBLISHED MAIL CUTOFF DATE EACH MONTH ARE GUARANTEED TO BE INCLUDED IN THE NEXT MONTH'S REIMBURSEMENT AND EDIT RUN.</p>

ALLHAT FORMS SHIPPING LOG – Version 2 - 7/98

Clinical Center Name _____

Center # _____

Mailing date _____

This shipping log contains ____ pages.

Participant ID labels	Number of forms included in this mailing:	
	<input type="checkbox"/> AL01 <input type="checkbox"/> AL02 <input type="checkbox"/> AL03 (Visit #s: _____) <input type="checkbox"/> AL04 <input type="checkbox"/> Discharge summary <input type="checkbox"/> Death certificate <input type="checkbox"/> AL07	<input type="checkbox"/> AL09 <input type="checkbox"/> AL12 <input type="checkbox"/> AL13 <input type="checkbox"/> AL15 <input type="checkbox"/> ECG <input type="checkbox"/> Yr 2 <input type="checkbox"/> Yr 4 <input type="checkbox"/> Yr 6 <input type="checkbox"/> Other: _____
	<input type="checkbox"/> AL01 <input type="checkbox"/> AL02 <input type="checkbox"/> AL03 (Visit #s: _____) <input type="checkbox"/> AL04 <input type="checkbox"/> Discharge summary <input type="checkbox"/> Death certificate <input type="checkbox"/> AL07	<input type="checkbox"/> AL09 <input type="checkbox"/> AL12 <input type="checkbox"/> AL13 <input type="checkbox"/> AL15 <input type="checkbox"/> ECG <input type="checkbox"/> Yr 2 <input type="checkbox"/> Yr 4 <input type="checkbox"/> Yr 6 <input type="checkbox"/> Other: _____
	<input type="checkbox"/> AL01 <input type="checkbox"/> AL02 <input type="checkbox"/> AL03 (Visit #s: _____) <input type="checkbox"/> AL04 <input type="checkbox"/> Discharge summary <input type="checkbox"/> Death certificate <input type="checkbox"/> AL07	<input type="checkbox"/> AL09 <input type="checkbox"/> AL12 <input type="checkbox"/> AL13 <input type="checkbox"/> AL15 <input type="checkbox"/> ECG <input type="checkbox"/> Yr 2 <input type="checkbox"/> Yr 4 <input type="checkbox"/> Yr 6 <input type="checkbox"/> Other: _____
	<input type="checkbox"/> AL01 <input type="checkbox"/> AL02 <input type="checkbox"/> AL03 (Visit #s: _____) <input type="checkbox"/> AL04 <input type="checkbox"/> Discharge summary <input type="checkbox"/> Death certificate <input type="checkbox"/> AL07	<input type="checkbox"/> AL09 <input type="checkbox"/> AL12 <input type="checkbox"/> AL13 <input type="checkbox"/> AL15 <input type="checkbox"/> ECG <input type="checkbox"/> Yr 2 <input type="checkbox"/> Yr 4 <input type="checkbox"/> Yr 6 <input type="checkbox"/> Other: _____
	<input type="checkbox"/> AL01 <input type="checkbox"/> AL02 <input type="checkbox"/> AL03 (Visit #s: _____) <input type="checkbox"/> AL04 <input type="checkbox"/> Discharge summary <input type="checkbox"/> Death certificate <input type="checkbox"/> AL07	<input type="checkbox"/> AL09 <input type="checkbox"/> AL12 <input type="checkbox"/> AL13 <input type="checkbox"/> AL15 <input type="checkbox"/> ECG <input type="checkbox"/> Yr 2 <input type="checkbox"/> Yr 4 <input type="checkbox"/> Yr 6 <input type="checkbox"/> Other: _____

Signature of person completing this form: _____

7.17.2 Ordering a supply of study forms - the AL14

You will be sent a supply of study forms when you are preparing to begin the study. When you find that you are running low on any form, please use the AL14 (Study Forms Request) to order a re-supply. You should indicate in the space provided how many packs of each form you think you need for the next month (or longer, depending on storage space at your site). Include this form in your regular mailing of forms to the Clinical Trials Center. You may fax the form to the CTC. Forms will be shipped by 1st class mail which take 7-10 days. However, if you need forms urgently write RUSH on the AL14 and forms will arrive within 3 working days. If you need any type of label (address or participant ID labels) or ALLHAT stickers, affix one to the AL14 and send or fax it to the CTC.

ALLHAT STUDY SUPPLIES REQUEST FORM - VERSION 6

Date: _____ Site name: _____ Site number: _____ Code: _____

Form #	#/pack	# of packs	Form #	#/pack	# of packs
AL03 - Follow-up Visit	25		AL10 - Drug Order	25	
AL04 - Event Report	10		AL13 - Significant Adverse Events	10	
AL05B - Follow-up ECGs	25		AL14 - Supplies Request	25	
AL07 - Refusal/Loss to Follow-up	10		AL15 - Permanent Transfer	10	
AL08 - Forms Shipping Log	25		Patient Out of Town Worksheet	25	
AL09 - Correction Forms	25		Cardboard for NCR Forms	10	
Mailing Labels ___ CTC ___ ECG				sheet	
Eat Right to Help Lower Your High: ___ Blood Pressure ___ Blood Cholesterol English or Spanish				25	
Bilingual Diet Booklets: ___ "Cut Down on Salt . . ." ___ "Protect Your Heart . . ." ___ "Cut Down on Fat . . ."				10	
Postcard Visits				10	
Visit Reminders: ___ Post Card ___ Business Card				25	
Binders: ___ MOO ___ Study Documentation ___ Training ___ Adherence Survival Kit				Each	
ALLHAT Special Edition Health Matters				Each	
Adherence Posters: Yellow 24 X 16 ___ English ___ Spanish Yellow 11 X 8½ ___ English ___ Spanish				Each	
Videos: ___ Staff Training ___ Blood Pressure				Each	
ALLHAT Tip Cards				Set	
ALLHAT Medication Pocket Cards				20	
ALLHAT Stickers ___ ALLHAT ID cards ___				25	
Labels/Comments - Affix label samples anywhere on this page - Do not obscure other orders					

Include this form in your next shipment to the CTC, or fax to: (713) 500-9530

Signature: _____ Telephone number: _____

7.18 Documentation of corrections - the AL09

You will have several occasions to use the AL09:

- (1) When you discover an error on a study form that has already been sent to the CTC, use this form to request that a correction be made to that form. If a form has been sent to the CTC in error, you can use the AL09 to delete or replace that form.
- (2) In rare cases, the CTC may discover an error prior to the computer edit checks, and request a correction using this form. In this case, most of the form will be completed for you, and you will be asked to agree or not with the change.

For all instances, use the participant ID label where indicated. (You may write in the participant's name so it appears on the NCR copies.) Indicate the date that the form is complete in "Today's date" using the mm/dd/yy format, using leading zeros as necessary.

In order for a correction to be processed efficiently, we need to have the form number and form date in Item #2a and #2b. The form number is simply the digits associated with the form type. For example the AL03 would be "03". Complete the form date using mm/dd/yy and leading zeros as necessary.

In Item #3, indicate whether the form is being (1) deleted -- give the reason, (2) replaced -- give the reason and attach the newly-completed form, or (3) the form is being corrected-do not submit a new form.

If an error has been discovered regarding the participant's name complete items #5a, b and c. The Clinical Trials Center will correct the ACROSTIC accordingly and issue new participant labels.

If the form is being **deleted** or **replaced**, item #4a & #4b should be skipped. If the form is being **corrected**, give the item number from that form that is being corrected, the original response (#4a), and the corrected response (#4b) as indicated. Make one correction per line. If the current or corrected response is blank, write "blank", to avoid ambiguity.

In Item #6a, check "Clinic" if you are requesting a correction. If you receive this form from the CTC requesting a change, "Coordinating Center" will already be checked. Print the name of the person requesting the change in #6b.

Item #7 serves as a reminder -- if you are requesting a change to a form, you must also make the change on your hardcopy! When you make this change on your copy of the form, put the date and your initials or signature in #7.

Item #8 is for CTC use only.

You should send the white & yellow copies of this form to the CTC with your regular shipment of study forms, unless you are requested by the CTC to fax these to the CTC for specific changes. The yellow copy will be returned to your clinic after the CTC has corrected the data on the masterfile. The yellow copy should be retained with the pink copy in the participant's ALLHAT clinic chart.

Routine edit checks will be made monthly at the CTC, and will list the participant identifying information, the date of the form with the error, and the nature of the error. In response to these edits, you need not complete an AL09, but indicate your response to each edit directly on the edit report and return the original reports to the CTC.

ALLHAT CORRECTION REQUEST

Place ID Label Here
Also place on Yellow and Pink copies.

1. Today's Date: ____ - ____ - ____
MM DD YY

2.a. Form AL ____

2.b. Form Date: ____ - ____ - ____
MM DD YY

3. Is form being:

___ Deleted Reason: _____

___ Replaced Reason: _____

___ Corrected
↓

4.a. Item Number(s)	Description of Error(s)
_____	_____
_____	_____
_____	_____

4.b. Item Number(s)	Corrections
_____	_____
_____	_____
_____	_____

5.a. ___ Correction is to the participant's Name/Acrostic
b. Participant's CURRENT Name appears as: _____
c. Participant's CORRECT Name is: _____

The Coordinating Center will automatically update the participant's ACROSTIC if applicable .

6.a. Correction requested by: ___ Clinic ___ Coordinating Center
b. By: _____

7. Date corrected on form: ____ - ____ - ____ By: _____
MM DD YY

For Coordinating Center Use Only.

8. Date correction made to the master file: ____ - ____ - ____
MM DD YY
By: _____

7.19 Reimbursements

Your ALLHAT agreement indicates particular amounts that you will be reimbursed for antihypertensive trial randomizations, lipid trial randomizations, required follow-up visits, and study event documentation.

ALLHAT forms and edits that are received by the established mail cutoff each month will be processed for payment. Edits are run on these forms by the 5th day of every month. Checks are cut for forms clearing edit by the 2nd week of the month. Reimbursement will be temporarily withheld for forms that have problems with missing or inconsistent information. When these problems have been resolved, reimbursement will be made for those forms with the next monthly reimbursement. A list will be provided of every form for which reimbursement is made, and for every form that is causing a delayed reimbursement.

Study events will be reimbursed in several parts made separately for the endpoint form itself (the AL04), the death certificate or discharge summary, and for additional documentation for the 10% sample for verification.

The VA clinic reimbursements will be handled through Dr. William Cushman, VA regional coordinator. Reimbursements for other clinical sites are being handled through the Clinical Trials Center.

7.20 Changing ALLHAT Personnel at your Clinical Center

To change the name, phone, number of any ALLHAT personnel at your Clinical Center, make the appropriate changes to the Clinical Site Information Sheet and fax it to the Clinical Trials Center in Houston. These changes will be made and an updated Clinical Site Information Sheet will be mailed to your center. Upon receipt you should verify that all information is correct and maintain this sheet in your Study Documentation Binder.

7.21 Changing the Principal Investigator at your Clinical Center

To change the Principal Investigator at your Clinical Center, make the appropriate changes to the Clinical Site Information Sheet and fax it to the Clinical Trials Center. Changes will be made as described above and the Clinical Trials Center will request an updated FDA 1572 form and any necessary IRB paper work.

7.22 Changing the Address of your Clinical Center

To change the address of the Clinical Center where you conduct ALLHAT visits, make the appropriate changes to the "Clinic Address" on the Clinical Site Information Sheet and fax it to the Clinical Trials Center. Changes will be made as described above and the Clinical Trials Center will request an updated FDA 1572 form and any necessary IRB paper work.

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 ALLHAT 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 Format for *ALLHAT* Informed Consent

1. Thank the patient for coming and (or) taking the extra time to talk with you. If appropriate, you can tell the patient their doctor asked you to discuss the program with them.
2. Explain there are different "families" of blood pressure medicines:

Diuretics (water pills) -

- have been used for 30-40 years
- have been proven to prevent heart attack and stroke
- cause fluid loss to lower blood pressure
- are relatively cheap

Beta blockers -

- have been used for 20-30 years
- have also been proven to prevent heart attack and stroke
- cause decreased heart rate to lower blood pressure
- are also relatively cheap

Alpha blockers, ACE inhibitors, calcium blockers -

- are relatively new drugs
- some doctors think they may be better at preventing heart attack and stroke but have never been tested
- cause reduced tension in blood vessel wall to lower blood pressure
- relatively expensive

3. Explain why we are doing the study:

Doctors really don't know which family of blood pressure medicines is best at helping people over 60 avoid a heart attack or stroke.. We do know all these medicines lower blood pressure, but the reason we treat high blood pressure is to prevent the heart attacks, stroke, and other diseases it causes. *ALLHAT* is designed to find out if any of the newer, more expensive medicines is better at preventing heart attacks than the older, more

proven treatments.

4. Explain why they should be in the program:

ALLHAT is designed for people over sixty who have high blood pressure and an increased chance of developing a heart attack. Because of your (name those that apply: diabetes, heart disease, vascular disease, cholesterol level, heart enlargement, or simply "other medical problems or medical history") you are at increased risk of having a heart attack.

We know that high blood pressure and heart disease run in families, so your joining *ALLHAT* may help doctors prevent heart disease in your children and grandchildren when they get to be your age.

5. Explain briefly what the study involves:

Treatment of your blood pressure in the *ALLHAT* program is very much like the blood pressure treatment you've been used to all along. You'll need to take your blood pressure medicine every day and to come back to the doctor for regular check-ups, just like you do now. Your blood pressure medicines and any related blood tests will all be paid for by the program. The only difference in your treatment is that your blood pressure medicines will be assigned to you by *ALLHAT* instead of your doctor. All of the *ALLHAT* medicines are proven safe and effective, and all are widely used in people with high blood pressure. You probably are taking at least one of these medicines, or a medicine closely related to an *ALLHAT* medicine, right now.

The four different *ALLHAT* medicines are made to look exactly alike so that neither you nor I will know which medicine has been assigned to you. This process is called "double-blind" and it helps to keep us "honest" in measuring the effects of the four treatments in preventing heart attacks.

Another good thing about the program is that you will receive special attention as an *ALLHAT* patient. Information on your health will be carefully reviewed by doctors and other specialists involved in the program so that you will get the best possible care for your high blood pressure. Did you know that people who get involved in programs like *ALLHAT* often have much lower rates of death and hospitalization than people who don't? We like to think part of this difference is due to the extra attention that programs like *ALLHAT* provide. (If applicable to site: You will also be seen promptly without a long waiting time, provided you come on time for your appointments.)

6. Suggest that they look at a brochure explaining the program in detail and indicate that they may ask any questions they like. Tell them they should discuss it with their family and that you would be happy to talk to any family members as well.

A.3 Key summary points about informed consent

1. Provide the patient with adequate information about the program and its purpose (video, patient brochure, talking with you), provide ample opportunities for questions and discussion.
2. Explain the study's obligation to the patient and any benefits related to participation:
 - We don't know which blood pressure medicine is best at preventing heart attacks in people with high blood pressure. The newest and most expensive medicines may not be the best. **ALLHAT** will help find out which is best regardless of cost.
 - Participating patients will be closely watched and monitored. As a result, study participants may do better than those who don't participate -- this has usually been the experience of people agreeing to join studies like **ALLHAT**.
 - They and their doctors will be among the first to know the results of the program and will be ready to apply its findings.
 - They will be contributing to the welfare of people in general, other people of their age, people with high blood pressure, and to the future health of their children, grandchildren and other loved ones.
 - Effects of the medicines will be carefully monitored and promptly treated.
 - All information will be kept strictly confidential.
3. Describe the patient's responsibilities as a participant:
 - Once enrolled, they should faithfully take their medicines and keep their follow-up appointments.
 - Although they can drop out at any time, they should be as sure as they can right now that they're willing to stay in the program for the full five to seven years.

A.4 Frequent Comments and Questions by Study Patients

I don't want to be no guinea pig!

Explain to the patient that they are important to you as a person and that their welfare is your greatest concern. Make it clear that you respect their independence and autonomy. An important difference between them and a guinea pig is that guinea pigs can't say no, while patients can say no at any time. Let them know that you want them to have all the facts they need to make an informed decision about something as important to their health as **ALLHAT**. Give the patient a sense that they are in control of their decision to join or leave the program and that you respect their ability to make that decision once they have all the facts.

I don't want to be experimented on!

Remind the patient that none of the medications, tests or other procedures in **ALLHAT** is experimental. All the medications used in **ALLHAT** have already been tested on thousands of patients and determined to be safe and effective. The only thing that is experimental in **ALLHAT** is the process -- medicines are assigned by chance, like the flip of a coin, rather than by the doctor. Explain to them that the entry criteria and their doctor's close involvement insure that any of these medicines would be safe and effective choices for their treatment. Point out that the "research" aspect of the program is mainly in the collecting standardized,

confidential information on their health and comparing it to other patients like them. Emphasize that all information will be kept strictly confidential.

It may be helpful to point out that patients try out medicines and treatments all the time. Though you don't want to encourage this practice, you recognize that it happens, and it's a way that patients themselves "experiment" with their health. They try new medicines or natural remedies, for instance, and they sometimes try different doctors, clinics and hospitals. New medicines come along all the time and at some point a doctor has to prescribe them for the first time -- in a way, that's "experimenting", too. No one would want to go to a doctor who only prescribed medicines that were in use when they were in medical school!

I don't want to start a new medication!

Explain that they may already be taking one or more of the **ALLHAT** medicines or a medicine closely related to them. Point out that high blood pressure treatment usually starts with prescribing one drug at a low level. Doctors usually increase the dose or add other drugs until the blood pressure is controlled. Once controlled, the medicines are usually kept at the same dosage level, even though the body changes over time and may be more sensitive to the medicines than when the patient was younger. Experts in high blood pressure now recommend that doctors consider cutting back or even stopping blood pressure medicines after several years or as patients get older. This is because blood pressure in older patients may be controlled on fewer drugs or lower doses, with fewer side effects and lower cost. **ALLHAT** starts at low doses of a single drug and many older patients can have their blood pressure controlled on the lowest dose.

What if I get a side effect from the medicine?

Remind them that **ALLHAT** patients will get extra attention and will be followed more carefully than in usual practice, in case they have a side effect or other problem. Tell them to contact you as soon as possible if they think they are having a side effect, but point out that people often tend to blame any minor changes in the way they feel on changes in their medicines. Relate experience in studies like **TOMHS** and **SHEP** where the highest rate of side effects was in people assigned to placebo (or, to those who didn't get any active treatment at all)! Reassure them that you will stop the **ALLHAT** medicine immediately if you determine that they are having a serious side effect from it.

I'm worried that my blood pressure might not be controlled in ALLHAT.

Assure them that you will be monitoring their blood pressure very carefully to be sure it is well controlled. Tell them that this is a key part of the **ALLHAT** program, and that it was designed by national experts in high blood pressure treatment to be sure that all patients have good blood pressure control. Point out that patients in high blood pressure programs like **ALLHAT** tend to have better control of their blood pressure because they are followed more closely.

I don't want to be in ALLHAT because of what has happened to black people in studies in the past!

Acknowledge that African-Americans have been exploited in the past and that you understand their reasons for fear and mistrust. Explain that justifiable reactions to the terrible tragedies of the past have led to a critical lack of information in blacks, who are the racial group most likely to suffer the consequences of hypertension. Tell them that the study was started by Dr. Louis Sullivan when he was Secretary of Health, specifically to try to reduce the high rates of diseases related to high blood pressure in blacks. Assure them that **ALLHAT** has been approved by several review board which include many nationally known African-American experts in hypertension (Dr. Jackson Wright of Case Western Reserve University, Dr. Charles Francis of Harlem Hospital, Dr. Edward Cooper of the University of Pennsylvania, Dr. Keith Ferdinand of Xavier University). The study has also been endorsed by the National Medical Association, and many African-American physicians and nurses are participating in the program.

Explain that one of the critical problems in choosing high blood pressure treatment in blacks is that almost all the information on drug treatment comes from studies of whites, mostly young white men. There are good reasons to think that blacks may respond differently to blood pressure medicines, but the only way to test this is to include large numbers of black patients. Explain that you believe the benefits to outweigh any potential risks and that you have no ethical concerns at all in asking them to participate. Remind them that they have the right to say no and to drop out of the program at any time.

I don't pay (or pay very little) for my medicines, so free ALLHAT medications are not very important to me.

Point out that medical care in the U.S. is changing dramatically right now. Government and private programs that provide free medicines may not continue paying for medicines or may pay only for the cheapest ones. **ALLHAT** will last eight years and will continue to provide free medicines for as long as the patient participates.

Consent Form for ALLHAT Hypertension Treatment Study

The ALLHAT hypertension treatment study at _____ has been explained to me, and I have read the ALLHAT Patient Information Brochure. I know that I have the opportunity to ask any questions that I may have. I understand that, if I am eligible, I will be invited to take part in the study and that I will be expected to participate until the summer of the year 2001.

The purpose of this research study, the procedures to be followed, possible discomforts and risks, and expected benefits have been described to me. It has been explained to me that high blood pressure (hypertension) is a common condition and 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. It has been explained to me that I do not have to participate in this study in order to receive treatment for my high blood pressure. I further understand that as a participant in this study:

- 1) My high blood pressure and its effect on my body will be measured by standard medical tests. Whether I qualify for the study will be determined after a brief evaluation period. During this time, it may be necessary for my doctor to change or temporarily stop my present high blood pressure treatment. However, if my blood pressure should increase to more than is considered normal, medications will be given to lower it.
- 2) There are several drugs which are effective in lowering high blood pressure. Treatment with these drugs is likely to reduce the risk of heart disease, stroke, and early death. Four of these drugs have been selected as part of this research study because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better. One of the four drugs will be assigned to me by chance, like flipping a coin, rather than by my doctor. Neither of us will know which drug I will receive, although this information can be easily provided if needed in an emergency.
- 3) If necessary, other drugs may be used in combination with my assigned study medicine, in order to lower my blood pressure to a satisfactory level. All medications that I will receive will be standard medications commonly used by doctors in treating high blood pressure. No new or "experimental" medications will be used in this study.
- 4) There may be side effects from these drugs, such as rashes, stomach upset, other allergic reactions, and other side effects. The possible side effects that may occur with the drugs have been explained to me as well as the fact that I can ask any questions about these possible side effects or any other aspect of the study that I do not understand. The doctor, therapist, nurses and others involved in my treatment under this study will watch closely for such side effects and when necessary will stop the medication which appears to be responsible if such side effects occur and will give me different medication.
- 5) Should I need different or stronger drugs to lower my blood pressure than I receive at first, my doctor will explain to me any side effects that these medications have.

- 6) All information about me, including my medical history, laboratory data and findings of physical examinations, will be kept confidential to the extent permitted by law. My research records, just like hospital records, may be subpoenaed by court order. In certain instances, representatives from the National Heart, Lung, and Blood Institute or the FDA (Food and Drug Administration) may need to see my records in order to verify the study data. Study results may be published; however, my identity will not be revealed. At the end of the study, all paper forms with my name or other identifying information will be kept in locked rooms for a period of five years and then will be destroyed.
- 7) The *ALLHAT* researchers are requesting my Social Security Number under Public Health Service Act 42 USC 285a. I understand that my name and Social Security or Medicare Number will be used to help the *ALLHAT* researchers locate me in the future if I cannot be located at my home address by my doctor; they may be used to help *ALLHAT* researchers know if I am hospitalized; and they may be used to search vital status records in a follow-up study conducted in the future. I understand that providing this information is voluntary, that I may still participate in *ALLHAT* even if I refuse to provide this information, and that I will not be denied any federal right, benefit, or privilege by my refusal to provide this information.
- 8) My name, Social Security Number, Medicare Number, and any other publicly identifying information will be kept in computerized records separate from my *ALLHAT* medical data. These records will be kept indefinitely in a locked place and only used for the purposes stated in (7) above.
- 9) All medical information about me will be kept in computerized records for analysis with such data from all other participants, but these records will **not** contain my name or Social Security Number or Medicare Number, or any other publicly identifying information. These computerized medical records will be kept indefinitely for future use by authorized researchers.

I understand that my participation in this study is entirely voluntary. I am free to withdraw my consent and to discontinue participation in this study at any time. No penalty or loss of benefits will occur if I refuse to participate or if I withdraw from the study. I have been given the names and telephone numbers of persons whom I may contact for answers to questions about the study, my rights as a research subject, and what to do if I have research-related injuries. The above points have all been explained to me to my satisfaction and, understanding them fully, I hereby give my consent to enter this treatment study. I will be given a copy of this informed consent form.

Printed Name of Participant Signature of Participant Date

I have reviewed the patient brochure with the participant and fully explained to the participant the nature and purpose of the procedures described above and in the brochure and such risks as are involved in carrying them out.

Date Signature of Person Obtaining Consent

A-7 Participant's Initials _____

Consent Form for ALLHAT Cholesterol-Lowering Treatment Study

The ALLHAT cholesterol-lowering treatment study at _____ has been explained to me, and I have read the *ALLHAT Patient Information Brochure*. I know that I have the opportunity to ask any questions that I may have. I understand that, if I am eligible, I will be invited to take part in the cholesterol-lowering study and that I will be expected to participate until the summer of the year 2001.

The purpose of this research study, the procedures to be followed, possible discomforts and risks, and expected benefits have been described to me. It has been explained to me that high blood cholesterol is a common condition and that persons with high blood cholesterol are more likely to have a heart attack than those who have low cholesterol. It has been explained to me that I do not have to participate in this study in order to receive treatment for my high cholesterol. I further understand that as a participant in this study:

- 1) My cholesterol and its effect on my body will be measured by standard medical tests. I will be eligible for the study if my cholesterol levels are moderately, but not extremely, high and I am **not** already on drug treatment for high cholesterol.
- 2) There are several drugs which lower high cholesterol. One of these drugs, *pravastatin*, has been chosen for this research study because it is commonly used by doctors when treating patients with high cholesterol. Doctors do not know whether lowering cholesterol levels like mine with *pravastatin* will reduce my chance of having a heart attack. Whether I receive *pravastatin* or not will be assigned by chance, like flipping a coin, rather than by my doctor.
- 3) If I am assigned to receive *pravastatin*, my doctor may adjust the dosage or even prescribe an additional drug to lower my cholesterol to a satisfactory level. If I am not assigned to receive *pravastatin*, my doctor may later decide to prescribe a cholesterol-lowering drug if my cholesterol rises or my clinical condition otherwise requires it. In either case, I will continue to receive encouragement to follow the recommended heart-healthy diet. I understand that the ALLHAT study will not provide non-study medicines. If other medications are prescribed, my doctor will explain to me any side effects they might have. No new or "experimental" medicines will be used in this study.
- 4) There may be side effects from *pravastatin*, such as muscle pains or trouble sleeping, other allergic reactions, and other side effects. Inflammation of the liver may occur in a small number (about 1%) of patients taking *pravastatin*. If I receive this drug, I will be tested for this complication at regular intervals throughout the study. My doctor may perform additional tests to confirm this, and may stop my study drug. Inflammation of the liver disappears when the drug is stopped. The possible side effects that may occur have been explained to me as well as the fact that I can ask any questions about these possible side effects and any other aspect of the study that I do not understand. The doctor, therapist, nurses and others involved in my treatment under this study will watch closely for such side effects. If necessary, they will stop the medication which appears to be causing such side effects and will give me different medication if I need it.
- 5) All information about me, including my medical history, laboratory data and findings of physical examinations, will be kept confidential to the extent permitted by law. My research records, just

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Participant's Initials _____

like hospital records, may be subpoenaed by court order. In certain instances, representatives from the National Heart, Lung, and Blood Institute or the FDA (Food and Drug Administration) may need to see my records in order to verify the study data. Study results may be published; however, my identity will not be revealed. At the end of the study, all paper forms with my name or other identifying information will be kept in locked rooms for a period of five years and then will be destroyed.

- 6) The *ALLHAT* researchers are requesting my Social Security Number under Public Health Service Act 42 USC 285a. I understand that my name and Social Security or Medicare Number will be used to help the *ALLHAT* researchers locate me in the future if I cannot be located at my home address by my doctor; they may be used to help *ALLHAT* researchers know if I am hospitalized; and they may be used to search vital status records in a follow-up study conducted in the future. I understand that providing this information is voluntary, that I may still participate in *ALLHAT* even if I refuse to provide this information, and that I will not be denied any federal right, benefit, or privilege by my refusal to provide this information.
- 7) My name, Social Security Number, Medicare Number, and any other publicly identifying information will be kept in computerized records separate from my *ALLHAT* medical data. These records will be kept indefinitely in a locked place and only used for the purposes stated in (7) above.
- 8) All medical information about me will be kept in computerized records for analysis with such data from all other participants, but these records will **not** contain my name or Social Security Number or Medicare Number, or any other publicly identifying information. These computerized medical records will be kept indefinitely for future use by authorized researchers.

I understand that my participation in this study is entirely voluntary. I am free to withdraw my consent and to discontinue participation in this study at any time. No penalty or loss of benefits will occur if I refuse to participate or if I withdraw from the study. If I refuse to participate in the cholesterol-lowering trial, or if I withdraw from the cholesterol-lowering trial later, I can still participate in the blood pressure part of this study and I can still receive treatment for high blood cholesterol from my doctor if I need it. I have been given the names and telephone numbers of persons whom I may contact for answers to questions about the study, my rights as a research subject, and what to do if I have research-related injuries. The above points have all been explained to me to my satisfaction and, understanding them fully, I hereby give my consent to enter this treatment study. I will be given a copy of this informed consent form.

Printed Name of Participant

Signature of Participant

Date

I have reviewed the patient brochure with the participant and fully explained to the participant the nature and purpose of the procedures described above and in the brochure and such risks as are involved in carrying them out.

Date

Signature of Person Obtaining Consent

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Participant's Initials _____

**THE ANTIHYPERTENSIVE AND
LIPID-LOWERING TREATMENT
TO PREVENT HEART ATTACK
TRIAL**



Patient Information Brochure

**National Heart, Lung, and
Blood Institute**

National Institutes of Health

**The University of Texas-Houston
School of Public Health**



Patient Information Brochure

What is the ALLHAT Program?

ALLHAT is a nationwide Program that will test the performance of different types of drugs often used to treat high blood pressure and high blood cholesterol. The test will try to determine whether newer blood pressure-lowering drugs, which are more costly than older medicines, are better at reducing the risk of heart attacks. *ALLHAT* will also test whether a newer cholesterol-lowering drug prolongs life.

ALLHAT is being funded by the ***National Heart, Lung, and Blood Institute***, part of the National Institutes of Health. It is being conducted in doctors' offices, medical clinics, and other health care centers throughout the United States. The Program will have two parts: a high blood pressure part and a high cholesterol part. About 40,000 patients will be enrolled in the high blood pressure part. One-half of these patients (20,000) will also be involved in the high cholesterol part of the study. The Program is expected to last until the summer of 2001, unless results call for it to be ended earlier.

This brochure contains information on both parts of *ALLHAT*. Your doctor will discuss with you whether you are eligible for one or both parts.

Who Can Participate?

Men and women aged 55 years or older who have high blood pressure and one or more additional risk factors for heart attack, but who are basically in good health, can participate in the high blood pressure part of *ALLHAT*. In addition, people involved in the blood pressure part who also have moderately high cholesterol and have not been taking a cholesterol-lowering drug for the past two months may participate in the cholesterol part of the Program.

What Drugs Will Be Used In ALLHAT?

The ***blood pressure part*** of *ALLHAT* will test whether treatment with one of three newer types of drugs used to lower blood pressure is better in preventing heart attacks than a standard form of treatment with a diuretic drug. The newer drugs being used are *lisinopril*, *amlodipine*, and *doxazosin*, and the diuretic is called *chlorthalidone*.

Chlorthalidone has been used to treat high blood pressure for more than 25 years and has been proven to reduce the risk of heart attack and stroke in people with high blood pressure. The newer drugs have been used to treat high blood pressure since the 1980s and are known to lower blood pressure as well as *chlorthalidone*. They are even thought by some doctors to have fewer side effects than *chlorthalidone*, but this has not been proven in side-by-side comparisons. Since all these drugs lower blood pressure in slightly different ways (see *How Do the ALLHAT Drugs Work?* on page 11), there may also be differences in their ability to prevent heart attack and stroke, over and above their blood pressure lowering effects. However, this has never been shown in side-by-side comparisons.

Even though much remains to be proven, the newer drugs have been rapidly replacing longstanding treatments, such as chlorthalidone, even though they have not been shown to be more effective. The newer drugs are also very expensive — they can cost up to 30 times as much as the longstanding treatments!

Your doctor and other doctors and scientist working on *ALLHAT* believe that the benefits of these newer drugs must be proven for the welfare of all patients. This is why we are conducting the blood pressure part of *ALLHAT* and are asking you to participate.

For cholesterol part only:

The ***cholesterol part*** of *ALLHAT* will test whether a cholesterol-lowering drug called *pravastatin* will prolong life and reduce the risk of heart attack in men and women aged 55 and older who have moderately high blood cholesterol levels.

Cholesterol in the bloodstream is a major component of the plaques that build up in arteries. These plaques can reduce and sometimes block blood flow. When blood cannot get to the heart, a heart attack results. *Pravastatin* is one of several new drugs that safely and effectively lower high blood cholesterol. This part of *ALLHAT* will involve 20,000 volunteers from among the people who are already in the blood pressure part of the Program.

Doctors know that lowering high cholesterol in the bloodstream in middle-aged people, especially in men, reduces their risk of having heart attacks and other kinds of heart disease. What doctors do not know is whether older people, especially women, obtain the same benefits from cholesterol-lowering as

younger people. Since the changes in blood vessels that lead to heart attacks can take many years to develop, it is possible that starting treatment after age 55 might have no effect on the length of life or on heart disease at all. It is also possible that any decrease in heart disease might be balanced by an increase in other diseases, so that treatment does not prolong life.

ALLHAT will try to answer these important questions and so could influence treatments given to patients in the future. This is why we are doing the cholesterol part of *ALLHAT* and are asking those of you with moderately high cholesterol levels to participate.

What Happens in the Study?

Once you and your doctor have discussed the Program and you have agreed to participate in *ALLHAT*, you will be examined by your doctor to be sure you are eligible for the study. This examination may require more than one visit to the doctor or medical clinic to measure your blood pressure. The examination may also require that you have an electrocardiogram (ECG) tracing of your heartbeat and some other blood tests. During this brief time, you may also be asked to cut down or stop taking some of the blood pressure drugs you are now taking, so that your body can be ready to switch over to the *ALLHAT* blood pressure drugs. Your doctor will check your blood pressure closely and be sure you get any treatment you need to keep it under control.

Once your doctor decides that you are eligible for the high blood pressure part of the Program, and you agree to sign up, one of the four *ALLHAT* blood pressure drugs

will be chosen for you by chance — like the flip of a coin. This medicine will be given to you by your doctor at no cost to you for the length of the Program. All of these drugs are commonly used to lower blood pressure and the way they work is described in the section called *How Do the ALLHAT Drugs Work?* (page 11). Of every five patients who volunteer for the Program, one will be assigned by chance to receive the drug *lisinopril*, one to receive *amlodipine*, and one to receive *doxazosin*. The remaining two of every five patients will be assigned to the standard drug, *chlorthalidone*. All of the *ALLHAT* drugs will look alike, and neither you nor your doctor will know which drug you are taking. It is important that neither of you know which drug you are on because sometimes knowing that can affect the way you are treated or even the way you report on your health. In an emergency, your doctor can easily find out what drug you are taking.

The four *ALLHAT* blood pressure drugs are **not new or experimental drugs**, but they will not look like the tablets commonly supplied by a pharmacy or drug store. This is because the four drugs being used in *ALLHAT* will all be put into the same kind of capsules to make them look alike. Since these *ALLHAT* medicines look different than those given out at a pharmacy, the FDA (Food and Drug Administration) requires that the message *Caution: New Drug—Limited by Federal (USA) Law to Investigational Use* be placed on the drug bottle labels for these medicines. But, they are not new drugs; they will only look new.

As a participant in *ALLHAT*, you will be asked to see your doctor for regular blood pressure check-ups at least every three months during the first year and every four months for the next four to six years, or as long as *ALLHAT* lasts (see *How Long Will the Program Last?*, on page 7). These check-ups will be like your usual visits

for treatment of your high blood pressure, except for two things: first, your doctor will send some information about your health to the *ALLHAT* Center in Houston, Texas, and second, you will be asked to take one of the *ALLHAT* blood pressure medications instead of being given your prescription for the pharmacy. Other than that, your treatment will be just the same as it would be without your being involved in *ALLHAT*.

It is very important that you continue to take the *ALLHAT* drugs for as long as the Program lasts and that you see your doctor regularly for treatment of your high blood pressure.

For cholesterol part only:

If you would like to be in the cholesterol part of *ALLHAT* and give your consent to do so, your doctor will examine you to see if you are eligible. If your cholesterol level is very high or you are already taking a cholesterol-lowering drug, you will not be eligible for this part of the Program since most doctors agree that, even in older people, treatment for very high cholesterol levels probably **does** reduce the risk of heart attack. It would not be wise to include you in a study where your cholesterol might not get special treatment.

Once your doctor decides that you are eligible for the cholesterol part of *ALLHAT*, and you agree to sign up, you will be assigned to one of two groups by chance, like flipping a coin. One group will be given the cholesterol-lowering drug *pravastatin*; the other group, called the usual care group, will not be given *pravastatin* through *ALLHAT*. If you are assigned to the *pravastatin* group, your doctor will give you

pravastatin at no cost to you, and will check some blood tests from time to time (about every 6-8 months) to be sure the drug is not giving you any side effects. If you are chosen for the usual care group, your doctor will be free to prescribe any other cholesterol-lowering treatment he or she feels might be necessary to reduce your risk of heart attack. Participants in both groups will be advised to follow a special low-fat diet.

How Long will the Study Last?

ALLHAT is expected to end in the summer of 2001. If clear answers about the value of newer drugs to lower blood pressure, or the importance of lowering blood cholesterol in older persons, are obtained before then, *ALLHAT* may be ended sooner.

What is Expected of Participants?

By agreeing to participate in *ALLHAT*, you agree to follow two important rules:

- You must take the drugs prescribed through *ALLHAT* every day for as long as the Program lasts.
- You must see your doctor regularly for treatment of your high blood pressure.

You will have check-up visits every three months during the first year of *ALLHAT* and every four months after that. At the beginning, you may need to see your doctor every month or so to adjust your blood pressure medication. This is important to make sure the *ALLHAT* medicine lowers your blood pressure to the right level

and that you are not having any problems with it. You may want to look at the section *How Do the ALLHAT Drugs Work?*, on page 11, for more facts about the drugs.

For cholesterol part only:

If you are also in the cholesterol part of *ALLHAT*, you will need to continue to follow the low-fat diet given to you at the beginning of the study. If you are assigned to receive *pravastatin*, you will need to take this medicine every day. In the first few months of *ALLHAT*, and every one or two years after that, your doctor will check your cholesterol level to make sure you are getting the right amount of *pravastatin*. You may be asked to increase or decrease the amount of *pravastatin* you are taking so that your cholesterol doesn't go too high or too low.

You should not worry if your doctor is treating you for other health problems besides high blood pressure or high cholesterol. Your treatments will continue. But, any tests or drugs taken for these other health problems will not be paid for by *ALLHAT*.

ALLHAT Check-up Visits

At each *ALLHAT* check-up, these following things will be done:

1. Your blood pressure will be measured.
2. You will be asked if you have stayed in a hospital overnight since your last visit, and if so, where and when.

3. You will be asked if you have had any of six major health problems since your last visit.
4. You will be asked how much of your *ALLHAT* medicine you have taken, and the doctor or nurse will collect all unused medications.
5. You will be given enough *ALLHAT* medicine to last until your next doctor's visit.

You may have noticed that many of these are things that usually happen when you see your doctor for treatment of your blood pressure. The only differences are some of the questions that you will be asked will be worded in a standard way, so that answers to these questions can be collected in the same way from all 40,000 patients in *ALLHAT*.

If your doctor finds that your blood pressure has not been adequately lowered by your assigned *ALLHAT* drug, he or she may decide to increase the dose of the drug. If your blood pressure stays high, you may be given a second or even a third drug to lower it to the desired level. Your doctor will be given a supply of four additional drugs commonly used to treat high blood pressure and can give you any of these drugs at no cost to you. Unlike your assigned *ALLHAT* drug, both you and your doctor will know the names of any other blood pressure drugs prescribed for you.

If your blood pressure is still not low enough, or if for some reason you cannot take these drugs, your doctor is free to choose other drugs for your blood pressure, but these will not be paid for by *ALLHAT*.

At the beginning of the study and about every two years after that, an electrocardiogram (ECG) and blood tests will be done. The ECG is a painless procedure that is done while you rest quietly on a couch. It monitors your heart beat for a few minutes to see if it is beating

normally. You will have about two tablespoons of blood drawn from your arm for the blood tests. One of the blood tests will be to check your potassium level, which can be affected by blood pressure medicines. If your potassium level is low, your doctor will give you **potassium pills** to take at no cost to you. The ECGs and blood tests done as part of *ALLHAT* will be sent to a central laboratory for measurement at no cost to you.

For cholesterol part only:

In addition to the blood tests every two years, patients who are taking *pravastatin* will have blood drawn at each check-up (every three months) for the first year and about every eight months after that. These tests will help your doctor be sure that the *pravastatin* is not causing any side effects or problems with your muscles, which have been reported in a few people who take this drug.

This is all there is to being part of *ALLHAT*. Most of the things that will happen in *ALLHAT* are things that doctors usually do for patients with high blood pressure and high cholesterol, except that the medications and some tests will be given to you at no cost and facts about your health will be collected in a standardized way. If you are like many older people, your doctor will probably be treating you for other problems not related to *ALLHAT*, and may advise you to have other tests or take other medicines for these problems. These tests and other medicines will not be paid for as part of *ALLHAT*, but it is important for your health that you follow your doctor's advice.

How do the ALLHAT Drugs Work?

Four different kinds of drugs that lower blood pressure will be used in *ALLHAT*, and each of them works in different ways. It might help to think about the pressure of blood in a blood vessel as being like water flowing through a pipe under pressure. One way to lower the pressure is to let some of the fluid out of the pipe, which is basically the way that ***diuretics***, or water pills, work. The diuretic that will be used in *ALLHAT* is called *chlorthalidone*.

Another way to lower the pressure is to make the pipes, or the blood vessels, wider. Normal blood vessels can get wider, or dilate, and get narrower, or constrict, in reaction to things like exercise, heat, or cold. Sometimes, blood vessels can become too narrow, or over-constricted, and stay that way, causing high blood pressure. ***Calcium blocking drugs*** keep calcium from causing the walls of the blood vessels to constrict, and are used in this way to lower blood pressure. The calcium blocking drug that will be used in *ALLHAT* is called *amlodipine*. ***Alpha-blocking drugs*** keep the nerves in the walls of the blood vessels from causing them to constrict, and this effect also lowers blood pressure. The alpha-blocking drug that will be used in *ALLHAT* is called *doxazosin*. Another class of drugs, called ***ACE (angiotensin converting enzyme) inhibitors***, act by preventing a substance that is released by the kidney from constricting the blood vessels. The ACE inhibitor that will be used in *ALLHAT* is called *lisinopril*.

You will be taking one of these drugs every day. Like all medicines, they may produce some unwanted ***side effects*** which are rarely serious but can be troublesome. You could have such side effects as drowsiness, tiredness, weakness, impotence, headache, dizziness and

cough which might be related to the medicines. Most people who take these drugs do not have any side effects at all, but if they do occur, your doctor will decide whether the drug you are taking should be changed or stopped.

Other risks and discomforts which might occur include bruising, bleeding, and a slight risk of infection from drawing blood. In addition, while your blood pressure medicines are being adjusted or decreased, your blood pressure may increase. During this period, you will be monitored closely and treated if your blood pressure increases high enough to put you in any danger.

For cholesterol part only:

Pravastatin lowers cholesterol in the blood by slowing down the speed at which the body makes cholesterol. *Pravastatin* is usually taken once a day.

Sometimes, though not often, people taking *pravastatin* may get stomach upset, tiredness, or muscle pains. If you have these or other problems while taking *pravastatin*, you should let your doctor know right away. *Pravastatin* can also cause mild liver trouble. Your doctor and the study doctors will be checking your liver functions by means of the blood tests. If this occurs, your doctor may reduce or stop the *pravastatin*.

How Will Patients be Protected?

Participants in the *ALLHAT* Program will be protected in several ways.

1. Patients whose doctors believe that they may have a bad reaction to the *ALLHAT* drugs will not be entered into the Program.
2. All patients in the Program will begin their drugs in small doses so that they can be closely watched. If a problem develops, it will be treated, and the *ALLHAT* medication will be cut back or stopped as needed.
3. Your own doctor and other doctors working in the Program will watch carefully for any problem that might be caused by the *ALLHAT* drugs.
4. A national committee of experts who are not directly working in *ALLHAT* will carefully review all the *ALLHAT* results every six months or more often if needed. If the results show great benefit or harm from one of the drugs, the Program will be stopped right away and patients and doctors will be told of the results.

We believe that the benefits of the *ALLHAT* Program for you and for society far outweigh any chance of harm to you, but this is a judgement you and your doctor should make together.

What Are the Benefits of Participating?

1. In addition to your regular medical care, the information given by you at each visit will be looked at by other doctors working on this Program. Special laboratories will do your blood tests and look at your ECGs using the most up-to-date methods.

2. Many services related to the Program are provided to you at no cost. You will not be charged for your *ALLHAT* drugs or laboratory tests.
3. This is a chance for you to join in a national research effort which could help people like you with high blood pressure or high cholesterol live more productive and longer lives.
4. The results of this Program may help your doctor choose the best treatment for your high blood pressure or high cholesterol.

Why Get Involved?

Only patients who have high blood pressure or high cholesterol can participate in this Program and provide the answers we need; so we turn to people like you. Perhaps, that is how it should be because we are trying to prevent future heart attacks and prolong life among people like yourself. You can help us. We in turn will make every effort to safeguard your welfare and provide the best possible care for your high blood pressure and high cholesterol. We promise to place your best interests ahead of our own interests in *ALLHAT*.

Where Can I Get More Facts?

This brochure tells the basic facts about the *ALLHAT* Program. Your doctor, nurse, or physician's assistant can provide you with further information about the Program. We urge you to ask any question you may have about the Program, its purpose, its design, and what it involves.

The success of the Program depends on the participation and cooperation of patients like yourself. Before

you agree to join us, please be sure that you understand the Program and that all your questions have been answered.

For more information about *ALLHAT*, your rights as a Program participant, and what to do if you have research-related injuries, you may contact any of the following people.

_____	_____
Name	Telephone number
_____	_____
Name	Telephone number
_____	_____
Name	Telephone number

I have reviewed this brochure with the participant and fully explained to the participant the nature and purpose of the procedures it describes and such risks as are involved in carrying them out.

_____	_____
Signature of Person Obtaining Consent	Date

Patient's Initials: _____

APPENDIX B

BLOOD PRESSURE MEASUREMENT PROCEDURES

B.1 Background

Blood pressure (BP) readings of high quality are fundamental to diagnosis and treatment of hypertension. Yet many factors, including influences of the subject, the observer, the equipment, and the circumstances of measurement, work against the attainment of this basic objective. Good results cannot be taken for granted, then, and special attention must be focused on BP measurement procedures.

These procedures for BP recording were developed for ALLHAT after extensive consideration and discussion of numerous approaches to measurement techniques. In addition to the selection of instruments and specification of criteria for measurements, ALLHAT specifies methods for the entire sequence of steps in BP recording. For all observers, whether inexperienced in BP measurement or accustomed to different procedures, it will be important to become intimately familiar with these procedures and to carry them out, as early as possible, as a matter of habit.

It should be emphasized that the steps outlined here can satisfactorily be followed for the vast majority of adult subjects participating in ambulatory care. Exceptional situations do, of course, arise with sometimes serious obstacles to successful BP measurement. It must be the responsibility of supervisory staff to encourage BP observers to note exceptional circumstances and to seek consultation when they arise so that participants will be appropriately evaluated.

B.2 Arm Measurement

The proper cuff size must be used to avoid under- or over-estimating the correct BP. To determine the proper cuff size, the observer must measure the arm circumference at the midpoint of the arm. This measurement is taken on the right arm that has been bared from the shoulder. (If the blood pressure is known to be different in the right vs. the left arm, use the arm with the higher pressure. In this circumstance, it must be assured that all **ALLHAT** Bp readings are recorded on the same arm.) With the participant standing, holding the forearm horizontal, the arm length is measured from the acromion (or bony extremity of the shoulder girdle) to the olecranon (or tip of the elbow), with a metric tape, allowing the tape to hang freely. The midpoint is marked on the dorsal surface. The participant should then relax the arm along the side of the body. The arm circumference is measured by drawing the tape snugly around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal. Also, the tape should not indent the skin. The chart of arm circumference measurements and corresponding cuff sizes (below) is consulted, and the indicated cuff size is checked on the study form and used. (A copy of this chart should be attached to the sphygmomanometer for easy reference.) If the proper cuff size is wider than the length of the arm, use the next smaller cuff in order to get the most reliable readings. This chart should be consulted for each arm measurement. The markings found on most BP cuffs should not be used for reference, as they may be incorrect.

After the initial determination of proper cuff size, this arm measurement does not need to

be carried out at each visit. Generally, the arm should be remeasured and the cuff size redetermined if the participant gains or loses a significant amount of weight (enough to possibly change the cuff size, in the judgment of the observer). Each participant should have the proper cuff size evaluated annually.

CUFF SIZE INDICATED BY MEASURED ARM CIRCUMFERENCE	
Arm Circumference (cm)	Cuff Size (cm)*
UP to 5.9	2.5 ("newborn")
6.0 to 15.9	6.5 ("infant")
16.0 to 22.5	9.0 ("child" or "pediatric")
22.6 to 30.0	12.0 ("adult" or "regular")
30.1 to 37.5	15.0 ("large arm")
37.6 to 43.7	17.5 ("thigh")
*Bladder widths shown are at least 40% of the largest corresponding arm circumferences.	

B.3 Application of the Blood Pressure Cuff

Next, the appropriate cuff (as determined in the arm measurement procedure) is placed around the bare upper right arm so that the midpoint of the length of the bladder lies over the brachial artery and the mid-height of the cuff is at heart level. The lower edge of the cuff, with its tubing connections, should be placed about 1 inch above the natural crease across the inner aspect of the elbow. The cuff is wrapped snugly about the arm, still with the palm of the participant's hand turned upward. The wrapped cuff should be secured firmly by applying pressure to the locking fabric fastener over the area where it is applied to the cuff.

B.4 Determining the Peak Inflation Level

It is necessary to determine, for each participant, the pressure level to which the cuff is to be inflated for accurate measurement of the systolic pressure. (This is because the cuff pressure at the start of the reading should always exceed the systolic pressure--otherwise the first of the Korotkoff sounds will be missed.) This starting pressure is called the "peak inflation pressure" and is determined as follows: The cuff tubing should be attached to the sphygmomanometer. The cuff should be inflated while the radial pulse is palpated and the mercury column watched closely. When sufficient pressure has been applied, the pulse will no longer be felt. When this pulse disappearance has been detected, the cuff is inflated another 20 mm Hg and then quickly and completely deflated. The observed pulse obliteration pressure is noted and 20 mm Hg are added. This sum is the peak inflation level; the cuff is to be inflated to this level for all readings at this examination.

NOTE: All readings are made to the nearest even digit. Any reading which appears to fall exactly between markings on the column should be read to the next marking immediately above, i.e., 2, 4, 6, 8 or 0. All readings are to be made at the top of the meniscus, or rounded surface of the mercury column. Three digits are to be entered for all BP readings - beginning, where appropriate, with the leading zero (e.g., 084).

B.5 Pulse Measurement

Part of the BP measurement procedure is the measurement of the pulse, as observed by

palpation of the radial artery at the wrist. For simplicity, the right arm is to be used consistently for measurement of both pulse and BP. This measurement serves two purposes: (1) to document the resting heart rate at the time of examination; and (2) to permit detection of gross irregularities of heart rhythm which may affect the interpretation of the BP readings.

The measurement of pulse and BP is performed only after the participant has been seated quietly, with feet flat on the floor, in an erect but comfortable posture, for at least five minutes without smoking. The elbow and forearm should rest comfortably on the table. With the palm of the hand turned upward, the radial pulse is palpated and counted for 30 seconds exactly. (The observer should not use the thumb to palpate the pulse.) The number of beats in 30 seconds is noted, multiplied by 2, and the product recorded as the heart rate.

B.6 Blood Pressure Readings

Next, the observer should proceed to carry out the first BP reading. The systolic value (1st phase Korotkoff) can be identified as the pressure level where the first of 2 or more sounds are heard in appropriate rhythm. The diastolic value (5th phase Korotkoff) can be identified as the pressure level where the last of these rhythmic sounds is heard. **PLEASE NOTE:** A single sound heard in isolation (i.e., not in rhythmic sequence) before the first of the rhythmic sounds (systolic) or following the last of the rhythmic sounds (diastolic) does not meet these criteria for the systolic or diastolic endpoints. *If the sounds are heard all the way to 0 mm Hg, record the 4th phase DBP.*

Once the cuff and device are connected, as required beforehand for determination of the peak inflation level, the steps in measurement are as follows:

- (1) Wait at least 30 seconds after complete deflation of the cuff following any preceding inflation.
- (2) Place the earpieces of the stethoscope, with the tips turned forward, into the ears.
- (3) Apply the *bell* of the stethoscope over the brachial artery, just between the elbow crease and the lower edge of the cuff, but not touching the cuff or tubing. The brachial artery is usually found at the crease of the arm, slightly toward the body.
- (4) By closing the thumb valve and squeezing the bulb, inflate the cuff at a rapid but smooth, continuous rate to the peak inflation level. The eyes of the observer should be level with the mid-range of the manometer scale and focused at the level to which the pressure will be raised.
- (5) By opening the thumb valve slightly, and maintaining a constant rate of deflation at approximately 2 mm per second, allow the cuff to deflate, listening throughout the entire range of deflation, from the peak inflation pressure past the systolic reading (the pressure where the first regular sound is heard), until 10 mm Hg below the level of the diastolic reading (that is, 10 mm Hg below the level where the last regular sound is heard).
- (6) The cuff is then fully deflated by opening the thumb valve, and is disconnected; the stethoscope earpieces are removed from the ears; and the systolic and diastolic readings are entered in the spaces provided on the form.
- (7) The cuff is now removed (recommended, but optional), and the subject's arm is raised, passively, overhead for 15 seconds. The arm is then lowered gently, and the cuff is replaced (if previously removed) and reconnected.

- (8) The BP measurement is repeated exactly as before. The observed SBP and DBP values are recorded, and the average (sum of reading 1 + reading 2, divided by 2) is calculated.
- (9) Remove the cuff and store the equipment safely after the last reading.

B.7 Blood Pressure Equipment and Mercury Toxicity Safety Responsibility

The condition of the instruments for BP measurement is too often neglected in common practice and should be a special responsibility of a designated staff member. This person should be acquainted with mercury toxicity safety procedures as well as construction and function of all the BP equipment. For the cuffs and stethoscope, their cleanliness and general working order can usually be determined by simple inspection. For the manometers, however, handling of breakable parts and of mercury and oxidized waste require more careful attention. Guidelines for suggested maintenance procedures for the manometers are outlined here in some detail.

B.7.1 General Guidelines

1. The objective of maintenance of all sphygmomanometers is to ensure their accuracy for BP measurement. The manometer column must be clean and the system free of mercury leakage. The zero level should be accurately read as 0 mm Hg at the top of the mercury meniscus.
2. These devices should be cleaned and checked thoroughly approximately every three months. More frequent inspections should be made to ensure there has been no mercury spillage or leakage and no obvious malfunction of the device. Instruments used in clinics should be inspected weekly. Those inspections should include a check of zero levels, mercury leakage, operation of valves, manometer columns for dirt or mercury oxide deposit, and condition of all tubing and fittings.

B.7.2 Common Problems with--and Solutions for-- Manometers

1. Dirty manometer column.
 - a. This is due to dirty or oxidized mercury and is usually evident near the zero. It is hard to see the meniscus to verify the proper mercury level, with the top of the meniscus exactly at 0.
 - b. Remove the glass manometer column (see Baum instructions).
 - c. Clean the glass column from its top towards its zero, with the "super" pipe cleaners available from Baum. Hold the column over a container to catch mercury as the cleaner is pushed through, and brush the soiled end of the cleaner into the container. Be careful of mercury that may splatter from the pipe cleaner.
2. Leaked mercury.

This can be due to any of the following:

- a. loose or leaky screw cap at top of manometer
 - b. manometer column cracked or chipped, or improperly seated
 - c. leaky manometer column gaskets
3. The mercury level will not remain constant when the bulb valve is closed.

- a. Connect the manometer to a cuff which is around a one pound coffee can. Pump up the cuff and begin to pinch the tubing closed, starting at the manometer tubing.
- b. By a process of pinching the tubing at 1-2 inch intervals up to the cuff and then down to the bulb, you will locate an air leak.
- c. If an air leak is found to be in the cuff bladder or the tubing other than the connections, the bladder may need to be replaced.
- d. If the air leak is found in the connections or in the bulb valve, a little silicone spray may alleviate the problem.

CAUTION: Mercury vapor is very toxic. Tiny droplets vaporize more rapidly than bulk. All loose mercury must be collected and inactivated. One effective and convenient product for mercury vapor reduction is "HgX," a powder produced by Acton Associates, 1180 Raymond Blvd., Newark, NJ 07102. It is recommended that all work be done in a container such as a plastic dish pan when mercury is to be transferred. Do not dispose of gowns, gloves or masks in a normal wastebasket.

B.8 Training Observers in the Clinical Centers

ALLHAT Clinical Centers may need to train additional staff members beyond those who attended the central training session. This should be accomplished by one of the staff members who attended the central training session. BP training for *ALLHAT* includes the following:

- A written pretest on the measurement of BP
- A slide presentation of the proper method of BP measurement
- Several video examples that the trainee will view to determine the systolic and diastolic readings
- Review of "answers" to the video examples
- Discussion
- Live BP reading performance evaluation

Each trainee will turn in his/her written test, final video reading sheet and live reading performance checklist as documentation of training. Verification of this will be kept in a computer file at the CTC to compare against BP readings on the forms (observer initials will be collected on the forms).

Each ALLHAT clinic will be provided with copies of the written exam, live performance evaluation, and the slides and video including the demonstration and practice measurements.

There is minimal administrative burden on the clinic staff when training new staff. The only administrative burden other than the actual training would be the central documentation that new staff have been trained (including copies of the documents noted above).

The following materials are needed for BP training at the clinic:

1. This training chapter
2. The appropriate forms (e.g., AL03 page 1) and paper
3. Copies of the written exam for a pretest
4. 2 X 2 slide projector and carousel - a text is provided with the slides
5. VHS videotape machine

6. Copies of the Videotape Practice Sheet
7. Copies of the Live BP Reading Performance Evaluation
8. Black ball-point pens

The written examination should be taken by the trainee and reviewed by the trainer. If there are any incorrect responses, these should be discussed and clarified. The trainer should indicate those responses that were discussed by initialing them.

When the videotape sample readings are done, remind the trainee to insert leading 0's where necessary and complete the entire form. If a systematic problem is discovered, retraining, possibly by extra live evaluations or by Y-tube readings where possible, may help to identify and correct the problem.

Videotape Training Tip: In working with the practice videotape sequences, at first ignore the diastolic readings until the systolic readings have been mastered; then proceed to add the determination of the diastolic readings to each sequence.

The trainer should observe each trainee performing a BP measurement per the **ALLHAT** instructions, and should use the checklist to document that each step is done correctly and in proper sequence. Discrepancies should be discussed.

The Clinical Trials Center will need to have complete documentation of the training (written test, live evaluation, videotape sample readings) before the trainee can be employed as a BP observer. We suggest that a supervisor keep the originals and send photocopies to the Coordinating Center. The Coordinating Center will instruct the Clinic Coordinator when retraining sessions should be scheduled, on an approximately annual basis.

Answers to Videotape Practice Readings			
Practice #	SBP/DBP	Practice #	SBP/DBP
1	164/106	7	118/076
2	112/064	8	096/058
3	138/098	9	164/106
4	120/074	10	120/074
5	142/084	11	118/076
6	134/076	12	112/064

ALLHAT

Blood Pressure Measurement Reminders

2

BP readings per visit

BP values: SBP, DBP5

sounds in appropriate time
sequence:

First = SBP

Last = DBP

mm/second = deflation rate

's: always even values

(2, 4, 6, 8, 0)

cuffs, mainly: adult and large arm

ALLHAT BLOOD PRESSURE MEASUREMENT
WRITTEN EXAMINATION

Name _____ Initials _____

Clinic name _____ Clinic number _____

Date (mm/dd/yy) ____ / ____ / ____

1. When ever the pulse is measured, it must be counted for _____ seconds and multiplied by _____ to give the number of beats per minute.
2. Whenever BP is to be measured, the participant must first be in the _____ position for _____ minutes without _____.
- 3.a. To find the pulse obliteration pressure, inflate the cuff while palpating the radial pulse until _____ and then inflate by an additional _____ mmHg.
- b. It is not permitted to use this inflation of the cuff for carrying out an actual **ALLHAT** reading: True False
4. The deflation rate of the cuff must be carefully controlled, at a rate very close to _____ mm per second.
5. The interval between readings must be at least _____ seconds.
- 6.a. The _____ cuff, the _____ cuff, the _____ cuff and the _____ cuff are the four sizes required to be available in each ALLHAT clinic.
- b. Use of the regular adult cuff when a larger one is required would (check which applies):
 (1) give a falsely high BP reading
 (2) likely cause difficulty in securely wrapping the cuff
 (3) be preventable by checking the arm circumference before wrapping the cuff, and being properly equipped
 (4) all of the above
 (5) none of the above

End of examination! Thank you!

ALLHAT BLOOD PRESSURE MEASUREMENT
VIDEOTAPE PRACTICE BLOOD PRESSURE MEASUREMENTS

Name _____ Initials _____

Clinic name _____ Clinic number _____

Date (mm/dd/yy) ____ / ____ / ____

Reading #	SBP/DBP mm Hg
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

ALLHAT Live BP Reading Performance Evaluation

Name _____ Initials _____

Clinic name _____ Clinic number _____

Date (mm/dd/yy) ____ / ____ / ____

A. Equipment and supplies -The trainee should indicate that all equipment and supplies needed for BP measurements are present. Check each item identified:

- ___ (1) Standard sphygmomanometer
- ___ (2) Cuffs - full set of 4 ("child or "pediatric," "adult" or "regular," "large arm," and "thigh")
- ___ (3) Inflation bulb
- ___ (4) Bell stethoscope
- ___ (5) Watch with second hand or digital second display
- ___ (6) Measuring tape
- ___ (7) Black ball point pen
- ___ (8) Study forms

B. Arm measurement - The following steps are properly carried out:

- ___ (1) Subject standing
- ___ (2) Arm bare from elbow to shoulder
- ___ (3) Arm at 90° angle
- ___ (4) Arm length measured
- ___ (5) Midpoint of arm marked at dorsal aspect
- ___ (6) Arm relaxed at side
- ___ (7) Circumference measured with tape horizontal --
- ___ (8) Through mark at midpoint
- ___ (9) No indentation of skin
- ___ (10) Value checked with chart to ascertain proper cuff size
- ___ (11) Proper cuff size checked on ALLHAT form

C. Preparation for BP readings

- ___ (1) Brachial artery palpated
- ___ (2) Midpoint of bladder within the cuff located
- ___ (3) Cuff applied with midpoint of bladder over brachial artery (correct cuff used)
- ___ (4) Arm positioned with midpoint of cuff width at "heart level"; lower edge 2-3 cm (1 inch) above crease
- ___ (5) Sphygmomanometer connected to cuff
- ___ (6) Sphygmomanometer scale (midpoint) at eye level
- ___ (7) Radial pulse located
- ___ (8) Cuff inflated quickly to disappearance of pulse
- ___ (9) Pressure increased by 20 mm Hg

- ___ (10) Cuff quickly and completely deflated
- ___ (11) Observed pulse obliteration pressure and peak inflation pressure noted

D. Measurement of pulse

- ___ (1) Five-minute period at rest completed
- ___ (2) Radial artery palpated
- ___ (3) Counting with watch, full 30 seconds
- ___ (4) Correct doubling of 30-second pulse, and correct recording on study form

E. Measurement of BP

- ___ (1) Brachial artery palpated
- ___ (2) Stethoscope in ears
- ___ (3) Bell over artery, without cuff or tubing contact
- ___ (4) Cuff inflated quickly and smoothly to peak inflation pressure
- ___ (5) Deflation at 2 mm Hg/second to 10 mm Hg below K5
- ___ (6) Cuff quickly and completely deflated
- ___ (7) Cuff disconnected
- ___ (8) Recording of SBP and DBP

F. Between readings

- ___ (1) Cuff removed (recommended, but optional)
- ___ (2) Arm raised passively overhead for 15 seconds
- ___ (3) Arm lowered and cuff replaced with attention to brachial artery and midpoint of bladder; lower edge 2-3 cm (1 inch) above crease of the elbow
- ___ (4) Cuff reconnected

G. Second BP reading

- ___ (1) Conforms with procedures as in E above

H. Completion

- ___ (1) Initials and signature on recording form
- ___ (2) Proper storage of equipment

I. Observed BP levels by trainer and trainee (optional)

SBP/DBP

Reading 1 ___ ___ / ___ ___

Reading 2 ___ ___ / ___ ___

I certify that this trainee has completed all procedures correctly:

Trainer's signature

Trainer's name (printed)

Remarks: _____

APPENDIX C

ALLHAT ECG DATA ACQUISITION PROCEDURES

C.1 Background and Purpose

Standard 12-lead ECGs will be acquired on ALLHAT participants at the baseline and biannual visits for the duration of the study. The ECG will be used to provide the study with reliable visual evidence of prevalent myocardial infarction (MI), ischemic heart disease, interim MI and the presence, progression or regression of ECG left ventricular hypertrophy.

A standard 12-lead ECG will be obtained using the ECG facilities available to each clinic. The original ECG tracing (not a copy) will be collected for the trial. The ECGs will be batched and mailed weekly to the Minnesota ECG Coding Center for coding. The clinic should make a second recording and keep it in the participant's file.

Special effort will be required to achieve accurate electrode placement and to avoid lead reversal. In the event of inadequate ECG quality, the tracing should be repeated at once to avoid participant recall.

All electrocardiograms submitted for ALLHAT must be properly standardized, free of baseline drift, muscle tremor, and 60 Hz interference. It is the responsibility of the clinic technician to record high quality ECGs and use uniform techniques daily.

The following sections are to be used by (1) technicians in charge of ECG recording and (2) clinical center personnel in charge of labeling and mailing ECGs to the Minnesota Coding Center.

C.2 Recommended Data Acquisition Procedures for ALLHAT

C.2.1 Basic ALLHAT Acquisition Requirements

To obtain the best quality ECG data under a variety of recording situations, clinics should strive to meet the following guidelines:

- a) the ECG machine should be multichannel and less than two years old at the onset of the study. ECGs produced on single-channel machines will be accepted.
- b) the ECG machine must meet the 1988 AHA specifications for machine performance.
- c) the ECG must be recorded in the supine position with the standard 12-lead placement.
- d) Because it is essential for the study to compare baseline ECG data with subsequent records, uniform procedure for electrode placement and skin preparation is required.
- e) for ECG machines that do not mark leads automatically, each lead must be identified by labelling leads as: I, II, III, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6. These labels are to be placed above the specific lead and must never obstruct the actual beats on the tracing.
- f) A 1 mV calibration pulse must precede limb leads and precordial voltages.
- g) Multichannel machines should be programmed to produce 5-6 seconds of data per lead

group. Single channel machines should record 5-6 seconds of data per lead. The ideal lead will consist of 4-5 good quality beats which are free of noise or drift.

C.2.2 Limb Lead Preparation and Placement

Begin with the RIGHT LEG, an important connection because it is the ground. Careless skin preparation and electrode connection here will influence all ECG leads. Prep the inner side of the right ankle in a circular motion using an alcohol gauze and mark the electrode position with a marker.

Repeat the same procedure on the LEFT LEG, RIGHT ARM inner wrist and LEFT ARM, in that order.

Place limb electrodes on the prepared four sites. Do not connect the electrode cables until the chest sites have been located and prepared.

If any part of the patient's limb has been amputated, the electrode is placed on the remaining portion of the limb.

C.2.3 Chest Lead Preparation and Placement

Clean the general area with alcohol preps and mark each lead position as you locate it. Shaving the chest is required in situations with excessive chest hair making electrode-skin contact impossible.

Using your right index finger, locate the sternal angle and left second rib. Count down to the fourth rib and identify the fourth intercostal space between rib 4 & 5. Locate the fourth intercostal space immediately to the left of the sternal border and mark the location of V2 (Figure 1).

Locate and mark electrode V1 position in the fourth intercostal space at the right sternal border, at the same level as V2 and immediately right of the sternum.

Identify the fifth rib and fifth intercostal space below position V2. Project this position horizontally to the midsternal line and mark this point, "E", the reference point for V3, V4, V5, and V6 (Figure 2).

Move the participant's elbow away from the body. Trace the left midaxillary line straight down from the center of the arm pit to where an imaginary horizontal line drawn from "E" would intersect. This is the location of V6.

V4 is located on a straight line exactly halfway between "E" and V6. V3 is exactly halfway between V2 and V4. V5 is located on a straight line exactly midway between V4 and V6.

Rub each chest electrode location with alcohol prep in a circular motion to remove oil

and dead skin. Place the electrodes on their sites in order (V1, V2, V3, V4, V5, V6).

Attach electrode cables to each electrode. **Be sure not to misplace the left and right limb electrodes.** This happens easily and more often than you may think.

Summary Table for Optimal Sequence of Electrode Placement (Figure 3)		
A. Locate and Mark	1. RL 2. LL	3. RA 4. LA
B. Prepare Skin	1. RL 2. LL	3. RA 4. LA
C. Attach Electrodes	1. RL 2. LL	3. RA 4. LA
D. Locate and Mark	1. V2 2. V1 3. Point E 4. V6	5. V4 6. V3 7. V5
E. Prepare the skin of the V – leads		
F. Attach electrodes of the V - leads		
G. Connect electrode cables to the limb electrodes		
H. Connect electrode cables to the chest electrodes		
I. Verify that the cables are connected correctly		

NOTE:

Electrode positioning for women: Electrode positions are determined with respect to anatomical locations on the thorax. On women with large breasts, place electrodes on top of the breast in their natural supine position. Do not attempt to place the electrodes under the breast or to move the breast upwards or laterally.

Figure 1. Proper Electrode Placement of Electrodes V1-V4

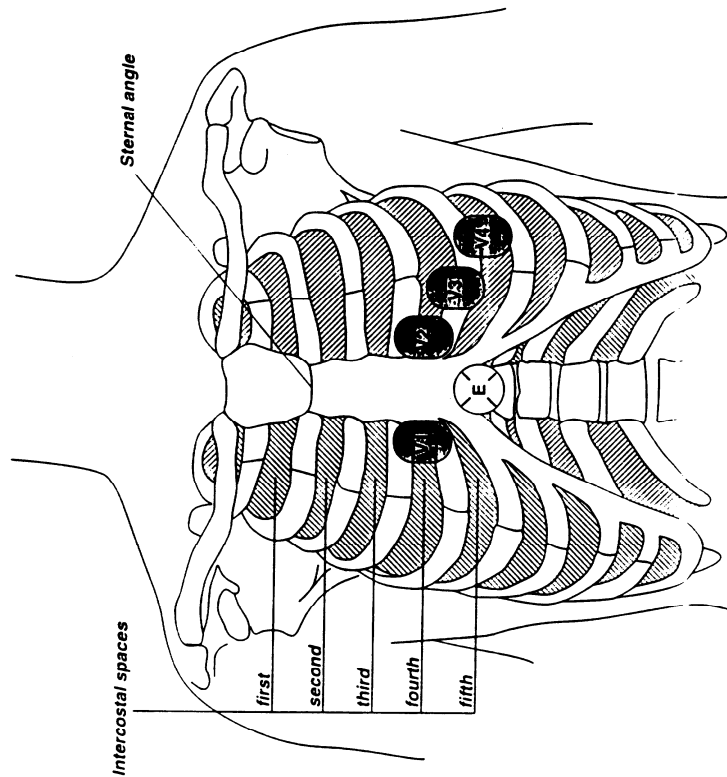


Figure 2. Proper Electrode Placement of Electrodes V1-V6

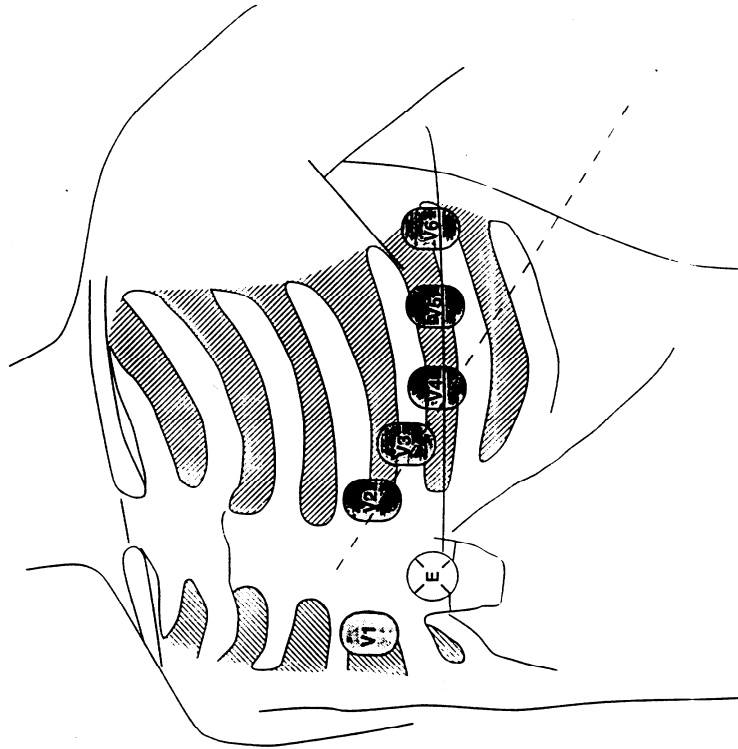
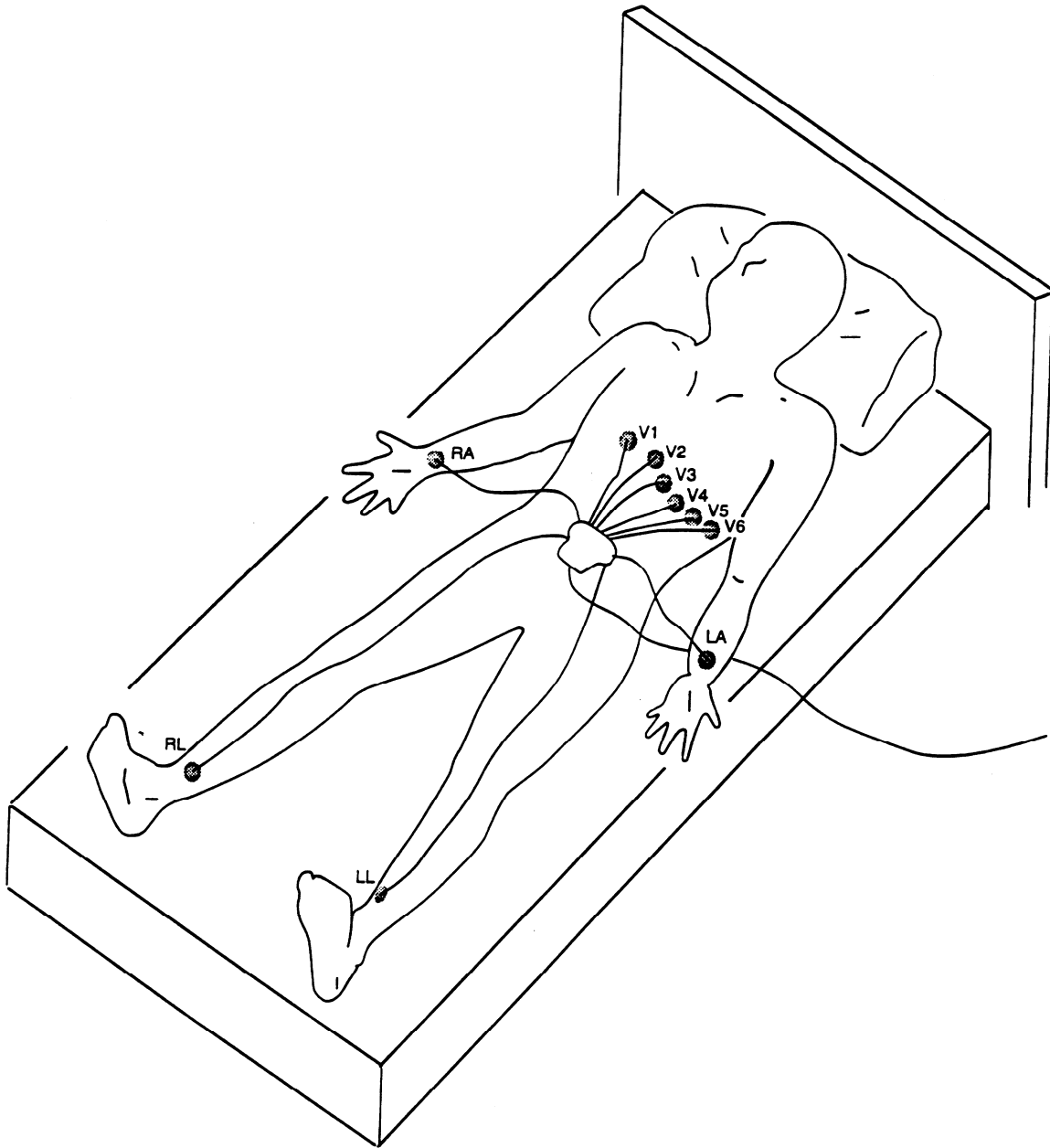


Figure 3. Proper Electrode Placement of Limb and Chest Leads



C.3 **Recording the 12-Lead ECG**

Ask the participant to relax, breath normally and remain still (without talking) while the tracing is recorded.

Record the ECG following the instructions and format provided for the cardiograph you are using. Be sure to record a calibration pulse at the beginning of each lead and that there are 4-5 good quality beats per lead. You should make two recordings - one to be mailed to the ECG Coding Center and one to keep in the participant's file.

Immediately place the participant's ALLHAT ID label on the front of the ECG being careful not to cover any part of the tracing. (This may require placing the label on the back of the tracing). Take care to use the proper label provided by the CTC. These labels will indicate "Baseline ECG", "2-yr ECG", "4-yr ECG", "6-yr ECG", or "Event ECG", and they include a space for the date recorded. Do not leave the date recorded blank!

C.3.1 Quality Checks (See page C-8)

Inspect the record immediately for quality. Repeat the recording for quality problems, using the following checklist:

Lead switch

The more frequent error is reversal of the right and left arm cables. Negative P-waves in lead I indicate a lead switch.

Excessive baseline drift in any lead

Drift in excess of 1 mm between baseline points (QRS onset) of any two successive complexes is excessive, often caused by inadequate skin preparation.

Excessive muscle tremor

Random noise in excess of 1/2mm may cause coding problems and requires a repeat recording. Muscle tremor is the involuntary muscle activity of a participant who is cold, tense, apprehensive, or uncomfortable. For this reason a clear explanation of the electrocardiogram test, reassurance, and covering the participant with a robe, sheet or blanket are helpful.

Electrodes falling off or poor electrode-skin contact

This is particularly common when electrodes are placed on hairy or loose skin. Here are some precautions to consider when connecting the participant:

- * Part the hair before attaching the electrode.
- * Lay a towel across the electrodes to prevent the weight of the cables from tugging at the electrode. You may have to reposition the electrode slightly.
- * It may be necessary to tape down an electrode.

Excessive 60 Hz noise

60 Hz noise is often associated with poor skin-electrode contact, participant is not relaxed, or unfavorable recording location with interference from nearby equipment. The technician should seek the source. (Watches, eye glasses, rings or bracelets do not cause interference).

C.3.2 ALERTS (See page C-13)

Review the ECG for abnormalities. If any of the following alerts exist, seek appropriate medical opinion to refer the participant:

- Atrial fibrillation/flutter
- Supraventricular tachycardia
- Sustained ventricular tachycardia
- Acute myocardial infarction
- Prolonged sinus arrest (>3 seconds)
- Mobitz 2 AV block
- Third degree AV block
- Marked sinus bradycardia (<40 beats per minute)

C.4 **Mailing ECGs (See page C-20)**

Mail the original ECGs once each week directly to the Minnesota ECG Center. Fill in the shipping log (Appendix C.3) being careful to transcribe the ID accurately. Send the original shipping log and the ECGs to:

- ECG Coding Center
- University of Minnesota, Division of Epidemiology
- 1300 South 2nd Street
- Suite 300
- Minneapolis, MN 55454

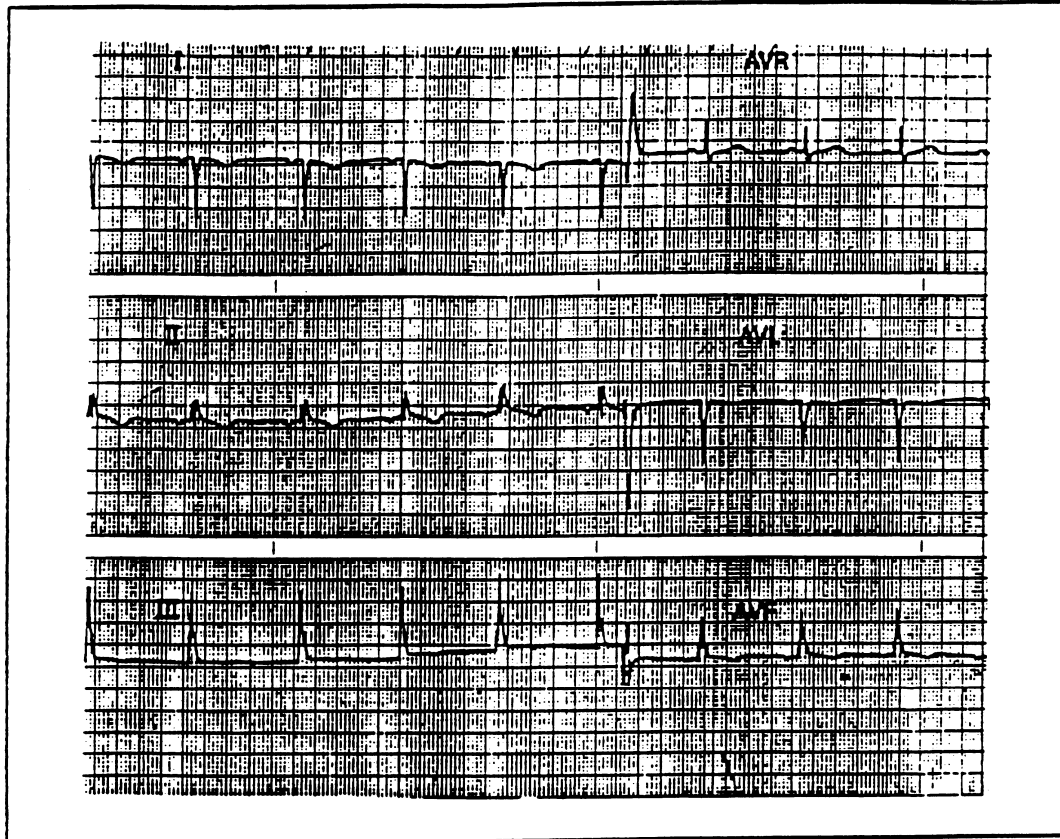
Address labels for the Minnesota ECG Center will be provided to you, and additional labels are available from the Clinical Trials Center.

IF YOU HAVE QUESTIONS ON ECG RECORDING AND MAILING, PLEASE CALL MARSHA MCDONALD AT THE ECG CENTER AT (612) 626-9677.

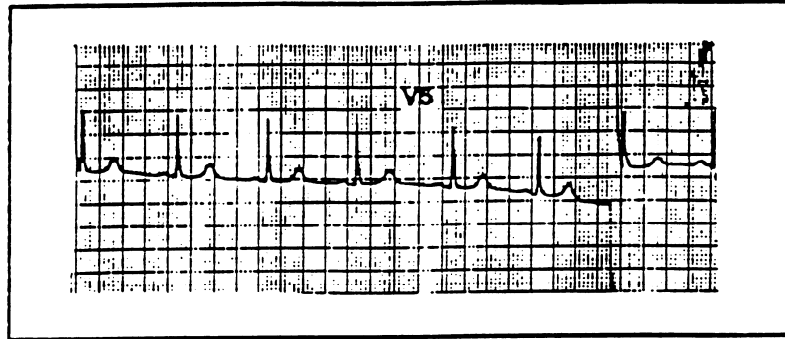
APPENDIX C.1

ECG QUALITY CHECKS

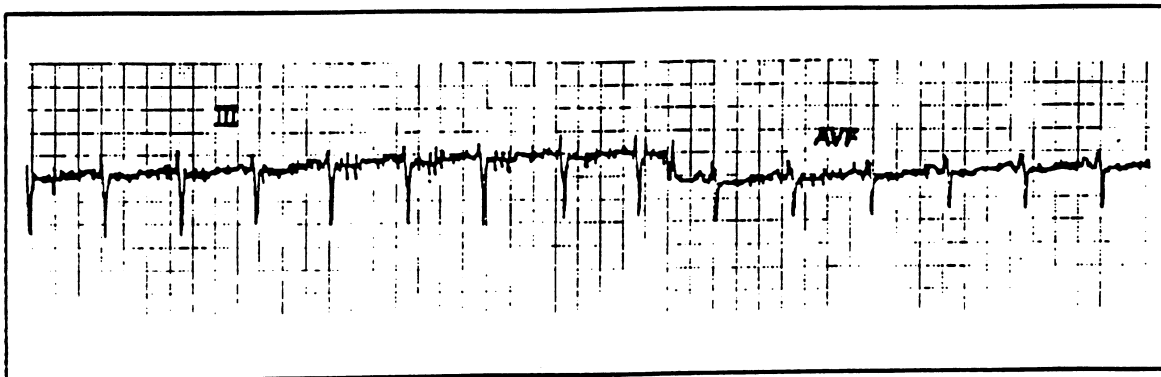
Right Arm/Left Arm Lead Switch



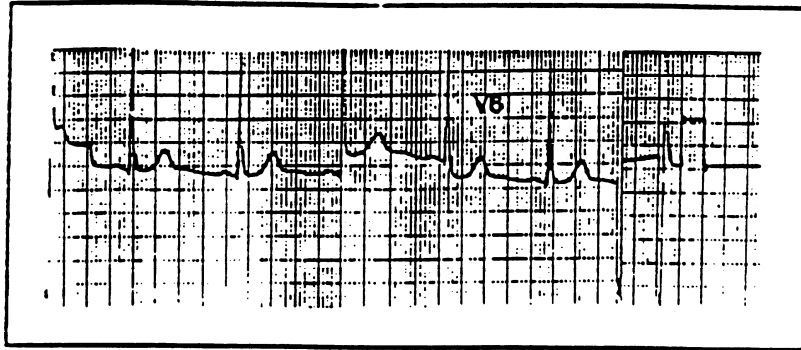
Unacceptable Overall Baseline Drift



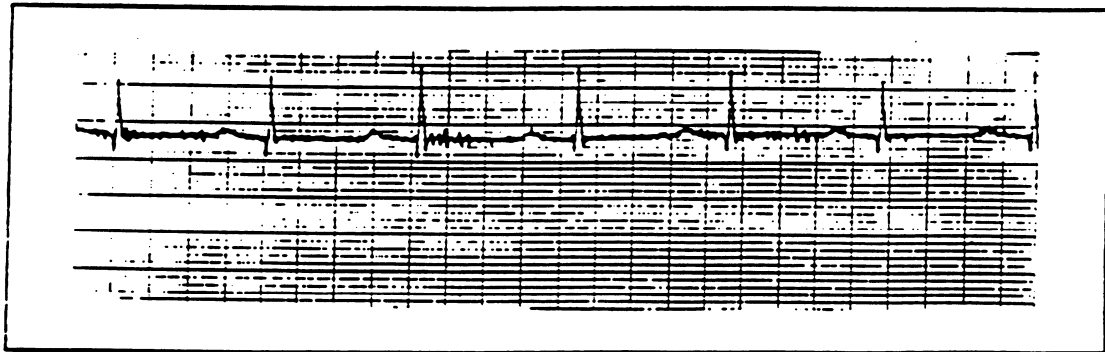
Unacceptable Noise Level



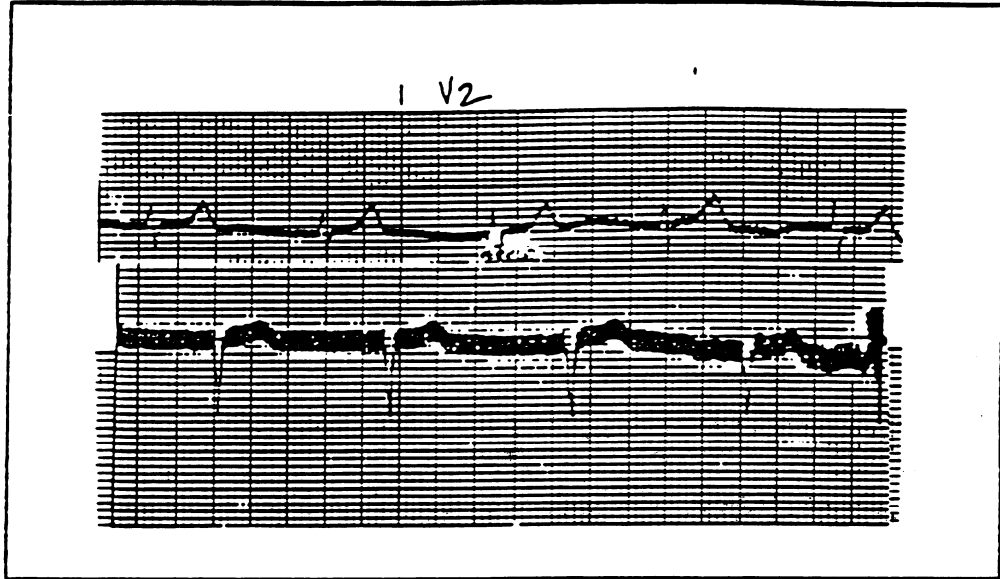
Unacceptable Beat-to-Beat Baseline Drift



Artifact Caused by Muscle Tremor



Sixty-Cycle Interference



APPENDIX C.2

ECG ALERTS

Atrial Fibrillation

ATRIAL FIBRILLATION
ABNORMAL ECG

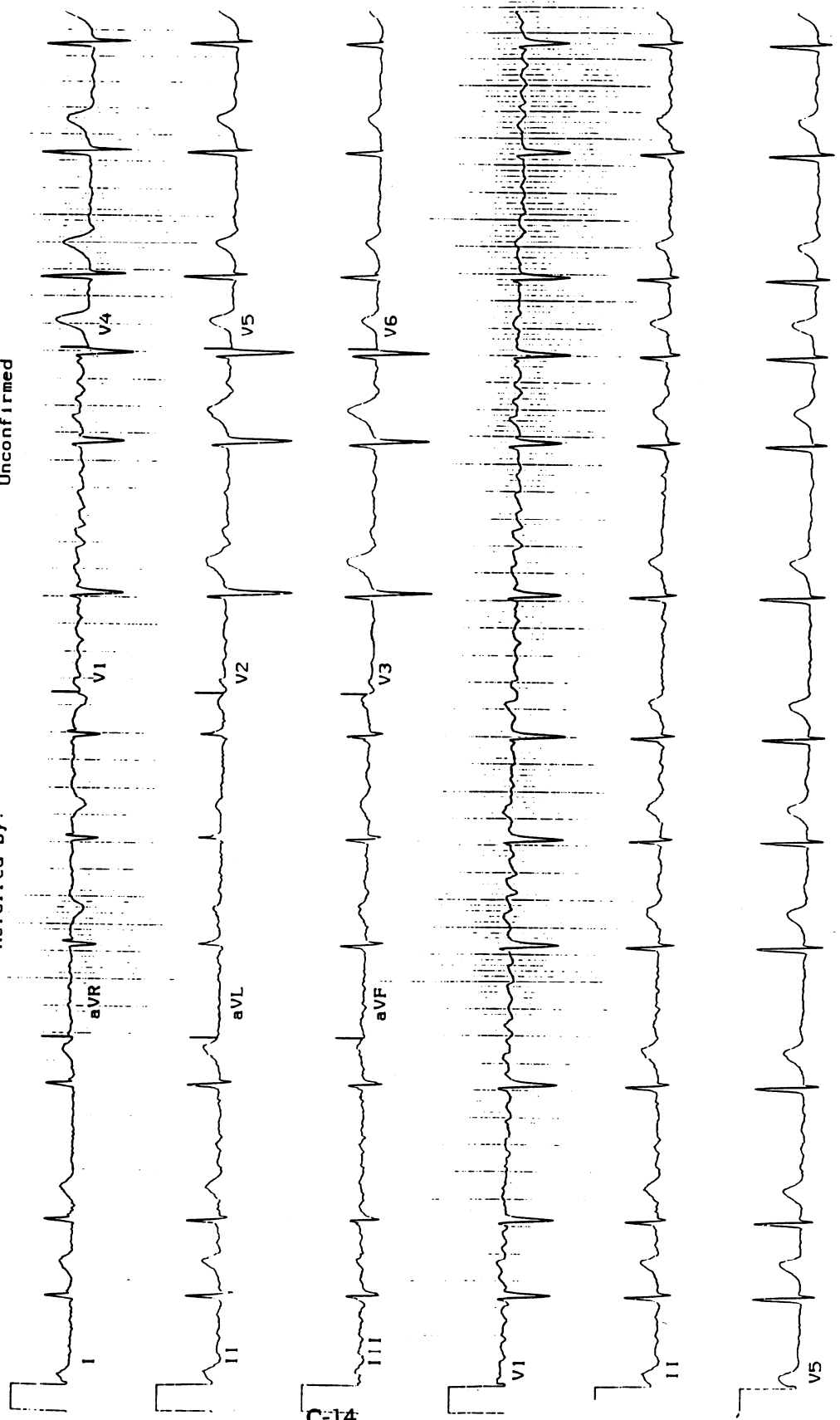
Med: Unknown
62yr 0cm 0kg
Sex: M Race: Unknown
Loc: 99 Room:

Vent. rate 72 BPM
PR interval * ms
QRS duration 84 ms
QT/QTc 368/398 ms
P-R-T axes * 11 28

25mm/s
10m V
100.
Pgm 004C
12SL v102

Referred by:

Unconfirmed

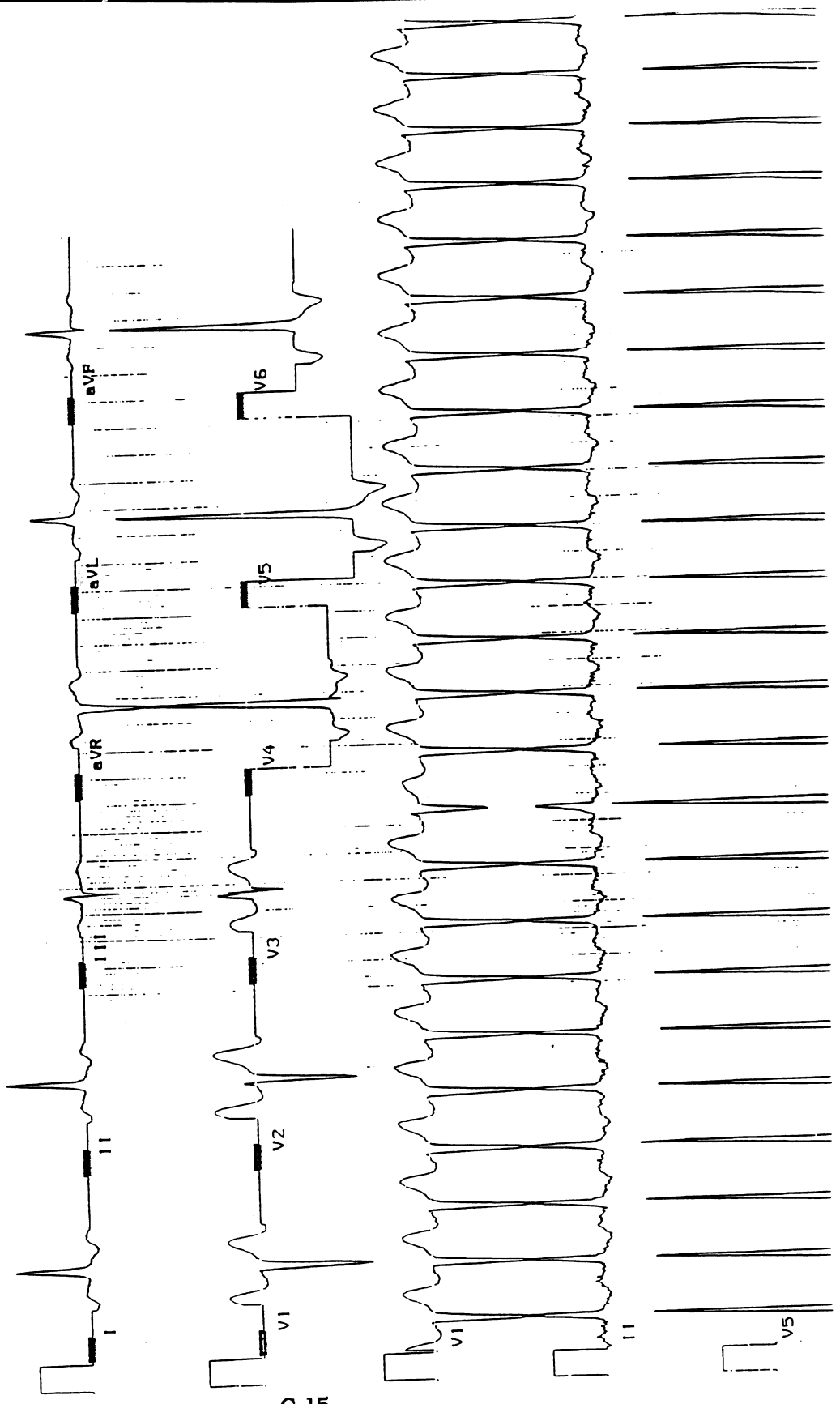


SINUS TACHYCARDIA WITH 1ST DEGREE AV BLOCK WITH OCCASIONAL PREMATURE VENTRICULAR COMPLEXES
 RIGHT ATRIAL ENLARGEMENT
 LEFT VENTRICULAR HYPERTROPHY WITH REPOLARIZATION ABNORMALITY
 ABNORMAL ECG

Tachycardia ≥ 140 bpm

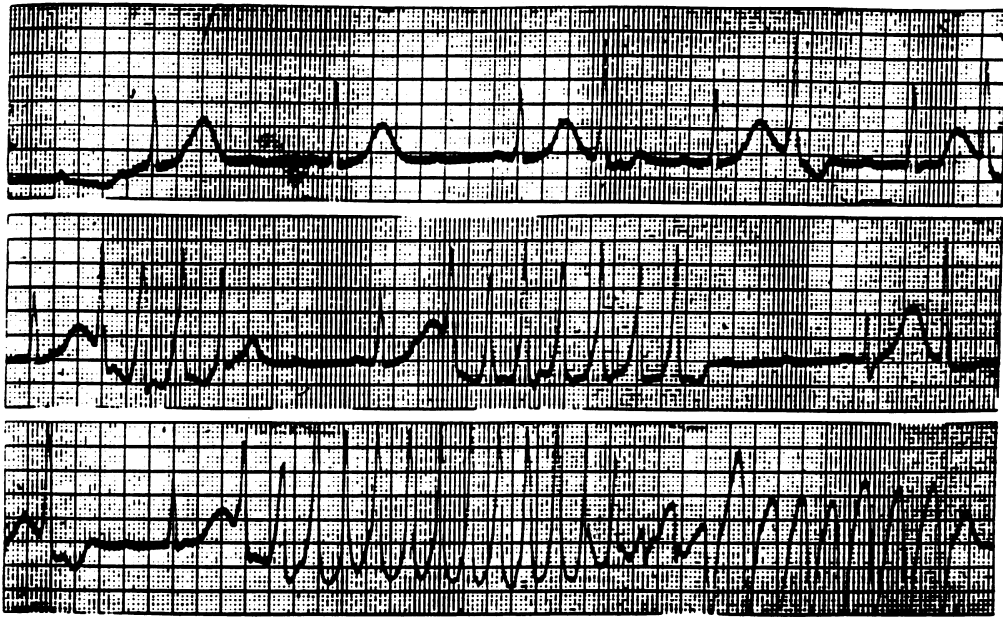
Med: 84yr Ht: Wt:
 Sex: M Race: Cauc
 Loc: 55 Room: 524
 Vent. rate 142 BPH
 PR interval 228 ms
 QRS duration 100 ms
 QT/QTc 300/460 ms
 P-R-T axes 35 22 182

Unconfirmed

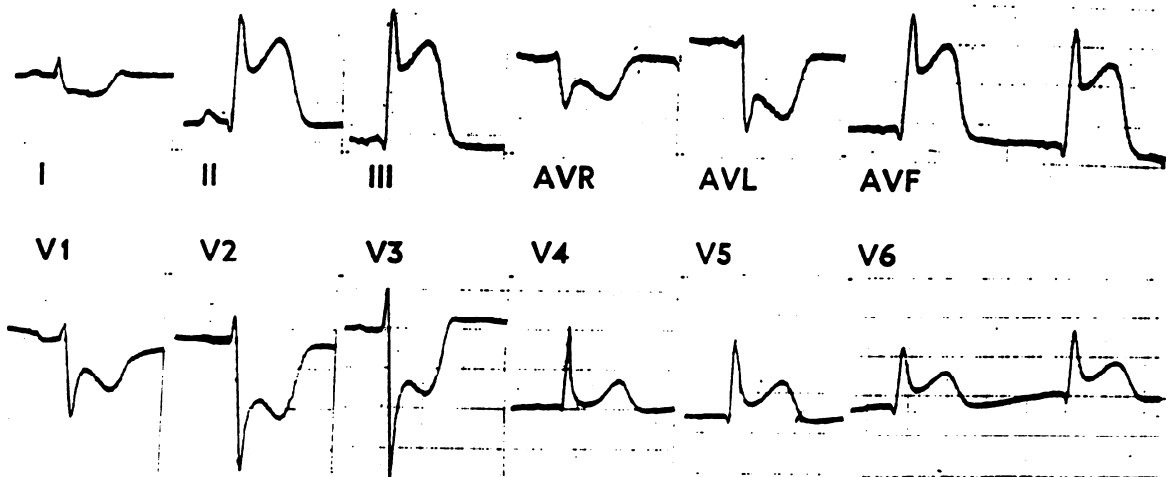


C-15

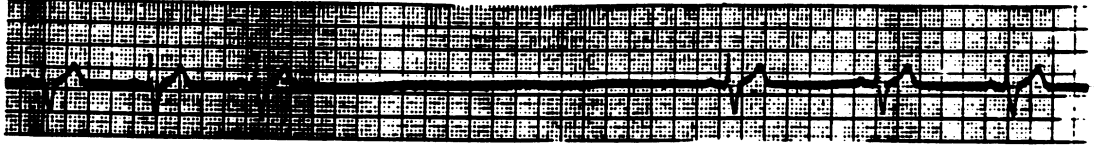
Ventricular Tachycardia



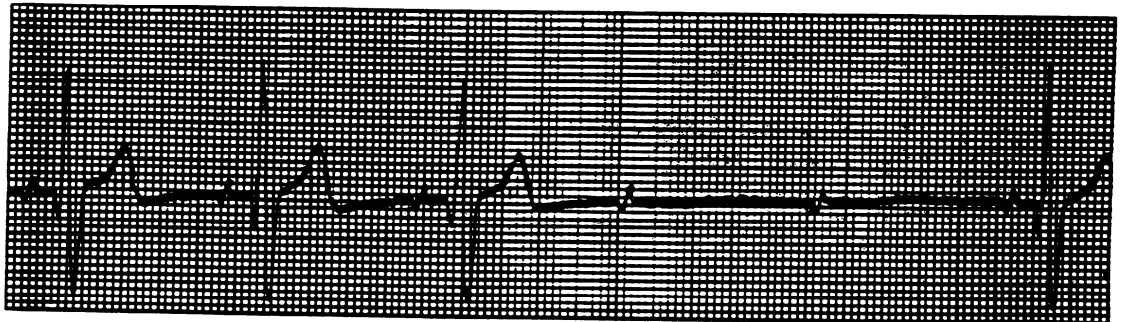
Acute MI



Sinus Arrest (>3 Seconds)



Mobitz 2 Block



Z5
 10mm/mV
 100Hz
 Pgm 004C
 125L v104

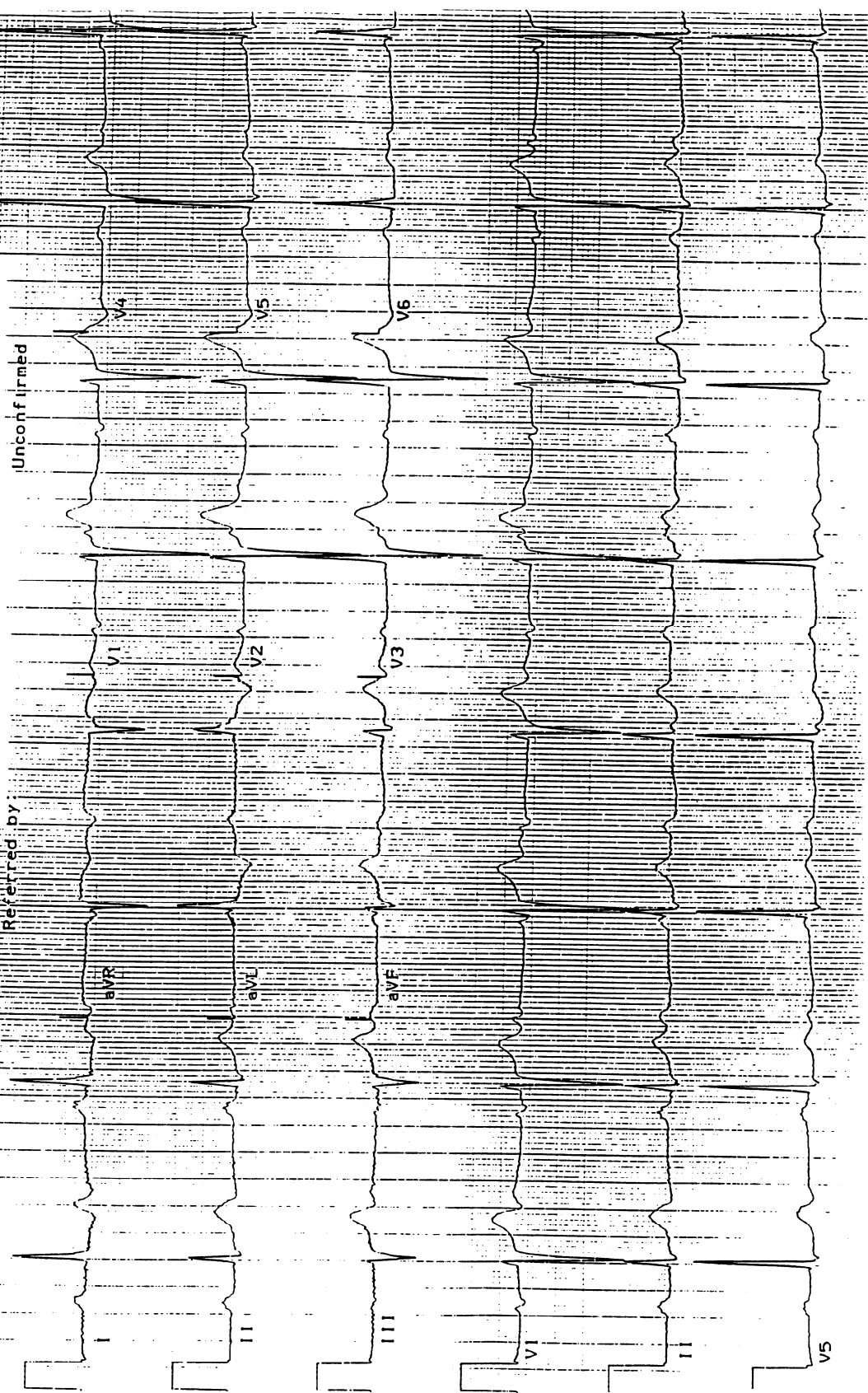
Med: Unknown
 99yr
 Sex: M
 Loc: 99
 Vent. rate: 100
 PR interval: *
 QRS duration: 16
 QT/QTc: 480/416
 P-R-T axes: * 2.09

Dec
 Oxs
 Unknown
 Room:
 BP: 100/100
 46 BPM
 * ms
 ms
 ms
 * 2.09

NORMAL SINUS RHYTHM WITH COMPLETE HEART BLOCK
 NONSPECIFIC INTRAVENTRICULAR CONDUCTION DELAY
 LEFT VENTRICULAR HYPERTROPHY WITH REPOLARIZATION ABNORMALITY
 ABNORMAL ECG

Third Degree AV Block

Referred by: Unconfirmed



Sinus Bradycardia

MARKED SINUS BRADYCARDIA
ABNORMAL ECG

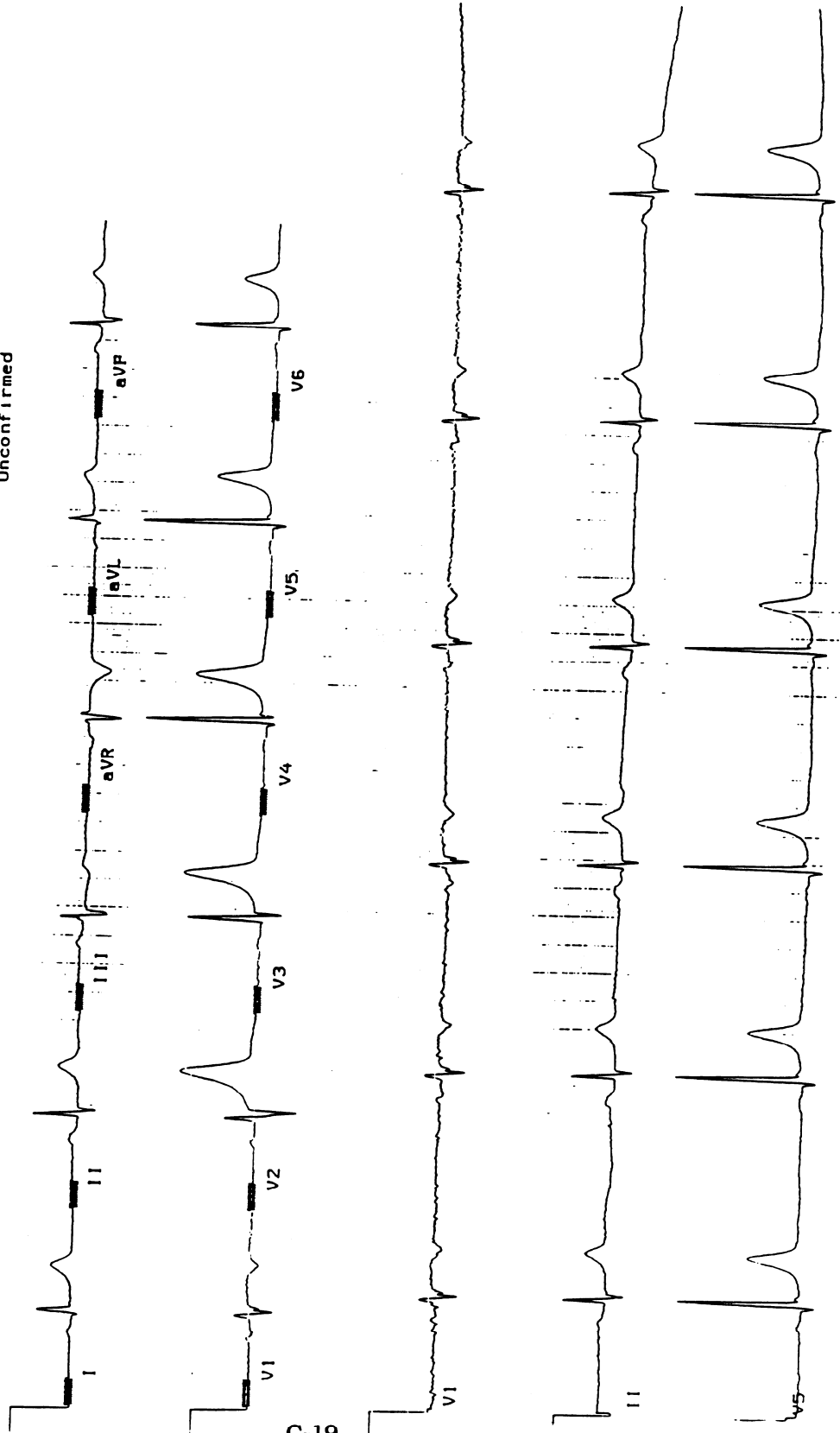
ID

1150
10mm
100Hz
Pgm 001AX1
125Ltm v104

Vent. rate 38 BPM
PR interval 180 ms
QRS duration 100 ms
QT/QTc 556/435 ms
P-R-T axes 62 23 20

Referred by:

Unconfirmed



C-19

APPENDIX C.3

MAILING ECGs

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Division of Epidemiology
School of Public Health

Suite 300
1300 South Second Street
Minneapolis, MN 55454-1015
612-624-1818
Fax: 612-624-0315

ALLHAT Shipping Form Baseline ECGs Only

Date Shipped: _____ Prepared by: _____
(please print)

Total No. ECGs: _____ Telephone: _____

Box For Office Use Only
Shipment #
Date Rec'd:

Instructions:

Please complete this shipping form and include it with your ECG shipment to the Minnesota ECG Coding Center. Enter each patient ID, the date shipped, total ECGs in the shipment, the name of the person preparing the shipment and a phone number where he or she can be reached. Only accurate shipping forms will be accepted, others will be returned.

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C-21

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Division of Epidemiology
School of Public Health

Suite 300
1300 South Second Street
Minneapolis, MN 55454-1015
612-624-1818
Fax: 612-624-0315

ALLHAT Shipping Form Follow-Up ECGs Only

Date Shipped: _____ Prepared by: _____
(please print)

Total No. ECGs: _____ Telephone: _____

Box For Office Use Only
Shipment #
Date Rec'd:

Instructions:

Please complete this shipping form and include it with your ECG shipment to the Minnesota ECG Coding Center. Enter each patient ID, the date shipped, total ECGs in the shipment, the name of the person preparing the shipment and a phone number where he or she can be reached. Only accurate shipping forms will be accepted, others will be returned.

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APPENDIX D

CENTRAL LABORATORY PROCEDURES

Contact the ALLHAT Central Laboratory by phone or fax if there are any questions or problems regarding laboratory procedures or ALLHAT results reports:

Telephone: 612-273-3645

Fax: 612-273-3489

D.1 Preparation

D.1.1 Laboratory Supplies

The Central Laboratory will provide a new ALLHAT site with an initial shipment of laboratory supplies once the site is authorized to begin randomizing participants. An initial shipment contains blood collection supplies, shipping supplies and Central Laboratory forms. These supplies will be shipped in bulk to be organized as needed by the clinic staff.

Copies of the Laboratory Supply Reorder Form (see page D-14) are included in the initial shipment of laboratory supplies. When a site's stock of any of the laboratory supplies begins to run low, clinic staff should submit a Laboratory Supply Reorder Form to the Central Laboratory. This form may be included in a shipment of blood samples to the Central Laboratory, mailed or faxed directly to the Central Laboratory. Always order well in advance of need, allowing 7-10 working days for the order to arrive after the request is received at the Central Laboratory. Supply orders for domestic ALLHAT sites are shipped via UPS Ground Service. Supply orders for Canada and Puerto Rico are shipped via Federal Express.

D.1.2 Participant Contact

Since ALLHAT depends upon the continued follow-up of each participant, every effort must be made to make the entire procedure as easy and painless as possible for him or her. The best way to achieve this is for the technician to be thoroughly knowledgeable about all aspects of the blood collection and processing procedures. All blood collections for ALLHAT involve collecting only one tube of blood. When completely filled the tube contains 7 mL of whole blood.

D.1.3 ALLHAT Lab ID Labels and Laboratory Test Request Form

Referring to the ALLHAT participant's visit schedule, determine whether blood needs to be collected at this ALLHAT visit. Use Laboratory ID labels (Lab Visit #:__ __) provided by the Clinical Trials Center (CTC), one to label the Test Request Form and the other to label the blood collection tube.

Write the ALLHAT visit number and the collection date on the labels intended for the ALLHAT participant. (Remember that the "Lab Visit #" is always the same as the ALLHAT Visit #.) Affix one of the Lab ID labels to the Test Request Form in the space provided (see pages D-15 and D-16). Keep the other Lab ID label for the participant close at hand so the blood collection tube can be labeled immediately after collection.

Complete the remaining information on the Test Request Form: date and time of collection and the number of hours elapsed since last food was ingested by the participant ('hours since last food'). Record 'hours since last food' at every lab visit whether or not the participant is fasting. If fasting status is unknown, write 'NA' in this field. Referring again to the participant's visit schedule, determine which battery of tests is required (e.g., ALL01, ALL02, etc.) at this visit, and check the appropriate battery or batteries on the Test Request

Form. It is only necessary to collect a single tube of blood, even if more than one test battery is ordered, provided the tube is adequately filled.

At Visit 2 (ALLHAT randomization visit):

Use the generic ALLHAT Laboratory ID labels printed with the ALLHAT ID number that the CTC has assigned to the participant and the words ‘Visit 2’. Clearly print the participant’s acrostic and the date drawn on these labels. The test battery ordered at Visit 2 is ALL01. (Canadian sites order the CALL01 test battery.)

At follow-up visits:

Use the labels provided by the CTC printed with both the participant’s ALLHAT ID number and acrostic. Write the ALLHAT visit number (Lab Visit #: __ __) and the date drawn on these labels. **The ‘Lab Visit #’ is always the same as the ALLHAT Visit #.**

D.2 Venipuncture

D.2.1 Blood Collection Supplies

Before performing the blood collection, make sure all supplies and labels are arranged in a convenient fashion in the venipuncture area and in the specimen processing area. The supplies needed for blood collection are as follows:

1	Plastic double-gel serum separator blood collection tube* <i>(Note: manufacturer does not guarantee vacuum or gel component beyond expiration date)</i>
1	sterile, disposable 21-gauge needle
1	plastic blood collection tube guide
1	pair disposable gloves
1	tourniquet
1	alcohol wipe
1	gauze pad
1	bandage (‘Band-Aid’)
1	ALLHAT Central Laboratory Test Request Form
2	ALLHAT Participant Laboratory ID labels (Lab Visit #: __ __)

* This blood collection tube is specially designed for transport. Do not substitute a glass single-gel serum separator tube. If a glass tube must be used, remove the serum after centrifugation to a plastic vial for shipment (see Section D.3.2).

DO NOT HAVE THE PARTICIPANT MAKE A FIST IN THE HAND OF THE ARM FROM WHICH BLOOD IS TO BE DRAWN. Clenching the fist during venipuncture may cause fluctuations in the potassium result.

Smelling salts, ice packs and washcloths should be readily available in the specimen collection area. Observe the patient during and after blood collection for signs or complaint of feeling faint during the blood draw.

Perform the venipuncture, allowing the collection tube to fill completely with blood. Release the tourniquet, remove the filled tube from the plastic tube guide and gently invert it five times—do not shake the tube. Remove the needle from the patient’s arm and immediately apply pressure to the site until bleeding stops, then apply a bandage to the patient’s arm.

D.3 Blood Processing

D.3.1 Immediate Processing

Handle all specimens as potentially infectious for laboratory workers and adhere to all OSHA rules regarding collection and processing of laboratory specimens.

Label the collection tube immediately after collection using a completed Laboratory ID label (Lab Visit #: __ __) for the respective ALLHAT participant. If not already completed, record the remaining information on the Test Request Form: date and time of collection and the number of hours elapsed since last food was ingested ('hours since last food'). Record 'hours since last food' at each lab visit whether or not the participant is fasting. If fasting status is unknown, write 'NA' in this field.

THE COLLECTED BLOOD MUST BE ALLOWED TO CLOT FOR A MINIMUM OF 30 MINUTES AND NO MORE THAN 45 MINUTES PRIOR TO CENTRIFUGATION. Keep the tube upright at room temperature for at least 30 minutes. If less than 30 minutes elapses, the specimen may clot during subsequent centrifugation, limiting the yield of serum from the tube. If the tube is allowed to sit at room temperature for more than 45 minutes, the red cells will begin to break down glucose in the serum and to leak potassium, thus affecting the laboratory measurement of these analytes.

D.3.2 Centrifugation

After 30-45 minutes has elapsed, place the filled blood collection tube into the centrifuge. Balance the centrifuge with another specimen or a water-filled tube of similar size. Centrifuge the samples at $1000-3000 \times g$ for 15 minutes. Consult the centrifuge's operating manual for the appropriate RPM setting to achieve the desired centrifugal force (at least $1000 \times g$).

Examine the tube after centrifugation to be sure that the serum separator gel is clearly positioned between the cells and serum – you should observe no seepage of cells at the gel/serum interface. Red cells in the serum may affect the potassium result even if no hemolysis is observed. Re-centrifuge the tube if necessary. After centrifugation is complete, store the tubes upright in the **refrigerator** until shipment to the ALLHAT Central Laboratory.

The plastic double-gel serum separator blood collection tube used for ALLHAT is specially designed for transport. Therefore, it is not necessary to remove the serum to another container for shipment. However, if desired, after centrifugation you may pipet the serum from the clot tube into a plastic vial labeled with participant's ALLHAT Laboratory ID label and send this to the Central Laboratory for analysis. (The Central Lab does not provide plastic vials for this purpose.) If the blood specimen is that collected at Visit 2, send the clot tube also (with an ALLHAT Laboratory ID label affixed) along with the serum vial in the shipment to the Central Laboratory.

D.4 Specimen Storage and Shipping

D.4.1 Specimen Storage Prior to Shipment

Specimens may be shipped on the date of collection or centrifuged as directed and then stored refrigerated for up to 5 days (maximum) before shipping. Specimens may be shipped Monday through Thursday only. Specimens collected on Fridays should be centrifuged as directed, refrigerated and then shipped the following Monday. **Do not ship on Fridays** except by prior arrangement with the Central Laboratory. **Do not ship on the day before a holiday.** Again, centrifuge the specimen as directed and store refrigerated at the site until shipment on the first weekday (Monday through Thursday) following the holiday.

D.4.2 Packaging Blood Specimens for Shipment

Shipping supplies are included in the initial shipment of laboratory supplies sent to each site, to be reordered as needed. The shipping components are as follows:

Styrofoam mailing box (foam box)

Cardboard sleeve with biohazard label (contains foam box)

Refrigerant pack – one or more refrigerant packs should be stored frozen ready for shipment, preferable inside an open styrofoam mailing box to avoid later difficulty in fitting the rigid pack and specimens into the mailing box

Plastic zip-lock bag

Absorbent material (paper towel or wadding)

To package specimens for shipment:

Wrap a sheet of absorbent wadding or paper towel around up to five centrifuged specimen collection tubes and put them into a zip-lock bag and seal.

Place the bagged specimens into the styrofoam box with the frozen refrigerant pack in place. If necessary, the edges of the frozen refrigerant pack may be placed under running water to thaw enough to facilitate fitting the pack into the box. Dry the pack thoroughly before inserting it into the foam box.

Place the lid on the styrofoam box and insert it into the cardboard sleeve. Fold and slide the completed ALLHAT Central Laboratory Test Request Form(s), one for each specimen included in the shipment, into the cardboard sleeve.

Close the cardboard sleeve (DO NOT SEAL WITH TAPE) and refrigerate until ready for shipment. Further shipping instructions follow.

D.4.3 Courier Service

Specimens are shipped to the ALLHAT Central Laboratory via Federal Express 'FedEx Priority Overnight' or 'FedEx International Priority' service. This service is provided at no charge to the ALLHAT clinic sites, dependent on proper completion of the FedEx airbill. If Federal Express does not provide pickup service in your area, alert the Central Laboratory as soon as possible. Arrangements can be made for the site to use an alternate courier service or to use postage-paid (USPS) shipping materials.

The ALLHAT Central Laboratory's FedEx account number is **1706-9868-1**. This account number is to be used only for ALLHAT specimen shipments to the Central Laboratory. The FedEx shipping address for the ALLHAT Central Laboratory is:

JEAN BUCKSA (612-273-3645) UNIV MN/ALLHAT CENTRAL LAB 420 DELAWARE ST SE RM D297 MINNEAPOLIS, MN 55455

The Central Laboratory will provide sites with the following Federal Express supplies as part of the initial shipment of laboratory supplies:

FedEx diagnostic specimen envelopes

Airbill pouches

Pre-printed FedEx airbills or international air waybills

FedEx Commercial Invoice forms (for sites in Canada and Puerto Rico)

The Federal Express airbills provided to ALLHAT sites have the ALLHAT Central Laboratory’s address pre-printed in the Recipient’s field as well as some other required information (see sample airbills in the next section). To avoid omissions or mistakes in airbill completion, sites are encouraged to reorder pre-printed airbills from the Central Laboratory as needed. All FedEx supplies may be reordered using the ALLHAT Central Laboratory Supply Reorder Form.

D.4.4 Completing the FedEx Airbill (Domestic)

If the FedEx airbill accompanying an ALLHAT shipment is improperly completed, the site may receive a FedEx Problem Encounter Form by FAX from the Central Laboratory (see page D-17). To complete the Federal Express airbill consult the sample airbill described below and the sample on the next page.

Field #1	(‘From’) - Print your clinic site’s address (sender’s address), phone number and the date of shipment
Field #2	(‘Your Internal Billing Reference Information’) – skip Field #2 unless your institution requires this information
Field #3	(‘To’) - The ALLHAT Central Laboratory’s address (recipient’s address) and phone number are pre-printed in this field
Field #4a	(‘Service’) - Check ‘FedEx Priority Overnight’ only – do not check any other option(s)
Field #4b	(‘Express Freight Service’) - Skip Field #4b
Field #5	(‘Packaging’) - Check ‘Other Pkg.’ When using FedEx Diagnostic Specimen Envelope
Field #6	(Special Handling – Does this shipment contain dangerous goods?) – Check ‘No’ . ALLHAT specimen shipments are <u>not</u> considered ‘Dangerous Goods’.
Field #7	(Payment) – Check ‘Recipient’ and write the ALLHAT Central Laboratory’s FedEx account number (1706-9868-1) in the space below it. Record number of Total Packages (1) and Total Weight of the shipment (very important!). It is the shipper’s responsibility to record accurate weight to <u>the nearest whole pound</u> . Do <u>not</u> write units after the package weight (i.e., LBS or lbs); do <u>not</u> record weight using symbols such as ‘<’.
Field #8	(Release Signature) – Skip Field #8.

Sample USA Airbill (domestic):

FedEx USA Airbill FedEx Tracking Number **808822283490**

1 From (please print and press hard)
 Date _____ Sender's FedEx Account Number _____
 Sender's Name _____ Phone (____) _____
 Company _____
 Address _____ Dept./Floor/Suite/Room _____
 City _____ State _____ ZIP _____

2 Your Internal Billing Reference Information
(Optional) First 24 characters will appear on invoice

3 To (please print and press hard)
 Recipient's Name JEAN RUCKSA Phone (612) 273-3645
 Company UNIV MN/ALLHAT CENTRAL LAB Check here if residence
 Address 420 DELAWARE ST. SE RM L297 (We cannot deliver to PO Boxes or P.O. ZIP Codes) Dept./Floor/Suite/Room _____
 City MINNEAPOLIS State MN ZIP 55455 Extra Charge: Not available in all territories

4 Delivery Options
 Hold **Monday** (Not available with FedEx First Overnight)
 Hold **Tuesday** (Available for FedEx Priority Overnight and FedEx 2Day only)
 Hold **Wednesday** (Available at all locations)
 Hold **Thursday** (Available for FedEx Priority Overnight and FedEx 2Day only)
 Hold **Friday** (Available for FedEx Priority Overnight and FedEx 2Day only)
 Hold **Saturday** (Available for FedEx Priority Overnight and FedEx 2Day only)
 Hold **Sunday** (Available for FedEx Priority Overnight only)

5 Service Conditions, Declared Value, and Limit of Liability - By using this Airbill, you agree to the service conditions in our current Service Guide or U.S. Government Service Guide. Both are available on request. **SEE BACK OF SENDER'S COPY OF THIS AIRBILL FOR INFORMATION AND ADDITIONAL TERMS.** We will not be responsible for any claim in excess of \$500 per package whether the result of loss, damage, or delay, non-delivery, misdelivery, or misrouting, unless you declare a higher value, pay an additional charge, and document your actual loss in a timely manner. Your right to recover from us for any loss includes intrinsic value of the package, loss of value, interest, profit, attorney's fees, costs, and other forms of damage, whether direct, incidental, consequential, or special, and is limited to the greater of \$500 or the declared value but cannot exceed actual documented loss. The maximum declared value for any FedEx Letter and FedEx Pack is \$500. Federal Express may, upon your request, and with some limitations, refund all transportation charges paid. See the FedEx Service Guide for further details.

Questions?
Call 1-800-Go-FedEx® (800)463-3339

The World On Time

Form ID No. **0210** **SNA12** **Senders Copy**

4a Express Package Service Packages under 150 lbs. Delivery commitment may be later in some areas.
 FedEx Priority Overnight (Next business day) **FedEx Standard Overnight** (Next business day)
 FedEx First Overnight (Earliest next business morning delivery to select locations) (Next business day)
 FedEx 2Day (Second business day) **FedEx Express Saver** (Third business day)
FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service Packages over 150 lbs. Delivery commitment may be later in some areas.
 FedEx Overnight Freight (Next business day) **FedEx 2Day Freight** (Second business day) **FedEx Express Saver Freight** (Up to 3 business days)
(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging FedEx Letter FedEx Pack FedEx Box FedEx Tube **Other** Other (Specify)
Declared value limit \$500.

6 Special Handling (When box must be checked)
 Does this shipment contain dangerous goods? No Yes (If "Yes" answer "Yes" or "No" and "Special Handling" required)
 Dry Ice (Dry Ice, 9, UN 1845) Cargo Aircraft Only (Dangerous Goods cannot be shipped in FedEx packaging)

7 Payment
 Bill to: Sender Recipient Third Party Credit Card Cash/Check
(Enter FedEx Account No. or Credit Card No. below)
 FedEx Account No. 1706-9848-1 Exp. Date _____
 Credit Card No. _____

Total Packages	Total Weight	Total Declared Value*	Total Charges
		\$ 00	\$

*When declaring a value higher than \$500 per shipment, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY section for further information.

8 Release Signature
 Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

321 WCS 0998 Rev. Date 7/98 Fed. #133222 ©1994-98 FedEx PRINTED IN U.S.A.

0075460152

RETAIN THIS COPY FOR YOUR RECORDS

To complete packaging of the shipment:

After completion of the airbill, keep the Sender's copy (pink copy) for your records – the package tracking number printed on the airbill is necessary to track a delayed or lost shipment. Insert the completed airbill into a self-stick airbill pouch and affix it firmly to the Diagnostic Specimen Envelope. Place the refrigerated shipping box containing the specimens into the Diagnostic Specimen Envelope and seal. If more than five specimens are to be sent at one time, a second or even a third shipping box containing up to five additional specimens each can be included in the same Diagnostic Specimen Envelope.

D.4.5 Completing the FedEx Int'l Air Waybill and Commercial Invoice (Canada and Puerto Rico)

If the FedEx international air waybill accompanying an ALLHAT shipment is improperly completed, the site may receive a FedEx Problem Encounter Form by fax from the Central Laboratory. To complete the Federal Express international air waybill consult the sample waybill described below and the sample on the next page.

Field #1	(Sender's address) - Print your clinic site's address (sender's address), phone number and the date of shipment
Field #2	(Your Internal Billing Reference Information) – skip Field #2 unless your institution requires this information
Field #3	(Recipient's address) – The ALLHAT Central Laboratory's address (recipient's address) and phone number are pre-printed in this field (Recipient's I.D. number for Customs purposes): <u>Canadian sites only</u> : Record the University of Minnesota's Export-Import Number (EIN#): 400-6600-7513
Field #4	(Shipment information) – Record the numeral '1' for Total Packages. Enter weight of package to <u>the nearest whole pound</u> in the Total Weight Field. Do <u>not</u> write units after the package weight (i.e., LBS or lbs); do <u>not</u> record weight using symbols such as '<'. The next field (Commodity Description – see sample air waybill) requires the shipper to provide a complete description of contents of the package and record the country of manufacture (USA). In the fields for Total Declared Value for Carriage and Total Declared Value for Customs, enter '\$2.00' (Currency: US) for each styrofoam box included in the shipment.
Field #5	(Broker Selection) – Skip Field #5
Field #6	(Service) – Check ' FedEx International Priority ' only – do not check any other option(s)
Field #7	(Packaging) – Check Box 3 ' Other Packaging ' when using FedEx Diagnostic Specimen Envelope
Field #8	(Special Handling – Does this shipment contain dangerous goods?) – Check ' No '. ALLHAT specimen shipments are <u>not</u> considered 'Dangerous Goods'.
Field #9a	(Payment-Duties and Taxes Paid By) – Check ' Recipient ' and write the ALLHAT Central Laboratory's FedEx account number (1706-9868-1) in the space below it.
Field #9b	(Payment-Transportation Charges Paid By) – Check ' Recipient ' and write the ALLHAT Central Laboratory's FedEx account number (1706-9868-1) in the space below it.
Field #10	(Required Signature) – Signature of sender is <u>required</u>

A **Commercial Invoice** (FedEx form M-1054) should accompany every Federal Express International Air Waybill for FedEx International Priority shipments from Canada or Puerto Rico to the United States. Though a Commercial Invoice is not generally required for shipping diagnostic specimens of no commercial value, Federal Express suggests that this form be included as it may facilitate passage of the shipment through US Customs. The following information must be provided:

1. International air waybill number from upper right corner of International Air Waybill
2. Date of exportation
3. Shipper/Exported (complete name and address of Sender)
4. Consignee (complete name and address of Recipient)
5. Country of Export (Canada or Puerto Rico)
6. Country of Manufacture (USA)
7. Country of Ultimate Destination (USA)
8. Number of packages
9. Type of packaging (styrofoam container)
10. Full Description of Goods (information must match exactly the description provided in 'Commodity Description' in Field 4 of the International Air Waybill)
11. Quantity (volume of blood)
12. Unit of Measure (in milliliters)
13. Weight (of pkg)
14. Unit value, Total Value and Total Invoice Value (record value in US funds in all three fields - \$2.00 per styrofoam container included in the shipment)
15. Total number of packages and Total weight
16. Signature of Shipper/Exporter and Date

A sample Commercial Invoice may be found on the next page.

To complete packaging of the shipment:

After completion of the International Air Waybill, keep the Sender's copy (pink copy) for your records – the package tracking number printed on the airbill is necessary to track a delayed or lost shipment. Insert the air waybill and commercial invoice into a self-stick air waybill pouch and affix it firmly to the Diagnostic Specimen Envelope. Place the refrigerated shipping box containing the specimens into the Diagnostic Specimen Envelope and seal. If more than five specimens are to be sent at one time, a second or even a third shipping box containing up to five additional specimens each can be included in the same Diagnostic Specimen Envelope.

Sample commercial invoice

COMPANY NAME

COMPANY ADDRESS

COMMERCIAL INVOICE

INTERNATIONAL
AIR WAYBILL NO.

400-6449-9503

(NOTE: All shipments must be
accompanied by a Federal Express
International Air Waybill.)

DATE OF EXPORTATION
7/5/96

EXPORT REFERENCES (i.e., order no., invoice no.)

SHIPPER/EXPORTER (complete name and address)

CONSIGNEE (complete name and address)

Jean Bucksa
UNIV MN/ALLHAT CENTRAL LAB
420 DELAWARE ST SE RM L275
MINNEAPOLIS, MN 55455-0288
USA

COUNTRY OF EXPORT
CANADA

IMPORTER — IF OTHER THAN CONSIGNEE
(complete name and address)

COUNTRY OF MANUFACTURE
USA

COUNTRY OF ULTIMATE DESTINATION
USA

MARKS/NOS.	NO. OF PKGS.	TYPE OF PACKAGING	FULL DESCRIPTION OF GOODS	QTY.	UNIT OF MEASURE	WEIGHT	UNIT VALUE	TOTAL VALUE
	1	styro foam container	15 mL fresh human blood; non-infectious; non-hazardous; on frozen 'blue ice' refrigerant pak; for research purposes only; EXTREMELY PERISHABLE-- DO NOT DELAY	15	mL	1 LB	\$ 2.00 US	\$ 2.00
						TOTAL WEIGHT		TOTAL INVOICE VALUE
						1.0 LB		\$ 2.00

SEE REVERSE SIDE FOR HELP WITH THE ABOVE SECTION

Check or
 F.O.B.
 C & F
 C.I.F.

THESE COMMODITIES ARE LICENSED FOR THE ULTIMATE DESTINATION SHOWN.
DIVERSION CONTRARY TO UNITED STATES LAW IS PROHIBITED.

I DECLARE ALL THE INFORMATION CONTAINED IN THIS INVOICE TO BE TRUE AND CORRECT.

SIGNATURE OF SHIPPER/EXPORTER (Type name and title and sign.) D-10

DATE Revised 1/99

D.4.6 Arranging for a FedEx Pickup

When an ALLHAT specimen shipment is ready to send to the Central Laboratory, contact Federal Express Customer Service to arrange for a pickup:

U.S. and Canada	800-463-3339 (1-800-GO-FEDEX)
Puerto Rico	787-793-9300

If a site cannot arrange its own FedEx pickups, contact the Central Laboratory to arrange for a ‘third party pickup’.

The FedEx shipping address for the ALLHAT Central Laboratory is:

JEAN BUCKSA (612-273-3645) UNIV MN/ALLHAT CENTRAL LAB 420 DELAWARE ST SE RM D297 MINNEAPOLIS, MN 55455

D.5 Specimen Receipt at the Central Laboratory

D.5.1 Shipment Receipt and Processing

The results reported to each ALLHAT clinic site depend on the quality of specimen received at the Central Laboratory. The site will be notified by phone or by fax (see page D-18) regarding problems encountered with the identification, condition or shipment of specimens. This form lists a number of common problems and suggested actions to be taken to avoid their recurrence.

Specimen conditions noted upon receipt in the laboratory and reported as part of the laboratory results are: specimen slightly hemolyzed, red cells present, specimen received at ambient temperature.

Note: slight hemolysis and/or red cells observed in the serum may affect the potassium result.

Blood must be recollected in the following situations: specimen moderately or grossly hemolyzed, blood collection tube received unlabelled, specimen too old for analysis, specimen received uncentrifuged or incompletely centrifuged, QNS for analysis (quantity not sufficient). When a blood collection is a redraw for an unsatisfactory specimen collected at a previous visit, write “**repeat collection**” on the request form.

D.6 Results Reporting

ALLHAT results are reported to ALLHAT sites by automatic fax beginning shortly after midnight on the day following analysis at the Central Laboratory. Results cannot be automatically faxed to machines that are turned off at night or to those that use an extension. Results will be mailed (USPS) to these sites as well as to sites without a fax machine. To ensure receipt of faxed laboratory results, always notify the Central Laboratory directly whenever there is a change in the site’s fax number or the person to whom the fax should be directed, even if the change is only temporary.

ALLHAT test battery results are reported in conventional units followed by the reference range for each analyte. Canadian sites receive results reported in both conventional and international (SI) units.

D.6.1 Alert Results

The Central Laboratory will phone the following **alert values** to the ALLHAT site coordinator. If unable to contact by phone, an Alert Results report (see page D-19) will be faxed to the site.

Potassium < 3.0 or > 6.0 mmol/L
 Glucose < 60 or > 400 mg/dL (< 3.33 or > 22.2 mmol/L)

D.6.2 Potassium Results

Note: Slight hemolysis and/or red cells observed in the serum may affect the potassium result.

Baseline battery

The potassium result reported from the blood collected at randomization will appear on the laboratory report in numeric form along with the following comment:

The ALLHAT normal reference range is 3.5-5.5 mmol/L.

And if the potassium result is more than 7.0 mmol/L, the additional comment will appear:

Potassium results over 7.0 mmol/L in patients with normal renal function are almost certainly artifacts of in vitro potassium release from cells. Such elevation may be observed if a blood specimen is not promptly and/or properly centrifuged. Please review centrifugation procedures with your staff.

Post-randomization batteries

Sites will be blinded to potassium results that fall within the ALLHAT normal reference range. The word '**Normal**' will appear on the lab report along with the comment:

Potassium result falls within 3.5 to 5.5 mmol/L.

However, when the potassium result falls outside of the ALLHAT normal reference range, the results will be reported as follows:

Potassium less than or equal to 3.1 mmol/L	Numeric result is reported with comment: Potassium result is significantly below ALLHAT reference range; recall patient immediately to have serum potassium rechecked locally
Potassium 3.2-3.4 mmol/L	Numeric result is reported with comment: Potassium result is below ALLHAT reference range; recheck locally at next normally scheduled clinic visit
Potassium 5.6 mmol/l or above	Numeric result is reported with comment: Potassium result is above ALLHAT reference range; recall participant immediately to have serum potassium rechecked locally
And if potassium is above 7.0 mmol/l	This additional comment will appear: Potassium results over 7.0 mmol/L in patients with normal renal function are almost certainly artifacts of in vitro potassium release from cells. Such elevation may be observed if a blood specimen is not promptly and/or properly centrifuged. Please review centrifugation procedures with your staff.

Potassium results falling outside the ALLHAT normal reference range are to be **rechecked locally**.

D.6.2.1 Delta Potassium Reporting

To monitor significant changes in serum potassium during ALLHAT participant follow-up, changes in potassium greater than 1.0 mmol/L (Potassium Change) and the number of days elapsed since the participant's last ALLHAT potassium was measured (Elapse Time) appear as part of the reported results.

D.6.3 Serum Alanine Transaminase (ALT)

Serum alanine transaminase (ALT) is always reported as a numeric result along with the ALLHAT reference range (ALLHAT reference range upper limit for ALT is 50 u/L). The ALT result is reported with an additional comment in the following circumstances:

ALT 101-150	Numeric result is reported with comment: Alert: ALT exceeds two times the ALLHAT normal reference range.
ALT 151+	Numeric result is reported with comment: Alert: ALT exceeds three times the ALLHAT normal reference range.

D.6.4 Lipid Results

ALLHAT participants should fast (12 hours optimum, 9 hours minimum) prior to blood collection for ALLHAT test batteries that include a lipid profile.

D.6.4.1 Lipid Eligibility

To alert the ALLHAT site that a participant may be eligible for randomization into the cholesterol-lowering part of the ALLHAT study, a comment associated with the LDL-cholesterol result may appear on the laboratory report received for the ALL01 test battery collected at Visit 2. When the LDL-cholesterol result falls within the range of **100-189 mg/dL**, it is reported with the following comment (ALL01 test battery only):

BASED ON THE LDL RESULT ALONE, THIS PARTICIPANT MAY BE
ELIGIBLE FOR THE LIPID LOWERING TRIAL.

D.6.4.2 Beta Quant

When the triglyceride result associated with the ALL02 test battery exceeds 400 mg/dL, a Beta Quant (lipoprotein ultracentrifugation) is automatically performed, provided the specimen received is a fasting specimen. If the blood is not a fasting specimen, the Central Lab cannot perform Beta Quant analysis. In this instance, the Central Laboratory will contact the ALLHAT site to request that a fasting specimen be drawn for the ALL02 test battery. When a blood collection is a redraw for a specimen collected at a previous visit, write “**repeat collection**” on the ALLHAT Test Request Form.

D.7 Questions or Problems

Contact the ALLHAT Central Laboratory by phone or fax if there are any questions or problems regarding laboratory procedures or ALLHAT results reports:

Telephone:	612-273-3645
Fax:	612-273-3489

COLLABORATIVE STUDIES CLINICAL LAB
ALLHAT Central Lab, RM L275 MAYO
420 DELAWARE STREET, S. E.
MINNEAPOLIS, MN 55455
PHONE: 612-273-3645
FAX: 612-273-3489

TO _____

Supplies Receiver Address
 (Return Address Label--please print)

ALLHAT site # : _____

Date: _____

SUPPLY REORDER FORM

Instructions: Complete the return address label located in the upper right corner of this page, providing the supplies receiver's name and complete address for your site. Please print clearly. Place a check mark next to each desired item below. This form may be enclosed with specimen shipments to the ALLHAT Central Laboratory or you may fax this form to the number listed above.

Please note that laboratory supply orders are shipped via UPS Ground Service (except Canada and PR). Please allow 7-10 working days for your order to arrive after your request is received at the Central Lab.

Forms:

- _____ ALLHAT Test Request forms (50) Canada site?
- _____ ALLHAT Supply Reorder forms (5)

Leave information within this box blank for Central Laboratory use. Date shipment sent to clinic _____ by _____
--

Blood Collection Supplies:

- _____ 21 gauge Vacutainer needles (100/box)
- _____ Vacutainer holder, reusable (20)
- _____ Vacutainer serum separator tube (50) *Do not use beyond expiration date printed on tubes--reorder as needed*
- _____ Alcohol swab (200/box)
- _____ Gauze pad (200/pkg)
- _____ Bandage (Band-Aid) (100/box)
- _____ Disposable gloves (100/box)
- _____ Tourniquet, reusable (10)

Shipping Supplies:

- _____ Styrofoam box with cardboard sleeve and refrigerant pack (10 assemblies)
- _____ Ziplock plastic bag (10)
- _____ Absorbent wadding (10 sheets)

Federal Express Shipping Supplies:

- _____ FedEx airbills (10) *Pre-printed with ALLHAT Central Lab address*
- _____ Int'l air waybills (Canada or PR only) (10)
- _____ Commercial Invoice Forms (Canada or PR only) (10)
- _____ FedEx Diagnostic Specimen Envelopes (10)
- _____ FedEx airbill pouches (10)

COLLABORATIVE STUDIES CLINICAL LABORATORY
ALLHAT Central Lab, Rm L275 MAYO
420 DELAWARE STREET, S. E.
MINNEAPOLIS, MN 55455
PHONE: 612-273-3645
FAX: 612-273-3489

Study: ALLHAT (Antihypertensive and Lipid-lowering to Prevent Heart Attack Trial)

Res. Acc't #: 
6 8 2 4 1 4 8

LAB Spec. Acc. #: _____
(for Central Laboratory use only)

INSTRUCTIONS: Apply ALLHAT Coordinating Center-generated label to box at right, and fill in all additional requested information on this form. Check the appropriate ALLHAT test battery below.

AFFIX LABEL HERE

Patient ID#: _____
 ALLHAT Visit #: ____
 ALLHAT Clinic Code #: _____
 Acrostic _____

SPECIMEN COLLECTION INFORMATION

DATE SPECIMEN COLLECTED	TIME SPECIMEN COLLECTED	HOURS SINCE LAST FOOD
	AM PM	

TEST REQUEST FORM

Baseline battery:



- Potassium, glucose, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol), ALT

Post-randomization batteries:



- Lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol plus beta quant if triglycerides >400 mg/dL)



- Serum potassium, creatinine



- ALT, total cholesterol



- ALT



- Potassium, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



- Potassium, creatinine, total cholesterol



- Potassium, glucose, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



- Potassium, glucose, creatinine, total cholesterol



- Lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



- Total cholesterol

COLLABORATIVE STUDIES CLINICAL LABORATORY
 ALLHAT Central Lab, Rm L275 MAYO
 420 DELAWARE STREET, S. E.
 MINNEAPOLIS, MN 55455
 PHONE: 612-273-3645
 FAX: 612-273-3489

Study: ALLHAT (Antihypertensive and Lipid-lowering to Prevent Heart Attack Trial)

Res. Acct #: 
 6 8 2 4 1 4 8

LAB Spec. Acc. #: _____
 (for Central Laboratory use only)

INSTRUCTIONS: Apply ALLHAT Coordinating Center-generated label to box at right, and fill in all additional requested information on this form. Check the appropriate ALLHAT test battery below.

AFFIX LABEL HERE

Patient ID#: _____

ALLHAT Visit #: _____

ALLHAT Clinic Code #: _____

Acrostic _____

SPECIMEN COLLECTION INFORMATION

DATE SPECIMEN COLLECTED	TIME SPECIMEN COLLECTED	HOURS SINCE LAST FOOD
		AM PM

TEST REQUEST FORM - Canada Sites

Baseline battery:



Potassium, glucose, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol), ALT

Post-randomization batteries:



Lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol plus beta quant if triglycerides >400 mg/dL)



Serum potassium, creatinine



ALT, total cholesterol



ALT



Potassium, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



Potassium, creatinine, total cholesterol



Potassium, glucose, creatinine, lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



Potassium, glucose, creatinine, total cholesterol



Lipid profile (cholesterol, HDL-cholesterol, triglycerides, calculated LDL-cholesterol)



Total cholesterol

ALLHAT Central Laboratory
 phone: 612-273-3645 FAX: 612-273-3489

ATTENTION: _____
 ALLHAT site # _____
 FAX# _____
 Date _____

Shipment date _____
 FedEx airbill package tracking number _____

Please consult your Sender's copy (pink copy) for this Federal Express shipment against the example of a properly completed airbill shown below. FedEx records reflect the following problem(s) with completion of the airbill for this shipment. A properly completed airbill will prevent your site's being charged for a shipment and will ensure that the ALLHAT Central Laboratory will be charged at the Government Contract rate. Thank you.

- [] 'FedEx Priority Overnight' box was not checked in Field 4a (Express Package Service) of airbill
- [] More than one box was checked in Field 4 (Express Package Service (4a) and/or Express Freight Service (4b) of airbill
- [] 'Recipient' box was not checked in Field 7 (Payment - Bill to:) of airbill
- [] ALLHAT Central Laboratory's FedEx Account No. (1706-9868-1) was not recorded on the 'FedEx Account No.' line in Field 7 (Payment - Bill to:) of airbill
- [] Shipment weight was not recorded in Field 7 (Payment - Total Weight) of airbill
- [] Shipment weight improperly recorded in Field 7 (Payment - Total Weight) of airbill. Note: it is the shipper's responsibility to record accurate weight to the nearest whole pound. Do not write units after the package weight (i.e., LBS or lbs) or record weight using symbols such as ' < '.
- [] Our Recipient's copy shows that you are using a discontinued version of the Federal Express airbill which may result in billing problems. Please discard airbills which show the options 'GOV'T. PACKAGE' or 'FedEx Govt. Overnight' in Field 4 and order new pre-printed airbills from the Central Laboratory as soon as possible using ALLHAT Central Laboratory Supply Reorder Form.
- [] Other:

FedEx USA Airbill Tracking Number: 808822283490

0210 SNA12 Senders Copy

1 From (please print and press hard)
 Sender's Name: _____ Sender's FedEx Account Number: _____
 Company: _____
 Address: _____
 City: _____ State: _____ ZIP: _____

2 Your Internal Billing Reference Information
 (Internal Field 44 instructions will appear on mailings)

3 To (please print and press hard)
 Recipient's Name: JEAN RUCKSA Phone: (612) 273-3645
 Company: UNIV MN/ALLHAT CENTRAL LAB
 Address: 420 DELAWARE ST SE RM 1297
 City: MINNEAPOLIS State: MN ZIP: 55455

4 Service Selection
 4a Express Package Service (Priority Overnight) 4b Express Freight Service
 4c Standard Overnight 4d Standard Freight

5 Packaging
 Flat Box Tube Mail Parcel Parcel

6 Special Handling
 Fragile No Fragile No Fragile No Fragile No Fragile

7 Payment
 Sender Recipient Third Party Credit Card Check

8 Release Signature
 Signature: _____

9 Total Packages: _____ Total Weight: _____ Total Declared Value: \$ _____ Total Charges: \$ _____

321 Revised 1/99

ALLHAT Central Laboratory
phone: 612-273-3645 FAX: 612-273-3489

ATTENTION:

ALLHAT site # _____
FAX # _____
Date _____ Time _____ # Pages _____

Date specimens received at Central Laboratory _____

Problems Encountered with Identification, Condition or Shipping of Specimens

The results reported to each ALLHAT clinic site depend on the quality of specimen received at the Central Laboratory. The following participants' specimens exhibit one or more problems (see problem key below):

ALLHAT ID#	Acrostic	Date Collected	Problem(s)	Comments
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____

Problem Key

- a Test order form incomplete (see comments)
- b Request form not included with shipment; PLEASE FAX ASAP!
- c Request form does not agree with ID label on tube
- d Improperly labelled specimen tube
- e Specimen received at ambient temperature
- f Incorrect collection tube used; use ALLHAT plastic tube
- g More than one tube collected per patient
- h More than one shipper rec'd same day containing <5 tubes each
- i Shipment sent on Friday or day before a holiday
- j Improperly packaged shipment; use ALLHAT shipping supplies

Central Lab cannot perform analyses in the following situations:

- k Specimen moderately or grossly hemolyzed; RECOLLECT SPECIMEN!
- l Unlabelled specimen tube; RECOLLECT SPECIMEN!
- m Specimen too old for analysis; RECOLLECT SPECIMEN!
- n Tube improperly centrifuged or uncentrifuged; RECOLLECT SPECIMEN!
- o Glass tube used--unable to analyze; RECOLLECT SPECIMEN!
- p Other (see comments):

Actions to be Taken Please review the following remedies for the problems identified above. If you have any questions please feel free to contact the ALLHAT Central Laboratory at 612-273-3645.

- a,b Review each test order form for correctness/completeness; include a form for each specimen in a shipment
- c,d,l Verify complete and correct labelling (using ALLHAT participant ID labels) of specimen tube and accompanying test order form
- e,f,g Verify that each specimen has been collected in one double-gel plastic transport tube, allowed to clot for 30-45 minutes (60 min max), then centrifuged at 1500 to 3000 xg for 15 minutes (consult operator's manual to verify proper rpm setting); examine each tube after centrifugation for presence of red cells in the serum; if red cells are observed, re-centrifuge the tube--if many cells are still observed remove the serum to a vial for shipment
- k Do not ship specimens observed to be moderately or grossly hemolyzed; recollect specimen as soon as possible
- i,m Ship to the Central Lab within 3 days after collection (holiday weekends excepted); never ship on Friday or day before holiday
- e,h,j Pack up to 5 tubes per ALLHAT styrofoam shipper with a frozen refrigerant pak; enclose in FedEx diagnostic specimen envelope
- p Other (describe):

ATTENTION: _____
 ALLHAT site # _____
 FAX# _____

ALLHAT Central Laboratory
 phone: 612-273-3645 FAX: 612-273-3489

Date _____

Please make note of the following **alert results** for ALLHAT participants seen at your site:

ALLHAT ID#	Acrostic	Date Collected	Analyte (units)	Result
-----	-----	-----	<input type="checkbox"/> Potassium (mmol/L) <input type="checkbox"/> Glucose (mg/dL) <input type="checkbox"/> Other:	-----
-----	-----	-----	<input type="checkbox"/> Potassium (mmol/L) <input type="checkbox"/> Glucose (mg/dL) <input type="checkbox"/> Other:	-----
-----	-----	-----	<input type="checkbox"/> Potassium (mmol/L) <input type="checkbox"/> Glucose (mg/dL) <input type="checkbox"/> Other:	-----

Results phoned to _____ at (time/date) _____

Unable to contact by phone; results FAXed at (time/date) _____

Tech _____

APPENDIX E

ALLHAT LIFESTYLE INTERVENTION

Purpose

The main rationale for lifestyle intervention in ALLHAT is to conform with guidelines for treatment of hypertension and dyslipidemia, as stated in reports of the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure [1] and the Adult Treatment Panel (ATP) on Treatment of High Blood Cholesterol [2] and by others [3]. In addition, antihypertensive lifestyle intervention should reduce the need for second and third step drugs, thereby supporting the trial's overall objective of comparing the primary drugs. Dietary and physical activity changes may also reduce the need to use cholesterol-lowering drugs.

The following targeted elements of lifestyle modification are paraphrased and amplified from the JNC and ATP reports:

- Lose weight, if overweight (> 120 % of desirable body weight, based for example on the Metropolitan Life Insurance Company Table [4] or body mass index [body weight in kilograms divided by the square of height in meters] above 27.8 in men and 27.3 in women).
- Exercise regularly (aerobically, if general health allows), e.g., brisk walking for 30 minutes or more at least 3 times weekly.
- Reduce saturated fat to 8-10% or less of total caloric intake.
- Reduce total fat to \leq 30% of total calories.
- Reduce cholesterol intake to \leq 300 mg per day.
- Reduce sodium intake to < 100 mmol per day (<2.3 grams of sodium or < 6 grams of sodium chloride)
- Limit alcohol intake to an averaged of no more than 1 ounce of ethanol per day (approximately) 24 oz. of beer, 8 oz. of wine, or 2 oz. of 100 proof spirits).
- Maintain adequate potassium, calcium, and magnesium intake, i.e. at least 75% of recommended, dietary allowances.[5]
- Smoking cessation.

Although there is limited information from clinical research on such interventions in older patients, pursuit of these goals in moderation are likely to be effective and to be safe, as long as no severe nutritional, endocrine, renal, or psychiatric conditions are present.

Protocol

The ALLHAT *Protocol* calls for initiating counseling, or reinforcing past counseling, on desirable lifestyles at Visit 2 (randomization into the antihypertensive component). The recommendations pertaining specifically to dietary fat composition are best deferred to Visit 3, when results of a lipid profile will be available for most patients. It is recognized that many patients will have been previously counseled in relevant areas, and that ongoing counseling will be necessary for any sustained effect. It is also recognized that time is limited in a busy office or

clinic for detailed counseling. Therefore, as an assist to ensuring a minimal level of patient information, the NHLBI Project Office is supplying two brochures for distribution. A description of these patient education materials follows.

Eat Right to Help Lower Your High Blood Pressure

This is a 30-page booklet, written by NHLBI staff at about the fifth-grade reading level, with large type and illustrations. While there are brief sections on increasing physical activity and limiting alcohol intake, the emphasis is on control of caloric intake, particularly fat calories, and of dietary sodium. There are tips for buying and preparing food, and for eating (both meals and snacks). A few recipes and menus are included. There is also some general information on hypertension and on the importance of taking prescribed medication.

Some key elements for reducing sodium intake while maintaining levels of the other cations are:

1. Try to cook from scratch. If convenience foods, such as canned soups and TV dinners, are used, read the label, because many are high in sodium.
2. Use herbs, spices, and fruit juices to season food.
3. Avoid adding salt in cooking or at the table.
4. Rinse canned foods like tuna and canned vegetables to remove salt water and juices.
5. Avoid highly salted snacks (most chips, nuts, and pretzels); many are also high in fat.
6. Increase use of fresh fruits and vegetables, as well as low-fat dairy products.

Eat Right to Lower your High Blood Cholesterol

This is a 14-page booklet similar in style to the high blood pressure one. The focus is on buying and preparing food, and eating (both meals and snacks) to reduce saturated fat and dietary cholesterol. Some menu suggestions are included.

Some key elements of the cholesterol-lowering diet are:

1. Choosing less fatty meats (fish, skinless poultry, lean cuts of red meat) and limiting portion size to $\leq 5-6$ ounces per day.
2. Choosing nonfat (skim) or lowfat (1/2-1%) milk, substituting ice milk or low-fat frozen yogurt for ice cream, and avoiding most cheeses.
3. Encouraging intake of fruits, vegetables, and complex carbohydrates (potatoes, rice, pasta).
4. Limiting the use of hard fats and shortening (butter, lard) in preparation and at the table, and substituting unsaturated vegetable oils and soft or liquid margarines where possible; limit fats and oils to $\leq 6-8$ tsp per day.

5. Decreasing intake of commercially baked cakes, cookies, muffins, pies, etc., except for those that are low-fat/non-fat or contain only unsaturated vegetable oils.
6. Limiting egg yolks to ≤ 4 per week and decreasing organ meats (liver, etc.).

Further Information

To obtain additional information, you or your patients can contact the NHLBI Information Center, at P.O. Box 30105, Bethesda, MD 20824-0105, or by telephone at (301) 251-1222. The NHLBI staff are in the process of revising several publications that provide more in-depth information on lifestyle modifications, both in the hypertension and cholesterol areas, written at the 8th-12th grade reading level. Such publications will probably be supplied to you, for optional use, by the Clinical Trials Center in a few months. Other sources of consultation are local dietitians and your regional coordinator. Future meetings of the ALLHAT Investigative Group will include information about useful resources, such as audiovisuals and ethnically - oriented materials.

References

- 1) National High Blood Pressure Education Program. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1993; 153:155-183.
- 2) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269:3015-3023.
- 3) Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions. *Report of U.S. Preventive Services Task Force*. Williams and Wilkins, Baltimore, 1989.
- 4) 1983 Metropolitan height and weight tables. *Stat Bull Metropol Insur Co* 1983;64:3.
- 5) National Research Council. Recommended Dietary Allowances (10th ed.). National Academy Press, Washington, D.C., 1989.

APPENDIX F

ASSESSING COMPLIANCE

F.1 Prologue

In a study of this kind, it is necessary to monitor the participants' adherence to the study protocol. Medication adherence and clinic attendance are monitored for making this evaluation. The following guidelines and advice are compiled from experience of many investigators in many clinical trials. In addition to its usefulness and importance for ALLHAT, you may find that these tips are useful in your practice as well.

Once a patient is entered into the ALLHAT program, the most critical factor for a successful study is adherence to study medication. If patients don't stay on their study medication then the study groups won't be sufficiently different to answer the study question and all the ALLHAT work will have gone unrewarded. Several factors are working in our favor to keep a high proportion of ALLHAT patients on their assigned treatment:

- (1) The clinical centers are very experienced in treating hypertension.
- (2) ALLHAT medications are not experimental; they are regular drugs used all over the country in everyday practice. They are all excellent blood pressure lowering agents.
- (3) The medications are provided at no cost.
- (4) Side effects due to the ALLHAT drugs are rare and should not be major obstacles in keeping ALLHAT patients on medications.

Years of prior experience in hypertension trials have taught us several lessons about maintaining drug adherence. Here are several pointers that will be of help in counseling ALLHAT patients. Look over this list frequently and try to routinely work the suggestions into your patients' ALLHAT clinical visits.

- (1) Make the clinic visits as convenient as possible and avoid long waiting times.
- (2) Give patients positive expectations about going onto an ALLHAT drug; really mean it, too.
- (3) Early on, in the first few weeks after starting medication is the highest risk time for going off. Be on the look-out early for complaints and be ready to intervene; tell patients not to go off drugs without calling you first.
- (4) Don't immediately stop study medication for mild side effects; wait it out. The majority of symptoms improve or go away by themselves. Before stopping drugs completely, try other things like reducing the dose of drugs or altering the dose schedule. In the Trial of Mild Hypertension Study (TOMHS), where the same or similar medications to ALLHAT were used, side effects were the same or greater in the placebo group compared to active therapy.
- (5) If ALLHAT patients go off study medications, restart them as soon as possible. Restart them regardless of what their BP level is at the visit (unless the patient is complaining of fainting or blacking out; refer this to the ALLHAT physician.)

F.2 Medication Adherence

Adherence to the Step 1 drug regimen and the pravastatin regimen is systematically monitored by making a count of pills taken by the participant between visits and by questioning the participant at each visit. The results of these measurements are reviewed by the Data and Safety Monitoring Board, the Project Office, the Steering Committee, and the Coordinating Center.

F.2.1 Pill Count and Interview

Monitoring of medications will be done at every clinic visit by two methods:

1. Direct pill counts or cylinder measurements, and
2. Questioning the participant about how regularly he/she has been taking his/her medicines.

The results of these measures are reviewed centrally as well as locally. Directions for these compliance assessments are given in the follow-up section of Chapter 2.

If adherence problems occur (pill count less than 80%, or by self-report), several mechanisms may be suggested to the participants 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 sporadically.

If non-adherence to medications persists as a problem, a conference might 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.

F.3 Adherence to Visit Schedule

During the follow-up phase of this trial participants are required to attend the clinic at regular intervals. Attendance at scheduled visits is documented by the completion of the ALLHAT Follow-Up Visit Form (AL03).

F.4 Promotion and Maintenance of Adherence

The following section contains suggestions for the Clinical Centers in establishing a high degree of adherence to the ALLHAT protocol, both in the area of medication adherence and in clinic attendance. The ability to implement these suggestions may vary from clinic to clinic, and some may work well in one clinic and not in another.

a) *Participant-Staff Relationship* - A 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.

c) Clinic Environment - The clinic environment should be warm and pleasant, and oriented to the comfort of the participant.

d) Participant-Staff Communications - Good communication is essential, and consistency is the key word to communication. In addition to consistency among staff in what is communicated to the participant, instructions should be clear and interactions should be friendly and individualized.

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 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.

f) Time in Clinic - It is especially important to keep waiting times short. 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.

g) Appointment Reminders - Participants (like the rest of us) do tend to forget. Therefore, appointment reminders might be used to prompt participants to come for Clinic visits. These might include telephone calls, letters, or postcards.

h) Interim Contact - During the period between Visit 1 and 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. This is the first test of their willingness and/or ability to comply with the required follow-up visits.

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 ALLHAT medication at the previous visit. Three or four months between contacts with the 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.

i) Participant Identity with ALLHAT

In those clinics *where it is possible*, the clinics should focus on promoting participant identity with the ALLHAT. Regular communication is important. Some suggestions include:

- Newsletters sent to the participants in the trial sharing information of interest


- Holiday cards
- Other written communication; e.g., notices of special events.
- Group events; e.g., educational programs
- Letter from a significant person outside the ALLHAT (e.g., congressman or governor) pointing out the importance of ALLHAT 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 and/or children 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 family member(s) could, for example, be invited to attend the Clinic visits, especially the initial visits. 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 - Some clinics may have the option to provide 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.

l) Staff Meetings - In clinical settings where this might be possible, regular staff meetings should be held to keep the ALLHAT physician informed regarding individual and overall adherence problems and to plan strategies for improvement. Notes on Clinic visit summaries can be used to indicate adherence problems. The ALLHAT 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 ALLHAT should be given an identification card. These will be provided by the CTC. 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 different doctor's office, for a major medical problem, in addition to scheduled Clinic visits. The outside of the ID card is shown on the next page. The card folds to credit-card size. The inside of the card provides space to record each visit and blood pressure.

<p><i>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</i></p> <p style="text-align: right;"></p> <p>I, _____ am participating in <i>ALLHAT</i>. <i>ALLHAT</i> is a nationwide program using different kinds of high blood pressure drugs. The hypertension part of this program is double-blind. I may be taking any one of the following antihypertensive drugs: <i>chlorthalidone, amlodipine, lisinopril or doxazosin.</i></p>	<p><i>ALLHAT</i> ID: _____</p> <p>Bottle #: _____</p> <p>For additional information please contact:</p> <p>Name: _____</p> <p>Telephone: _____</p> <p>In an emergency, if unblinding is <i>essential</i>, call (713) 704-2078 and ask for a pharmacist.</p> <p><i>This card should be shown to any physician or dentist treating you for any illness.</i></p>
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n) Re-education - A periodic review of the purposes of the study can be a strong motivation. discuss the purpose of the double blind, when to call the ALLHAT physician, and length of planned follow-up (this is easily forgotten).

F.5 "Red flags" that may indicate future adherence problems

The best approach to possible adherence problems is to be proactive and "head them off at the pass", if possible. There are many behaviors and other life events which may indicate upcoming adherence problems:

1. Complaints about adverse effects (especially at the first visit after randomization).
2. Missed visits.
3. Frequent rescheduling or "putting off" of required visits.
4. Difficulty in reaching by phone or failure to return calls.
5. Humor dealing with negative aspects of the trial.
6. Complaints about clinic visits.
7. Sarcasm about trial or medication.
8. "Distance" during interview.
9. Length of time since participation in study was discussed with physician.
10. Impatience during clinic visits.
11. Length of time at each mandatory visit.
12. Unusual or unexplained change in adherence.
13. Unconcern of participant about adherence rate.
14. Any expression that participant may discontinue treatment.
15. Reassignment to new primary manager.
16. Hospitalization.

F.6 Resources for advice on medication and visit adherence

Several tools will be available from the Clinical Trials Center to provide assistance with monitoring medication and visit adherence. These include:

- (1) Visit schedule provided for each participant at randomization listing all visit windows and expected procedures,
- (2) Routine monthly monitoring reports listing "average" adherence by clinical site, and listing poor medication and visit adherers.
- (3) Lists of patients who are expected to have visits in the next month or so.

Adherence problems may be brought to your attention during individual patient visits and/or review of routine monthly reports from the Clinical Trials Center. If you are having an adherence problem with specific patients, or if you feel that there is an overall adherence problem in your clinic, you should feel free to contact your Regional Physician or Nurse

Coordinator to discuss these issues. Regardless of the nature and magnitude of the problem, it is imperative that these be dealt with in an effective and timely manner. Adherence to the medication and visit regimens is crucial to the success of ALLHAT.

If all is going well in your clinic in regards to compliance, you might notice that your numbers look "better than average" on the monthly reports. If so, you are due the most sincere thanks and congratulations. Your Regional Coordinator may ask you to share a few of your compliance tips with other sites.

APPENDIX G

QUALITY CONTROL

G.1 Training and retraining

Every clinic is expected to send at least two representatives to a central training session. These training sessions will deal extensively with the protocol, will train clinic staff members present in the proper blood pressure measurement procedures for ALLHAT, will describe the ECG data acquisition, the central laboratory procedures, drug handling procedures, and will discuss forms completion. In addition, the clinics associated with the Department of Veterans Affairs and community health centers will have special sessions addressing administrative issues particular to their clinic settings.

Periodic refresher sessions may be necessary to address problems or issues related to any trial procedure, e.g., blood pressure measurement, ECG acquisition, compliance and retention. These will be held in conjunction with yearly Steering Committee meetings.

G.2 Blood pressure measurement quality control

Every blood pressure observer for ALLHAT is expected to complete the training described in Appendix B. The Clinical Trials Center will keep a computer record of every person completing this training. These records will be checked against the forms to monitor the training of blood pressure observers in the study.

In addition to checking for trained observers, the Clinical Trials Center will periodically generate reports on "blood pressure terminal digit preference". This refers to the distribution of the last digit of your blood pressure readings. A person who is careful about measuring blood pressure should have an approximately even distribution of terminal digits, e.g.:

Digit	0	2	4	6	8
	20%	20%	20%	20%	20%

Of course, no one has a perfect distribution of terminal digits, but there are cases that will be flagged, e.g., any observer with at least one digit occurring over 30% of the time, or less than 10% of the time (digit avoidance). Specific recommendations for alleviating this problem will be made at the time of the report.

G.3 Ongoing quality control efforts

G.3.1 Monitoring reports

Recruitment reports will be generated at least weekly, by clinic and region and for the antihypertensive trial and the cholesterol-lowering trial. These will be distributed to the Project Office, Steering Committee and Regional Coordinators.

Other routine monitoring reports include data on visit and medication adherence, quality control and study endpoint documentation. These will be generated at least monthly by clinic and region, and will be distributed to the Project Office, Steering Committee and Regional Coordinators.

Reports for clinic use include randomization verification reports, visit schedules and reminders, endpoint documentation reports, and limited cross-forms edits. These will be generated no more often than monthly. Visit schedules are generated as participants are randomized and include all visit windows and expected special procedures for the duration of the study. Reports and appropriate listings will be sent to the clinics, and summary reports will be sent to the Project Office, Steering Committee and Regional Coordinators.

G.3.2 The role of the regional coordinators

Each clinical site will have a Regional Physician Coordinator and Regional Nurse/Study Coordinator. A list of these coordinators may be found in the Quick Reference Manual, page **Error! Bookmark not defined.**

The role of the Regional Coordinators is to:

1. provide guidance with protocol questions dealing with clinical issues,
2. answer questions regarding the clinical management of patients in the study,
3. provide an additional source to the Clinical Center investigator and study participants,
4. assist the Clinical Trials Center in monitoring the data collection (this may involve site visits by the nurse coordinator),
5. and, for the VA sites, handle the reimbursements for study visits and endpoints.

In addition to being available to answer protocol or management questions, the Regional Physician Coordinator or Regional Nurse Coordinator should be contacted for:

1. Any protocol violation or any perceived need for a protocol violation,
2. Any NONEMERGENT need to unblind a Step 1 drug bottle number,
3. Anticipated need to discontinue blinded antihypertensive study medications or study pravastatin,
4. Clinical indication for the use of open-label diuretics, calcium channel blockers, ACE inhibitors, or alpha blockers,
5. Inability to achieve blood pressure or lipid control with study medications,
6. Questions regarding potential adverse drug effects, especially if the study medications are suspected,
7. Questions regarding patient eligibility,
8. Questions regarding completion of study forms,
9. Difficulties in patient recruitment,
10. For VA sites, questions about reimbursements.

G.4 Changes to the Manual of Operations

Changes will be made to the Manual of Operations to clarify study procedures as needed. When changes are made, they will be distributed to all holders of ALLHAT Manuals. An inventory will be kept, and distributed with each change, of all pages that have been revised and their revision date.

G.5 Problem resolution and quality control site visits

Some problems identified through routine monitoring reports and by other means may appear to be particular to a clinical site. If so, these will be brought to the attention of the Regional Coordinator, the Project Office, and the Executive Committee. These problems may include, but are not limited to:

1. Lag in recruitment,
2. Problems in recruiting the expected proportion of African-American participants,
3. Large numbers of missed visits,
4. Large numbers non-compliers,
5. Large numbers of losses to follow-up,
6. Large numbers of undocumented study endpoints or any cases of very late documentation,
7. Large numbers of missing or incomplete procedures, or incorrectly completed forms,
8. Failure to follow-up on quality control issues, e.g., cross-forms edit queries,

The following steps will be taken when the monitoring reports (or other indicator) indicate a problem at the clinic level:

1. Upon first detection of a problem, the Regional Physician or Nurse/Study Coordinator will contact the center by telephone, with a follow-up letter to the clinic and copies to the CTC and Project Office. Determination will be made if the problem is minor, major and correctable, or major and uncorrectable. If the problem is determined to be major and uncorrectable, the CTC and Project Office should be notified and immediate action taken (i.e., go directly to Step 4).
2. If a correctable problem is not resolved or improved within two reporting periods, the CTC and Project Office will become directly involved. Minor problems will be evaluated in the context of overall performance (one minor problem is not good, but may be acceptable; a minor problem that seems to be getting worse, or many problems may require action).
3. If the problem is major and potentially correctable, or the reason for the problem is undetermined, a site visit will be necessary. In many cases this collaboration between investigator, regional coordinator, CTC and Project Office may correct the problem.
4. If the problem is major and not correctable, consideration may be given to (a) dropping the site altogether if they have not randomized anyone or (b) ceasing recruitment at that site but continuing follow-up.

- a. If the clinic has not randomized anyone within two months of training, IRB/OPRR approval, and receipt of forms and supplies, consider dropping the site from the study.
 - b. If the clinic has < 10 randomizations and has not randomized anyone within 4 weeks, consider advising the clinic to stop randomizing but to continue following their randomized patients.
5. Special care must be taken that these decisions are made uniformly for all clinical centers.

DOXAZOSIN CLOSEOUT

February 2000

***** **CONFIDENTIAL** *****

EXTREMELY URGENT - REVIEW MATERIALS NOW

As a result of data monitoring by the ALLHAT Data and Safety Monitoring Board (DSMB) and another special Advisory Committee, the Director of the National Heart, Lung, and Blood Institute was advised that the doxazosin arm of the antihypertensive component be discontinued. The Director has accepted that recommendation. Please refer to the letter to your site's Principal Investigator for further explanation of why this decision was made.

This package contains the following items, which are described more fully in the attached pages:

- Notification letter to PI
- Packet for non-UT IRB
- Doxazosin transition timeline - to be used as faxed acknowledgement to the CTC several times (last page of this packet)
- Flow chart - what to do for patients on each of the three lists (green cardstock)
- Lists of participants –
 1. *Participants assigned to doxazosin and not in the lipid trial*
 2. *Participants assigned to doxazosin and in the lipid trial*
 3. *Participants not assigned to doxazosin*
- Letters to participants – *personalized*
- Important Questions and Answers about ALLHAT for Participants for you to include with the letters, with a few extras
- Postage-paid envelopes
- Return address labels for your site
- Instructions for drug return/disposal – doxazosin codes
- Photocopy of revised AL10 (ALLHAT Drug Order Form), including open-label chlorthalidone
- Five photocopies of the ALLHAT Transition Form
- FAQ's for Regional and Study Coordinators

***** **CONFIDENTIAL** *****

TO SITE PI'S
Revised 1/25/00

(Date)

Dear (PI name):

We are writing to provide important information concerning the Antihypertensive and Lipid-Lowering Therapy to Prevent Heart Attack Trial (ALLHAT), which has led to a modification of the protocol. This information is not public at this time and we ask that you keep this confidential until the patients in ALLHAT are informed and the NHLBI publicly releases the results. You should, however, send a copy of this letter to your IRB right away.

Following a review in January, the Director of the National, Heart, Lung, and Blood Institute accepted the recommendation of an independent data review committee. Accordingly, the doxazosin arm is being terminated. The recommendation was based on a very low probability of finding a favorable outcome for the group assigned to doxazosin compared to those assigned to chlorthalidone in the primary end-point (non-fatal myocardial infarction or coronary heart disease [CHD] death), coupled with less effectiveness in preventing congestive heart failure (CHF). A statistically significant 25 per cent higher rate of a secondary endpoint, combined cardiovascular disease (CVD) was observed in the doxazosin arm compared with the chlorthalidone arm. The higher rate of combined CVD (which includes the primary CHD end-point, angina pectoris, coronary revascularization, CHF, stroke, and peripheral arterial disease) was driven by a highly significant two-fold higher rate of CHF compared with the diuretic arm, but there were trends in the same direction for stroke and some other components. The primary CHD outcome, and total mortality were not different between the doxazosin and chlorthalidone arms.

It was determined that participants assigned to doxazosin should be informed of their BP treatment assignment and that the major clinical findings regarding this treatment and its comparison agent, chlorthalidone, be reported as soon as possible. Regarding other comparisons, the DSMB emphasized the crucial importance of continuing the rest of the BP and lipid-lowering components.

In order to communicate appropriate messages about the implications of these results for various participant groups, the Steering Committee has prepared letters and closeout materials for you to use to contact all your ALLHAT patients. The letters, the closeout forms, and the details on what procedures to follow will be provided to you within the next two weeks. Only those patients assigned to doxazosin and not in the lipid-lowering trial will be closed out. All other patients will be asked to continue, as the other questions ALLHAT is addressing remain unanswered. Those patients assigned to doxazosin and in the lipid-lowering trial portion of ALLHAT will be offered the use of open-label

chlorthalidone, which the study will provide at no cost. All of this will be explained in the material you are to receive. If you have any questions, please contact your Regional Coordinator.

All of us who are conducting ALLHAT greatly appreciate your participation as a site principal investigator. You and your patients have already helped to answer one of the questions for which ALLHAT was designed. The other questions to be answered by ALLHAT remain of fundamental importance for hypertension treatment. As detailed information is reported to the scientific and wider community, we will keep you fully informed.

Thank you for all your efforts to date and for your continuing diligent participation in ALLHAT.

Sincerely,

Curt Furberg
Jackson Wright
Jeff Cutler
Barry Davis

PARTICIPANTS ASSIGNED TO DOXAZOSIN AND IN LIPID COMPONENT -
PRAVASTATIN
Revised 2/2/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that the medicine to which you were assigned (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify me, and for me to notify you.

It is very important that we meet together to decide on a treatment for your high blood pressure, discuss what the study results mean for you, and answer questions that you have. Please call my clinic by the end of March at the number listed below to make an appointment. **DO NOT STOP TAKING YOUR ALLHAT MEDICINE UNTIL WE DECIDE ON THE BEST TREATMENT FOR YOU, BECAUSE THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED.** Be sure to bring your ALLHAT medicine to the clinic with you. At that time, a different medicine also being used in ALLHAT will be available to you free of charge. Blood tests required by the study will still be free.

You are also a valuable participant in the cholesterol-lowering part of ALLHAT. You were assigned to receive the cholesterol-lowering medicine Pravastatin, and it will still be provided to you free of charge. Since that part of the study will continue, you should continue with your ALLHAT visits every four months and try to follow the dietary recommendations given to you.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped us to answer one question. We depend on your continued participation to help us find the benefits of lowering serum cholesterol in people whose serum cholesterol is slightly elevated.

Sincerely,

Address
Phone

Center and site #

PARTICIPANTS ASSIGNED TO DOXAZOSIN AND IN LIPID COMPONENT -
USUAL CARE
Revised 1/31/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that the medicine to which you were assigned (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify me, and for me to notify you.

It is very important that we meet together to decide on a treatment for your high blood pressure, discuss what the study results mean for you, and answer questions that you have. Please call my clinic by the end of March at the number listed below to make an appointment. **DO NOT STOP TAKING YOUR ALLHAT MEDICINE UNTIL WE DECIDE ON THE BEST TREATMENT FOR YOU, BECAUSE THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED.** Be sure to bring your ALLHAT medicine to the clinic with you. At that time, a different medicine also being used in ALLHAT will be available to you free of charge. Blood tests required by the study will still be free.

You are also a valuable participant in the cholesterol-lowering part of ALLHAT. You were assigned to the Usual Care group in this part of the study. Since that part of the study will continue, you should continue with your ALLHAT visits every four months and try to follow the dietary recommendations given to you.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped us to answer one question. We depend on your continued participation to help us find the benefits of lowering serum cholesterol in people whose serum cholesterol is slightly elevated.

Sincerely,

Address
Phone

Center and site #

PARTICIPANTS ASSIGNED TO DOXAZOSIN AND NOT IN LIPID COMPONENT

Revised 2/2/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that the medicine to which you were assigned (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify me, and for me to notify you.

It is very important that we meet together to decide on a treatment for your high blood pressure, discuss what the study results mean for you, and to answer questions that you have. This will be your last ALLHAT visit. Please call my clinic by the end of March at the number listed below to make an appointment. **DO NOT STOP TAKING YOUR ALLHAT MEDICINE UNTIL WE DECIDE ON THE BEST TREATMENT FOR YOU, BECAUSE THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED.** Be sure to bring your ALLHAT medicine to the clinic with you.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped the study to find out that one of the blood pressure medicines is less effective than the others at preventing heart failure. We still do not know which of the other ALLHAT medicines are best for treating high blood pressure.

Sincerely,

Address

Phone

PARTICIPANTS NOT ASSIGNED TO DOXAZOSIN

Revised 2/1/00

(Date)

Dear (patient name):

You have been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is about to release its first results.

The purpose of the ALLHAT trial is to compare the ability of four commonly-used blood pressure medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When you joined ALLHAT, you were assigned by chance to take one of the four blood pressure medicines. Your safety has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that one of the medicines being used in ALLHAT (doxazosin) appears to be the least effective of the four in preventing heart failure. **YOU ARE NOT ASSIGNED TO THAT ALLHAT MEDICINE.**

At your next ALLHAT visit, we will review your medicines for your high blood pressure and answer questions that you have. **DO NOT STOP TAKING YOUR ALLHAT MEDICINE - THE MEDICINE IS HELPING TO KEEP YOUR BLOOD PRESSURE CONTROLLED.** Be sure to bring your ALLHAT medicine to the clinic with you. We will continue to see you every four months for your ALLHAT visits and blood tests required by the study will still be free.

All of us who are conducting ALLHAT greatly appreciate your participation, which has helped us to answer one question. We depend on your continued participation to help us to find out which of the other ALLHAT medicines are best for treating high blood pressure.

Sincerely,

Address

Phone

Center and site #



Date: _____

Dear Dr. _____:

Your patient, _____, has been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is releasing its first results.

The purpose of ALLHAT is to compare the ability of four commonly-used antihypertensive medications to reduce the risk of heart disease, stroke, and early death. All four of the ALLHAT medicines were selected because they are commonly used by doctors when treating patients with high blood pressure and because doctors do not agree on which of the four is better.

When your patient joined ALLHAT, he/she was assigned by chance to take one of the four blood pressure medicines. The safety of ALLHAT participants has been monitored closely throughout the study by an independent panel of experts. During the most recent review, it was determined that one of the ALLHAT medicines (doxazosin) appears to be the least effective of the four in preventing heart failure. Although heart failure was not the main focus of the study, the study reviewers have decided that the difference is important enough to notify the me, the patient, and now you. The following applies to the participant named in the first paragraph:

- This patient was not originally assigned to receive doxazosin.** He/she will continue ALLHAT follow-up and receive their Step 1 blinded medicine as usual unless there are contraindications. It is important that these participants continue to take the blinded study medication.
- This patient was originally assigned to receive doxazosin for the study and is also participating in the lipid-lowering part of ALLHAT.** He/she will meet (or has already met) with me to talk about this first ALLHAT result, discontinue the study doxazosin, and decide on an appropriate hypertension treatment. The diuretic chlorthalidone will be available free of charge for the remainder of ALLHAT. *Patients originally selected to receive Pravastatin* will continue to receive pravastatin free of charge, will continue their ALLHAT visits every four months, and will try to follow the dietary recommendations given to them. *Participants originally selected for the Usual Care group* will continue their ALLHAT visits every four months and try to follow the dietary recommendations given to them.
- This patient was originally assigned to receive doxazosin for the study and is not participating in the lipid-lowering part of ALLHAT.** He/she will meet (or has already met) with me one more time to talk about this first ALLHAT result, discontinue the study doxazosin, and decide on an appropriate hypertension treatment. That visit will be their last ALLHAT visit. An ALLHAT history is attached for this patient.

All of the ALLHAT participants have received letters describing the result and have been informed about their study assignment (doxazosin or not). They have been told to not stop taking their ALLHAT medicine until the best antihypertensive treatment is determined for them. I would be happy to consult with you regarding antihypertensive therapy for participants originally assigned to doxazosin.

All of us who are conducting ALLHAT greatly appreciate your patient's participation, which has helped us to answer one question. We are still depending on our remaining participants to help to determine which of the other ALLHAT medications are best for treating high blood pressure.

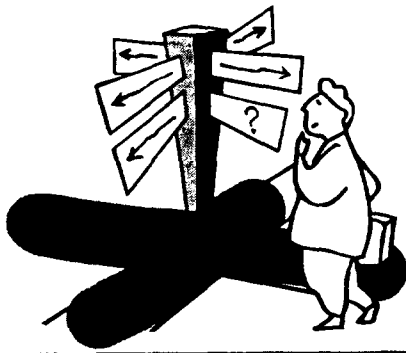
Sincerely,

Telephone:



TRANSITION TIMELINE
Revised 2/8/2000

Target Date	Description
Th 1/6/00	DSMB split vote on continuation of doxazosin arm
F 1/21/00	Special review group recommends to discontinue doxazosin arm
M 1/24/00	Agreement from Dr. Lenfant, Director, NHLBI
Th 2/3/00	ALLHAT Steering Committee notified
Week of 2/7/00	Print letters to patients, printed & folded, ready to mail with lists & histories, instructions, FAQ's
F 2/11/00	Deadline for Steering Committee comments on results paper Finish close-out forms and instructions and send to printer
Week of 2/14	<ul style="list-style-type: none">➤ Mail sites the letters to mail to the patients, with instructions & histories & lists, postage-paid envelopes, return address stickers, FAQ's - URGENT FED EX➤ Submit short results paper for expedited review (NEJM)
By T 2/29/00	Letters mailed from sites to participants
T 2/29 - F 3/3/00	Transition forms and instructions to sites
M 2/28/00	<ul style="list-style-type: none">➤ Mail second fax-back form to sites➤ List of non-responders (no fax back sheets) to regions for immediate follow-up - this report will be weekly to region
W 3/1/00	FedEx open-label chlorthalidone to sites
Sat 3/11/00	Release of results at ACC meeting
W 3/15/00	Routine patient newsletter distributed to clinics, including article on doxazosin transition
Weekly beginning 4/00	Report on transition forms receipt, by region and clinic, to regions and NHLBI and CPHS
Monthly beginning 4/00	Progress report to NHLBI, CPHS
5/25/00	This is the routine mail cutoff for May 2000. All transition visits must be done and submitted to CTC by this time.



TRANSITION PROCEDURES FOR ALLHAT DOXAZOSIN PARTICIPANTS

<p>Participants assigned to doxazosin and in the lipid trial (Pravastatin or Usual Care)</p>		<ul style="list-style-type: none"> • will continue to be followed for the lipid trial until March 2002. • have a transition visit (new form AL20) on or after 3/8/2000 to discontinue Step 1 medication and prescribe other antihypertensive medicine. Complete the transition form (AL20) and mail to the CTC in time to meet the 5/25/00 mail cutoff. • Participants not currently prescribed the Step 1 medication still must have a transition visit (AL20). • Should also have an AL03 in each visit window. The transition visit (AL20) does not take the place of the AL03. The two may be on the same day. • You may use the ALLHAT open-label medications, open-label chlorthalidone (provided) and/or any other antihypertensive medicine at your discretion to control BP.
<p>Participants assigned to doxazosin and <u>not</u> in the lipid trial</p>		<ul style="list-style-type: none"> • will have a transition visit (new form AL20) on or after 3/8/2000 to discontinue Step 1 study medication and prescribe of other antihypertensive medicine. Complete the transition form (AL20) and mail to the CTC in time to meet the 5/25/00 mail cutoff. • The transition visit (AL20) will be their last ALLHAT visit. • Participants not currently prescribed the Step 1 medication still must have a transition visit (AL20). • Should also have an AL03 in each visit window up to the time of the transition visit (AL20). The transition visit does not take the place of the AL03. The two may be on the same day, but the AL03 cannot be after the transition visit (AL20). • You may provide <i>1 bottle (a 4-month supply)</i> of the ALLHAT open-label medications, open-label chlorthalidone (provided) and/or any other antihypertensive medicine at your discretion to control BP until the participant can make arrangements for other care if needed.
<p>Participants not assigned to doxazosin</p>		<ul style="list-style-type: none"> • will continue with their Step 1 medication as usual • continue to be followed as usual until March 2002

The following instructions and materials will facilitate this process during this exciting and challenging time for ALLHAT. Please review these carefully, and be sure that everyone on your staff is informed.

Letter to your Principal Investigator



This letter explains why the doxazosin arm of the antihypertensive trial is being discontinued. It is critical that every Principal Investigator be very familiar with the contents of this letter.

Packet for non-UT IRB

- If your site is approved through The University of Texas, you may discard this particular packet and skip to the next section of these instructions.
- If your site is approved through a non-UT IRB, please forward the IRB packet to their office as soon as possible.

This packet includes a short explanation of the enclosures, a copy of the notification letter to your PI, and samples of the letters to the participants. **Do not wait for IRB approval prior to sending the letters to the participants.**



Doxazosin Transition Timeline - last page of this packet



Closing down one part of a study is a tremendous amount of work to be done in a relatively short time. To help you keep track of all of the tasks, a timetable is enclosed. The timetable is designed as a checklist - you should fill in the date completed for each step. The most important dates for you to remember:

- All letters to participants must be mailed no later than Monday, February 28, 2000.
- All transition visits for participants assigned to doxazosin must be completed, and the form (AL20) must be received at the CTC, no later than May 25, 2000 (the mail cutoff date for May).

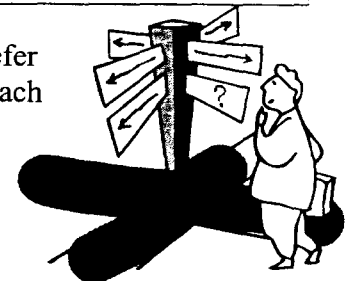
Please review this timeline carefully and schedule your clinic activities accordingly.

You need to fax this form back to the CTC several times:

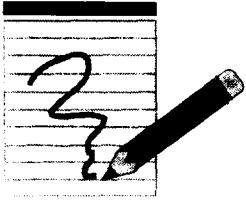
- ♥ by Monday, February 21, 2000 so that the CTC will know that you received the package
- ♥ by Wednesday, March 1, 2000 to let the CTC know that all of the letters have been mailed

Flow Chart - green cardstock tip card

The green cardstock tip card should be posted NOW where ALLHAT staff may refer to it during transition visits. This card will help you to remember what to do for each participant based on their ALLHAT treatment assignments. The help card is similar to the chart on the previous page.



Patient Lists



There are three lists of patients, per the chart on the previous page:

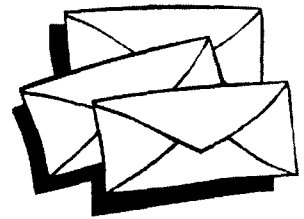
- Participants assigned to doxazosin who are also in the lipid trial.
- Participants assigned to doxazosin who are not in the lipid trial.
- Participants not assigned to doxazosin.

Patients reported as dead as of the January data cutoff are excluded from the lists, but patients who are reported as lost or refused are included and flagged.

You should use these lists to keep track that letters have been sent. For patients assigned to doxazosin (two of the lists), there is also space for you to indicate when you saw the patient, to check off that you collected the Step 1 medications, and completed a transition form (AL20). You will receive the transition forms and instructions in the mail in about a week or two.

Letters to Participants

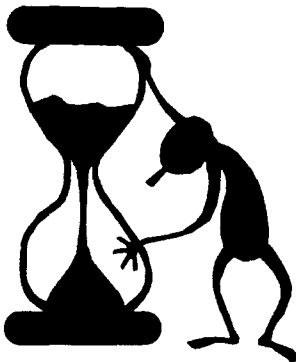
Every participant not already reported as deceased must be sent a letter explaining the first results of ALLHAT and how the results affect their participation in ALLHAT. This includes participants not assigned to doxazosin, and also includes participants reported as refusals or losses to follow-up. The letters have been prepared and folded for you. There are three different types of letters:



- Participants assigned to doxazosin who are also in the lipid trial (Pravastatin or Usual Care) - green paper
- Participants assigned to doxazosin who are not in the lipid trial - blue paper
- Participants not assigned to doxazosin - white paper

The letters already include the participants' ID numbers and names, as well as your Principal Investigator's name and your clinic's contact information. We suggest that your Principal Investigator sign each letter, but this is not required.

You will notice that the letters are double-sided - one side is in English and the other is the same letter in Spanish.



All letters must be in the mail by February 28, 2000, as there will be general press release around March 6. IT IS IMPORTANT THAT YOUR PARTICIPANTS HEAR THIS INFORMATION FROM YOU AND NOT FROM A PRESS ANNOUNCEMENT. A fax-back form is enclosed to indicate that all of the letters have been sent. If patients will be attending clinic before March 1, you may want to hand-deliver the letters to them - a good way to do this is to put them in the charts for those patients. If you anticipate a problem getting the letters out by this date, please contact your Regional Coordinator NOW.

Important Questions and Answers About ALLHAT for Participants

You will be getting questions from participants, their families, and from other physicians about ALLHAT's first results. A list is included of the questions that will probably be among the most frequently asked, along with appropriate responses. **Copies of this document are folded with the letters to the participants, and extras are provided as well for your use when you talk with someone in the clinic or by telephone.**



Postal Supplies



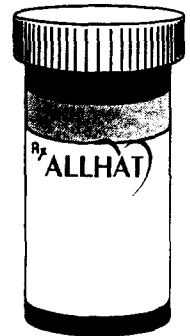
Postage-paid envelopes are included in this package, as well as return address stickers for your clinic according to the latest information that we have on file at the CTC. You do need to address the envelopes!

This is a perfect opportunity to try and find and retrieve participants who are lost to follow-up or refusing to participate. For losses to follow-up, try sending the letter by certified mail. For losses to follow-up and refusals, try following the letter by a telephone call within a few days. You might be surprised who you find and return to telephone or clinic follow-up.

Instructions for Disposal of Doxazosin (Step 1 Blinded) New AL10 (Drug Order Form)

STARTING IMMEDIATELY, NO ADDITIONAL BOTTLES OF DOXAZOSIN SHOULD BE DISPENSED TO PARTICIPANTS. DOXAZOSIN BOTTLE CODES ARE:

12	39
13	42
20	43
22	46
27	55

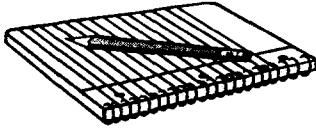


All participants assigned to doxazosin will require an extra visit called a *transition visit* to tell them about these first study results, to collect their bottles of the Step 1 medicine, and to prescribe other medicine to control their blood pressure. Prescription of other antihypertensive medicines is up to the Principal Investigator. Open-label chlorthalidone will be provided to use for participants who are discontinuing doxazosin, but its use is not required. You may also select from the available ALLHAT Step 2 and Step 3 medicines. You may prescribe other antihypertensive medication(s) at the participant's expense.

You should expect to receive an initial supply of open-label chlorthalidone (12.5 mg) about the time that you received this package. The ALLHAT Drug Order Form (AL10 - purple border) has been revised. A photocopy is enclosed with this packet so that you can order more open-label chlorthalidone as you need to do so.

The one-page "*List of ALLHAT Bottle Codes for Doxazosin*" should be used when you return unused doxazosin to the DDC or destroy the medications locally. You should return all of the bottles from your inventory as well as those returned to you by your ALLHAT participants no later than **June 1, 2000**. Use this sheet now to help you remove these Step 1 medications from your inventory.

ALLHAT Doxazosin Transition Form - five photocopies



If you are able to schedule transition visits March 8 or soon thereafter, and you do not receive the NCR copies from the CTC in time, please use these. Photocopy additional copies if you need to do so. You can submit the completed photocopied forms to the CTC, but be sure to keep a copy for your files.

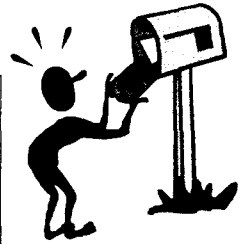
Frequently Asked Questions (FAQ's) for Regional and Study Coordinators

The enclosed FAQ's provide additional detail and rationale about the doxazosin transition timeline and procedures. Also included is a draft ALLHAT Health Matters article about the transition. (This article will appear in the next ALLHAT Health Matters participant newsletter.)



Things to Watch For

In the next few weeks, you should receive the following:



	By:
A supply of open-label chlorthalidone	M 2/21/00
<ul style="list-style-type: none">• Transition forms (AL20) and instructions for all participants assigned to doxazosin• Certificates of appreciation for participants assigned to doxazosin but not in the lipid trial• Letters to other MD's• Participant ALLHAT histories for participants assigned to doxazosin and not in the lipid trial	W 3/6/00
Participant Health Matters newsletter, which contains additional information about the first ALLHAT trial results and how they affect ALLHAT	W 3/15/00

**If you have any questions,
please call your Regional Study Coordinator as soon as possible.**

LIST OF ALLHAT BOTTLE CODES FOR DOXAZOSIN

Please use this list to return unused bottles to the ALLHAT Drug Distribution Center:

**McKesson Bioservices
ALLHAT DDC, Attn: Returns
687D Lofstrand Lane
Rockville, MD 20850**

Phone: (301) 309-2426

Fed Ex government account (US): 1715-7850-7

Fed Ex from Canada or Virgin Islands: 1807-9476-0

- If none of the bottle codes are in your inventory, please indicate 0 under "Number of bottles on hand" and fax this sheet to the DDC.
- If the bottles are destroyed locally, please indicate by checking the appropriate box for each code and faxing this sheet to the DDC.

Clinic number and site code: _____

Investigator (please print): _____

Bottle Code	Lot numbers	Number of bottles on hand	Check if destroyed locally
12	ALL		<input type="checkbox"/>
13	ALL		<input type="checkbox"/>
20	ALL		<input type="checkbox"/>
22	ALL		<input type="checkbox"/>
27	ALL		<input type="checkbox"/>
39	ALL		<input type="checkbox"/>
42	ALL		<input type="checkbox"/>
43	ALL		<input type="checkbox"/>
46	ALL		<input type="checkbox"/>
55	ALL		<input type="checkbox"/>

Printed name of person preparing shipment / destroying bottles: _____

Signature of person preparing shipment / destroying bottles: _____

Date shipped, if applicable: _____

ALLHAT Drug Order Form

Clinic: _____ Site: _____ Date: _____
Month Day Year

Clinic Name: _____

Requestor's telephone No.: (____) _____

Important Notice!
 Please note changes in shipping address or drug receiver's name in the comments box below.

Fax form to Drug Distribution Center
@ (301) 251-1863

Alternatively, you may telephone your request to the DDC @ **(301) 309-2426**.

Blinded Antihypertensive Agents (Circle bottle number(s) and enter quantity required for each dose. Dose 0 bottles do not need to be ordered except when Dose 0 is needed for rechallenge. Large bottles (134ct) should be dispensed to participants on maintenance therapy with 3 to 4 months between scheduled visits. All orders received before 4:00 PM Eastern Time are shipped out same day for delivery next business day. **Please try to limit ordering to a monthly basis when possible.** In addition to meds, the DDC supplies trays, drug accountability notebooks, and non-CRC caps, which may be ordered in COMMENTS box.)

Bottle Code	Dose 1	Dose 2/3	Bottle Code	Dose 1	Dose 2/3	Bottle Code	Dose 1	Dose 2/3	Bottle Code	Dose 1	Dose 2/3	Bottle Code	Dose 1	Dose 2/3
10									40			50		
11			21			31			41			51		
						32						52		
			23			33						53		
14			24			34			44			54		
15			25			35			45					
16			26			36						56		
17						37			47			Dose 0 Bottles		
18			28			38			48			Bottle Code(s)	Qty	
19			29						49					

Open Label Agents

Drug Name	# of Bottles
Chlorthalidone, 12.5 mg (134 ct)	
Atenolol, 50 mg (134 ct)	
Clonidine, 0.2 mg (134 ct)	
Reserpine, 0.1 mg (134 ct)	
Hydralazine, 25 mg (134 ct)	
Hydralazine, 50 mg (134 ct)	
Potassium Supp., 8 mEq (134 ct)	
Pravastatin, 10 mg (90 ct)	
Pravastatin, 20 mg (90 ct)	
Pravastatin, 40 mg (90 ct)	

COMMENTS

Signature of person completing this form

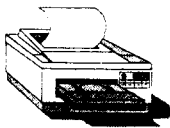



Center # and site code: _____

Investigator: _____

DOXAZOSIN TRANSITION TIMELINE

When part of a study is closed early, the following things must be accomplished in a timely manner:

	Description	Do by	Date Done
1	Write your center number and investigator's name at the top of this page, complete the date in the last column of this row and fax this page back to the CTC.	M 2/21/00 	
2	Date you received open-label chlorthalidone from the DDC CALL THE DDC AT (301) 309-2426 IF YOU DID NOT RECEIVE OPEN-LABEL CHLORTHALIDONE BY 2/21/00.	M 2/21/00	
4	Date when all letters have been sent to participants. Complete the date in the last column of this row and fax this page back to the CTC.	M 2/28/00 	
5	Date you received transition forms (AL20) and instructions from the CTC. CALL THE CTC (JUDY) AT 713-500-9512 IF YOU DID NOT RECEIVE TRANSITION FORMS (AL20) AND INSTRUCTIONS BY 3/6/00.	M 3/6/00	
6	Perform transition visits for all participants assigned to doxazosin. Send completed transition forms (AL20) to the CTC by 5/25/00 (May mail cutoff date).	By Th 5/25/00	
7	Package and return the doxazosin bottles to the DDC according to the instructions provided in the transition package. If the medications are destroyed locally, fax the completed inventory sheet to the DDC.	By Th 6/1/00	

CTC FAX NUMBER: 713-500-9530
ATTN: Judy

MAIL ALL LETTERS BY MONDAY, 2/28/00

Assigned to doxazosin & not in lipid trial

- Schedule the transition visits 3/8/00 or later.
- If participant has not called you by the end of March, call them to schedule an appointment for their transition visit.
- At the transition visit, discontinue the Step 1 medicine, provide new BP medicine as appropriate, as well as personalized certificate of appreciation. Update participant contact information. This is the participant's last ALLHAT visit.
- You may provide 1 bottle (a 4-month supply) of the ALLHAT Step 2, Step 3, or open-label chlorthalidone (provided) or prescribe any other antihypertensive medicine at your discretion to control BP until other care arrangements are made.
- If needed by the participant, locate other hypertension care source.
- REPORT ALL STUDY EVENTS.
- Complete Transition Form (AL20) and mail to the CTC to arrive by the May 25 mail cutoff.

Assigned to doxazosin & in lipid trial

- Schedule the transition visits 3/8/00 or later.
- If participant has not called you by the end of March, call them to schedule an appointment for their transition visit.
- At the transition visit, discontinue the Step 1 medicine and provide new BP medicine as appropriate.
- You may use the ALLHAT Step 2 or Step 3, open-label chlorthalidone (provided) or any other antihypertensive medicine at your discretion to control BP for the duration of ALLHAT.
- CONTINUE TO FOLLOW THE PARTICIPANT AND REPORT ALL STUDY EVENTS AS USUAL.
- Complete Transition Form (AL20) and mail to the CTC to arrive by the May 25 mail cutoff.

Not assigned to doxazosin

- CONTINUE TO FOLLOW THE PARTICIPANT AND REPORT ALL STUDY EVENTS AS USUAL.



ALLHAT TRANSITION FORM - ONLY FOR PARTICIPANTS ASSIGNED TO DOXAZOSIN
To be completed and sent to the CTC by the May 25, 2000 mail cutoff

<p align="center"><i>Place ID label here</i></p> <hr/> <p align="center">Patient name</p>	<p>1. Date of visit, or date last known alive (mm-dd-yyyy): ____ - ____ - ____</p> <p>2. Location: <input type="checkbox"/>1 ALLHAT clinic <input type="checkbox"/>2 Home <input type="checkbox"/>3 Phone (after May 1, 2000) <input type="checkbox"/>4 Lost to follow-up (Form complete - go to #9) <input type="checkbox"/>5 Refusal (Form complete - go to #9) <input type="checkbox"/>6 Otherwise unable to contact participant (Form complete - go to #9)</p>
---	---

3. a. Seated blood pressure readings (mmHg) (use 999 for telephone visits)..... ____ / ____

Patient should be seated for 5 minutes without smoking, feet flat on the floor, in an erect but comfortable position. **Blood pressure goals are <90 mmHg diastolic and <140 mmHg systolic.**

Average: ____ / ____

b. Initials of person performing blood pressure measurements (use 999 for telephone visits)

4. Collection of blinded Step 1 medication Done 1
Not done 2
Not prescribed at last visit 3

5. Participant is advised to take the following antihypertensive medication:..... a. None of the below 1
b. ALLHAT chlorthalidone 1
c. ALLHAT atenolol 1
d. ALLHAT clonidine 1
e. ALLHAT reserpine 1
f. ALLHAT hydralazine 1
g. Other antihypertensive medication 1

Number of overnight hospitalizations since the patient's last ALLHAT visit (none = 00, unknown = 99)

7. Number of visits to any doctor's office or clinic since the patient's last ALLHAT visit (none = 00, unknown = 99) ..
(Includes interim visits to **ALLHAT** clinic for blood pressure measurements and/or drug titration.)

8. Since the last ALLHAT visit, has the participant experienced any new occurrence of the following:
(Please check one for each of the items #8a-k.)

	Hospitalized	Diagnosis Only	Treatment Only	No
a. Acute myocardial infarction (including evolving MI with thrombolysis)	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Stroke (not TIA or "ministroke") -	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Cancer (a new <i>primary</i> diagnosis; excluding non-melanoma skin cancer).....	<input type="checkbox"/> 1	<input type="checkbox"/> 4	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d. Congestive heart failure.....	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
e. Angina pectoris (actual episode of chest pain)	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
f. Lower extremity peripheral arterial disease	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
g. Accident or attempted suicide.....	<input type="checkbox"/> 1		<input type="checkbox"/> 2	<input type="checkbox"/> 3
Any of the following procedures?	Yes			No
h. Kidney transplant or start of chronic dialysis	<input type="checkbox"/> 1			<input type="checkbox"/> 2
i. Coronary artery bypass graft (CABG) or transmyocardial laser revascularization	<input type="checkbox"/> 1			<input type="checkbox"/> 2
j. Coronary PTCA (angioplasty), stent or atherectomy	<input type="checkbox"/> 1			<input type="checkbox"/> 2
k. Lower extremity peripheral revascularization/bypass/angioplasty	<input type="checkbox"/> 1			<input type="checkbox"/> 2

Complete an Event Reporting Form (AL04) for all boxed events in Items #8a-k.

- ♥ No participant should retain any bottle (**whole or part**) of Step 1 blinded medication.
- ♥ Participants in the lipid component will continue with their routine ALLHAT visit schedule. Participants **not** in the lipid component will not continue with ALLHAT.
- ✓ Update participant contact sheet & release of info for medical records.
- ✓ Have participant sign release of information for study data to be sent to other private MD if applicable.

9. Signature and initials of person completing this form: _____

INSTRUCTIONS FOR ALLHAT TRANSITION FORM (AL20)
Please insert these instructions at the back of your MOO Chapter 3
February 16, 2000

- Q1** *For whom should I complete an ALLHAT Transition Form (AL20)?*
A1 ALLHAT Transition Forms (AL20's) are required for all participants who are assigned to doxazosin and who are not already reported as dead (AL04). You will find these participants listed on:
♥ ALLHAT Participants Assigned to Doxazosin and Not in the Lipid Trial
♥ ALLHAT Participants Assigned to Doxazosin and in the Lipid Trial
These lists were included with your first package of transition materials from the CTC.
- Q2** *Does this mean that all of these participants are done with ALLHAT?*
A2 **No!** The transition visit for participants assigned to doxazosin and *not in* the lipid trial will be their last ALLHAT visit. However, participants assigned to doxazosin and *in* the lipid trial will continue to be followed as usual until March 2002.
- Q3** *When should these visits happen?*
A3 You may start transition visits for these participants as early as you need to, although you will not have the NCR copies of the form until about March 6-8. All transition visits should be done and the transition forms (AL20's) completed and submitted to the CTC in time to arrive by the May 25, 2000 mail cutoff.
- Q4** *What happens during these visits?*
A4 ♥ Explain the reason for the visit and what will happen for the participant in terms of ALLHAT follow-up and antihypertensive medicine
♥ BP measurement
♥ Collection of blinded study medicine (Step 1) if the participant
♥ Prescription of other antihypertensive medicine
♥ Event information collection just like a normal study visit
♥ Update participant contact information and have patient sign release of info if necessary
♥ For participants whose transition visit is their last ALLHAT visit (assigned to doxazosin and not in the lipid trial), provide certificate of appreciation
- Q5** *What should I do about antihypertensive medicines for these participants?*
A5 As explained in the transition materials, you may provide the following at your PI's discretion:
♥ Open-label chlorthalidone from ALLHAT
♥ Open-label atenolol, clonidine, reserpine or hydralazine from ALLHAT
♥ Other antihypertensive medicine at the patient's expense
These may be used alone or in combination, per your PI's medical judgment. *For participants who are assigned to doxazosin and not in the lipid trial, only one 4-month supply of ALLHAT-supplied medicines may be dispensed to carry them until other hypertension care is arranged.*

General information: The ALLHAT Transition Form (AL20) is a one-page NCR form, with a white original and yellow copy. As with most other ALLHAT forms, send the completed white copy to the CTC, and keep the yellow copy for your files.

Because of the nature of these visits, clinic visits are preferred. If you cannot accomplish a clinic visit in time to meet the May 25 mail cutoff, home visits are encouraged. Only when you exhaust those two

possibilities should you consider a telephone visit. If you are currently following some participants by phone and they are not on the Step 1 medicine, you can do a phone transition at any time.

It will be difficult to complete transition visits for participants who are reported as lost or refusing, but forms still must be filed for those participants (see instructions below). Also, there will be a few participants for whom contact is impossible for a variety of reasons - for example, participants who are out of town for long periods of time and for whom out-of-town contact information is not correct.

IF A PARTICIPANT WHO IS CURRENTLY ON THE STEP 1 MEDICINE IS OUT OF TOWN OR YOU MUST COMPLETE THEIR TRANSITION VISIT BY TELEPHONE FOR ANY REASON, PLEASE DO SO AND SCHEDULE A CLINIC VISIT FOR AS SOON AS POSSIBLE, EVEN IF IT IS AFTER MAY 25, 2000. YOU STILL MUST COLLECT THE STEP 1 BOTTLES AND PRESCRIBE NEW MEDICINE FOR HYPERTENSION.

Progress notes: Just like other ALLHAT visits, you should keep separate progress notes to document all information on the AL20.

DIRECTIONS FOR ALLHAT TRANSITION FORM (AL20)

ID label: Affix participant's ID label in the space provided. Be sure to put a label on the yellow copy or print the participant's name to show through on the yellow copy.

Item #1 - Date of visit, or date last known alive: If the visit takes place in the clinic, at home, or by telephone, please insert the date of the visit in mm-dd-yyyy format. If the visit does not take place because the participant is lost, refusing or otherwise unable to contact, please insert the last date that the participant was last known (by you) to be alive.

Item #2 - Location: Check one box only. The "locations" are listed in order of preference. Attempt to do these visits in person - in the clinic or at the participants' homes - if possible. Only complete these visits by phone if all attempts to do in-person visits are unsuccessful - do not do a phone transition until on or after May 1, 2000. (The form says *after* May 1, but *on* May 1 is acceptable.)

If the participant is lost, refusing, or you are otherwise unable to contact the participant in the time allowed, check the appropriate box. For these participants, the rest of the form except for Item #9 (signature and initials) should be left blank.

Item #3a - Seated blood pressure readings: Take two blood pressure readings as you would for a normal follow-up visit. The same BP measurement procedures apply. Be sure to read to the nearest even digit, use leading zeros as necessary, and check your arithmetic on the average. If you completed the visit by telephone, complete all six BP spaces with 999.

Item #3b - Initials of person performing blood pressure measurements: The person performing the blood pressure measurements should PRINT their initials in #2b. Use 999 for telephone visits.

Item #4 - Collection of blinded Step 1 medication: It is important that the Step 1 bottles (empty, full, or partially used) be collected from participants who were prescribed the Step 1 medication at the previous visit. Only rarely should this be impossible. Mark the appropriate space, differentiating between "Not prescribed at the last visit" for participants who were not on Step 1 medication and "Not done" for participants who were indeed on Step 1 but forgot to bring it back to you.

Item #5 - Participant is advised to take the following antihypertensive medication: If the participant will start or continue with the ALLHAT chlorthalidone, atenolol, clonidine, reserpine or hydralazine, mark each box as appropriate. If the participant will start or continue with another antihypertensive medication, mark #5g (regardless of actual reason for prescription). If you are unsure of whether a medication is an antihypertensive medication, check your list of Hypertensive and Lipid Lowering Drugs (for Question 10 of AL03). If the list says that you should check the AL03 #10a-k, then you should check the AL20 #5g.

If the participant will not be on any of #5b-g, then check None #5a.

NOTE: Items #6, #7 and #8a-k appear here exactly as they appear on the AL03 (ALLHAT Follow-up Form). If you are also completing an AL03 on the same day as the transition visit, the information should be duplicated.

Item #6 - Number of overnight hospitalizations: This item asks for information on the number of *overnight hospital admissions* (not emergency room visits or overnight observations when the participant was not actually admitted) since the participant's last ALLHAT visit. (*Be sure to distinguish between the last non-ALLHAT office visit and the last ALLHAT office visit.*) Do not provide the number of days the participant was in the hospital, but the total number of admissions. If the participant has had none, please complete the item as "00" - do *not* leave this item blank.

Item #7 - Number of visits to doctor's office or clinic: We are interested in the number of visits to a doctor's office or clinic since the last ALLHAT visit. (*Be sure to distinguish between the last non-ALLHAT office visit and the last ALLHAT office visit.*) This should include all interim visits to your office as well as other physicians' offices or clinics, and should include interim drug titration visits for ALLHAT. DO NOT INCLUDE VISITS TO A CHIROPRACTOR OR ACUPUNCTURIST (UNLESS THE ACUPUNCTURIST IS A PHYSICIAN.) Again, if the participant had no interim visits to either your office or another office, complete the item as "00" - do *not* leave this item blank.

Item #8 - New occurrences of study events: Review this item very carefully. For each possible study event listed, a response is expected - "Hospitalized", "Diagnosis only", "Treatment only", or "No". You should use your clinical judgment plus guidance provided in Chapter 5 in determining the proper response to each of these:

- 8a) acute myocardial infarction, including evolving MI with thrombolysis - do not report apparent "silent" MIs ascertained on the basis of definitive ECG changes; these will be ascertained centrally.
- 8b) stroke (not a TIA or "ministroke"),
- 8c) a new primary diagnosis of cancer (***do not report recurring overnight hospitalizations for chemotherapy or other cancer treatment, and do not report non-melanoma skin cancers or recurrent or metastatic/secondary cancers.***) – note that this is the only event for which a "diagnosis only" (e.g., out-patient biopsy) is reportable via AL04
- 8d) congestive heart failure - ***acute episode only***
- 8e) angina pectoris - ***acute episode only***
- 8f) lower extremity peripheral arterial disease - does not include carotid disease, renal artery disease or aortic aneurysms
- 8g) accident or attempted suicide
- 8h) kidney transplant or start of chronic dialysis
- 8i) Coronary artery bypass graft (CABG)

- 8j) Coronary PTCA (angioplasty), stent or atherectomy
- 8k) Lower extremity peripheral revascularization / bypass / angioplasty

“Acute episodes” are those that bring the patient to medical attention or cause some change or addition to their daily treatment or routine.

Take special note of all events that are enclosed in the boxes on the form. For each of these events, the investigator will also obtain and submit a copy of the hospital discharge summary upon which the diagnosis is based. (For “diagnosis only” cancers, a pathology report is sufficient.) Form AL04 should be completed (one for each of these events; please refer to Chapter 5 for instructions).

We will not be collecting information via AL04 on non-hospitalized MI's or strokes. Both should still be checked on the AL20 as “treatment only” if treatment occurred. Do not report “silent” MI's discovered on the basis on definitive ECG changes; these will be ascertained as part of the central ECG coding of ALLHAT biennial ECGs.

Item #9 - Signature and initials: As usual, the person completing the form should sign and initial the AL20 in this item.

REMINDERS:

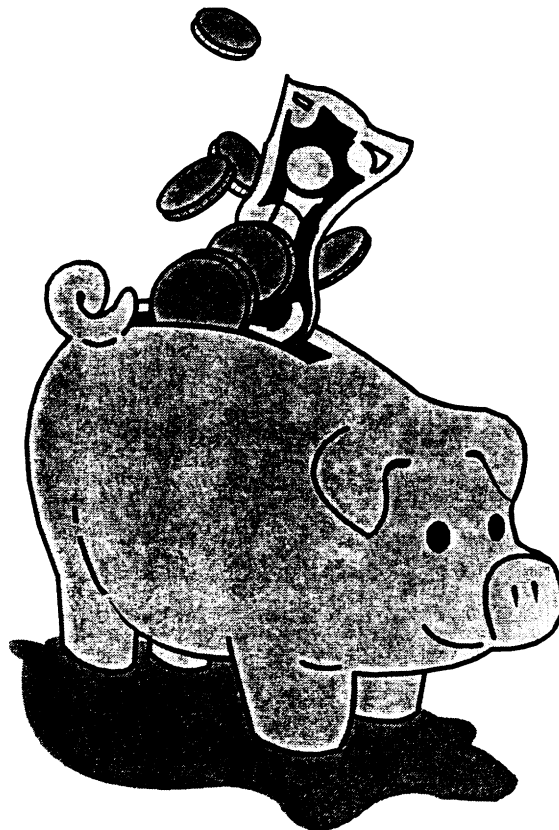
- ✓ Participants assigned to doxazosin and **in** the lipid trial **will continue** with their routine ALLHAT visit schedule.
- ✓ Participants assigned to doxazosin and **not in** the lipid trial **will not continue** with ALLHAT. Update the participants' contact information sheets and release of information for medical records. If applicable, have participants sign release of information for study data (patient histories) to be sent to their primary care or other doctors.
- ✓ Send all completed AL20's to arrive at the CTC no later than the May 25, 2000 mail cutoff.

Thank you!

GOOD NEWS!

YOU WILL RECEIVE PAYMENT
FOR ALL CORRECTLY COMPLETED
TRANSITION FORMS (AL20)!

The payment is the same as for an AL03.





Important Questions & Answers about ALLHAT!

1) **Q. Why is ALLHAT discontinuing the drug doxazosin?**

- A. As you may recall, one of ALLHAT's goals is to learn which of four types of high blood pressure medicines are the best in helping to control blood pressure and lowering risk of heart disease, stroke and early death. Because of your participation in ALLHAT, we have learned that doxazosin, one of the study medicines, is not working to lower the risk of some heart diseases as well as other blood pressure medicines can. This is exciting to ALLHAT because we have answered one of the study questions earlier than expected. It also means that ALLHAT no longer needs to study the medicine doxazosin.

2) **Q. Is doxazosin harmful to my health if I have been taking it?**

- A. Doxazosin is a Food and Drug Administration (FDA) approved medicine and is used for other types of health problems such as prostate troubles. ALLHAT has not found that Doxazosin is harmful, but the study has found that other high blood pressure medicines may lower your risk of heart disease better than doxazosin.

3) **Q. Are the other medicines in ALLHAT safe?**

- A. Yes, all of the ALLHAT drugs are FDA approved and have been used to lower blood pressure for many years. ALLHAT is learning, through your participation, which of four *commonly used* high blood pressure medicines are best for lowering the risk of heart disease, stroke and early death in patients with high blood pressure. A panel of

expert doctors, known to ALLHAT as the Data and Safety Monitoring Board, watches the information gathered from your ALLHAT visits and advises the National Heart, Lung and Blood Institute. Their job is to make sure that you are safe while participating in ALLHAT. If they detect that the medicines in the study are not helpful or are harmful to you then steps will be taken to make sure you stay safe.

4) **Q. If I am assigned to the drug doxazosin, what should I do?**

- A. If you have been informed through a letter from your ALLHAT clinic that you are **currently taking the medicine doxazosin** it is important that you:
- 1) **KEEP TAKING** your ALLHAT medicine doxazosin, as it is helping to keep your blood pressure controlled, until you can meet with your doctor to decide if a different high blood pressure medicine is right for you;
 - 2) Call your ALLHAT clinic and make an appointment to meet with your doctor within one month of receiving the letter;
 - 3) Bring your ALLHAT medicine to your ALLHAT appointment;
 - 4) Understand that this will be your last ALLHAT visit *unless* you are participating in the lipid-lowering part of the study;
 - 5) Remember that your participation in the ALLHAT has helped researchers to answer a very important question about high blood pressure medicine and you have been a valuable participant; and
 - 6) Support your family and friends who will be continuing with ALLHAT to take their medicines and keep their ALLHAT visits!

5) **Q. If I have been assigned to doxazosin and I am also in the lipid-lowering part of the study, will I still continue to be involved with ALLHAT?**

A. YES! You are a valuable participant in the in the lipid-lowering part of ALLHAT. You will continue to visit your ALLHAT doctor every four months. You will also continue to be given medication to control your blood pressure. Please be sure to:

- 1) **KEEP TAKING** the medicines given to you by your ALLHAT doctor;
- 2) Keep following any dietary advice that your doctor gives you;
- 3) Make an appointment in the next month to discuss your high blood pressure medicine with your doctor if you are currently taking doxazosin; and
- 4) **KEEP** coming to your ALLHAT visits!

6) **Q. If I am NOT assigned to the medicine doxazosin, why is it important that I continue to participate in ALLHAT?**

A. If you were NOT assigned to take doxazosin then it is *very important for you to continue* your participation in ALLHAT because we are still learning which medicines are the BEST at lowering health risks connected with high blood pressure. Your participation is the only way that we can answer this question! Please remember to:

- 1) **KEEP TAKING** your high blood pressure medicine, as it is helping to keep your blood pressure controlled;
- 2) Attend your regularly scheduled ALLHAT visits every four months; and
- 3) Continue to support other family and friends who are also a part of ALLHAT!

ALLHAT

7) **Q. If I have not been keeping up with my scheduled ALLHAT visits or have lost touch with my ALLHAT clinic, how can I get re-involved?**

A. If you are an ALLHAT participant but have not been taking your ALLHAT medicine, have missed appointments or have moved and do not have a new ALLHAT clinic we would like to hear how you are doing! You are still a part of ALLHAT and a very important part of the study. **Please call your last ALLHAT clinic.** We would like the opportunity to speak with you and answer any questions you may have.

8) **Q. If I am no longer in ALLHAT, how will my blood pressure be treated now?**

A. If you are one of the participants assigned to doxazosin and will no longer be participating in ALLHAT then your blood pressure health will now be treated by your regular family doctor. During your final ALLHAT visit your ALLHAT doctor will:

- Give you enough blood pressure medicine to last through your change from ALLHAT to regular care;
- Answer any questions you may have about high blood pressure and the future of your care.

If your family doctor is not your ALLHAT doctor then your ALLHAT doctor will also:

- Notify your family doctor of the changes happening with ALLHAT; and
- Help you find a family doctor if you do not already have one.

Q. I have questions about the changes in ALLHAT and how it affects me, whom should I ask?

A. We understand that you may have additional questions about the changes in ALLHAT and your future as a participant. Please *write your questions down* and bring them with you to your next ALLHAT visit. Your doctor will be able to go to your questions and help you to find the answers.



More ALLHAT Questions and Answers

Revised 3/1/00

1. *What is the reason for the higher rate of CHF in doxazosin users?*

One explanation for the superiority of chlorthalidone is that this drug is very effective in preventing CHF. Doxazosin may have no effect ("a placebo-like effect") in CHF prevention. If doxazosin precipitates CHF, which cannot be concluded in ALLHAT, several possible mechanisms may be hypothesized and deserve further investigation.

2. *How much of the difference in cardiovascular event rates between chlorthalidone and doxazosin can be explained by the observed 2-3 mm Hg difference in SBP?*

At least some of the difference in the risk of CHF and much of the difference in the risk of stroke may be explained.

3. *Is doxazosin harmful in patients with hypertension?*

ALLHAT compared 3 active drug regimens against an active standard regimen. Since there was no placebo or "no treatment" arm, it was not designed to evaluate the potential for any of the drug treatment arms causing harm. A comparative trial like ALLHAT can only determine whether a new treatment is superior, equal or inferior to a standard treatment. ALLHAT has shown that doxazosin is inferior to the diuretic chlorthalidone as initial treatment.

4. *Is doxazosin harmful if used in normotensive patients with BPH?*

ALLHAT did not study normotensive patients and, thus, cannot answer that question. Whether doxazosin causes CHF in normotensive patients with BPH deserves investigation.

5. *Do the findings for doxazosin extend to other alpha-blockers?*

They might very well do so, but no firm conclusions can be drawn. The question needs an answer. Until the answer is available, alpha-blockers should not be considered first-line (initial) therapy to lower elevated blood pressure in older hypertensive patients.

6. *ALLHAT is also investigating two other drugs, a calcium antagonist and an ACE inhibitor. Are these drugs also inferior to chlorthalidone?*

After accumulating over half of the information expected, ALLHAT has not yet reached any conclusions for these drugs. ALLHAT continues with ongoing oversight by a Data and Safety Monitoring Board, and the answer will be available in 2 years or earlier.

7. *Since ALLHAT continues the amlodipine treatment, can one conclude that calcium antagonists are safe?*

After accumulating over half of the information expected, ALLHAT has not yet reached any conclusions for these drugs. ALLHAT continues with ongoing oversight by a Data and Safety Monitoring Board, and the answer will be available in 2 years or earlier.

8. *My father is on doxazosin. Should he stop taking this drug immediately?*

No, he should continue taking his medication at least until he has seen his physician. We know that doxazosin is beneficial in lowering elevated cholesterol levels and for BPH. After reviewing your father's individual circumstances, the doctor may or may not think that another treatment will be of more benefit.

9. *Do the ALLHAT results apply to the use of doxazosin in combination with other antihypertensives?*

Doxazosin was used as initial therapy in ALLHAT. Whether it has value as "add on" therapy to achieve blood pressure control was not examined.

10. *Could the increased CHF noted in ALLHAT simply be the result of the overdiagnosis of CHF in patients who develop edema/fluid retention from doxazosin?*

That possibility was considered, but after detailed evaluation of clinical information on a sample of the cases, we believe it was not an important factor, and in particular could not explain the significantly higher combined rate of hospitalized and fatal CHF in the doxazosin arm.

11. *Why was this part of the trial not stopped earlier?*

Several considerations were deliberated by the Data Safety Monitoring Board, the Project Office, and the Clinical Trials Center when the difference in a major secondary endpoint between the doxazosin arm and the chlorthalidone arm appeared to be significant and in favor of the chlorthalidone. First it was noted there was no difference in the primary endpoint or in total mortality; second, it was noted that the major portion of the endpoint which was different was CHF events and further evaluation was needed to be assured that the cases reported were real and of similar severity in the two arms; and third, the average cholesterol level was lower (as expected) in the doxazosin arm and there was consideration of the potential of delayed benefit that might counterbalance the reduced prevention of CHF disadvantage. The next review was done in six months rather than the usual 9-12 months. At that time the overall evidence was more convincing that a protocol change should be made; the overall trends persisted and the statistical evaluation showed that the likelihood of doxazosin proving superior to chlorthalidone by the end of ALLHAT was extremely unlikely.

12. *Why did NHLBI ask an independent review group as well as the DSMB to review the ALLHAT data?*

The decision as to whether a change in the ALLHAT protocol of the magnitude of stopping one arm must be finally made by the Director of NHLBI, with advice from the DSMB and others, including independent experts, if necessary. Because the DSMB vote on the issue of whether to continue the doxazosin arm was a split vote with several members on each side of the issue, the Director, NHLBI, chose to obtain additional advice from independent experts as well. They unanimously recommended stopping the arm. Though it has not occurred very often in the past, NHLBI directors have sought advice from independent experts in similar difficult situations in large clinical studies.

FAQs For Regional & Study Coordinators

1) Q. Why is it critical that the participant's letters are mailed NO LATER THAN February 28, 2000?

A. There are two main reasons why these letters are important:

- 1) We anticipate a news release from NHLBI to the media early in March. It is better that participants learn this news from you and **NOT** the media!
- 2) The additional information provided with the letter will help the participants understand the changes **BEFORE** you meet with them for their final visit. This will make your transition process go much smoother!

2) Q. what should I do if one of my participants, who is NOT assigned to doxazosin, wants to stop being in the study because of concerns with the new findings?

A. Ask your PI to take some time to talk with this participant. It is important that the participant's concerns are heard and addressed. In most cases participants want to be reassured that they are safe and have their questions answered. It is also important to reinforce the presence of the DSMB that oversees the safety of study participants.

Taking a little **CAARE** will go a long way:

- **COMMUNICATE** with the participant;
- Be **AVAILABLE** to answer questions;
- Make sure the participant knows that we **APPRECIATE** them and they are an important part of the study;
- **RESPECT** the participant's concerns;
- Remember **EDUCATION** is the key to understanding!

Also, remember to thank your participant for their contribution to ALLHAT! Remind them that, as participants, they will be the first to learn about their new answers we hope to find as we continue the study!

3) Q. Do we have to try to notify participants that are lost or refusing?

A. Yes! It is our obligation to notify them of the new results and it is an **EXCELLENT** opportunity to reach out and **FIND ALLHAT** participants who have been lost and/or touch-base with those who are refusing. We suggest that you send **LOST/REFUSED** participants their transition letters through certified mail. Other suggestions to find these participants include:

- Calling the participant's last known phone number.
- Contacting the participant's other doctors.
- Contacting family members.

4) Q. Are there funds available to pay for additional costs accrued through phone calls and certified letters?

A. No. Unfortunately there are no additional funds available at CTC. If this is a concern for your clinic we suggest that you contact your regional coordinator.

5) Q. What are my treatment options for those participants who are on doxazosin? Can Step 2 or 3 be offered as an alternative?

A. Since diuretics have been shown to be effective first-line drugs for the control of hypertension, we are offering open-label chlorthalidone to all those doxazosin participants in the lipid-lowering trial. However, the step 2 or 3 open-label drugs will also be available, if the ALLHAT physician feels they are preferable first-line drugs for certain participants. (Of course, the step 2 and step 3 open-label medications remain available for use as second and third line antihypertensive medications for those participants remaining in ALLHAT.)

6) *Q. Will we be providing any medication to participants who are receiving Step 2 or 3 agents along with or in lieu of Step 1 doxazosin?*

A. If the participant is in the lipid-lowering trial they can continue to receive their step 2 or step 3 agents. The ALLHAT physician can also:

- 1) Provide open-label ALLHAT chlorthalidone, which will be available for these participants through ALLHAT; or
- 2) Prescribe a new medication of choice at the participants expense.

If the participant is NOT in the lipid-lowering trial, the ALLHAT physician can:

- 1) Provide one more four-month supply of their open-label ALLHAT step 2 or 3 med; and/or
- 2) Provide a four-month supply of open-label ALLHAT chlorthalidone in place of the doxazosin they were previously taking, if necessary.

However, it is important that you assist them in finding another physician (if the ALLHAT physician is not their primary care physician) BEFORE this medication runs out, so they can be discontinued from the ALLHAT medication and started on a new treatment plan in the safest way possible.

7) *Q. How soon will the open label chlorthalidone be available to offer to those continuing? How do I order it?*

A. An initial supply of open-label chlorthalidone should arrive at your clinic at the same time as your transition packets. When you need additional open-label chlorthalidone in your clinic, you may order it from the Drug Distribution Center, just as you have ordered additional ALLHAT medications previously. The new drug order forms (AL10) in your transition packet will include provisions for ordering open-label chlorthalidone.

8) *Q. What should we do if we are waiting for a supply of open-label chlorthalidone to arrive at the clinic?*

A. There are four options:

- 1) Provide other open-label ALLHAT drugs (REMINDER: atenolol is one of the generally recommended first-step drugs);
- 2) Write a prescription (REMINDER: generic diuretics such as hydrochlorothiazide; chlorthalidone are very inexpensive);
- 3) Dispense available free samples; OR
- 4) Continue any unused ALLHAT doxazosin up to the transition visit.

9) *Q. What do I do about a participant that I have not heard from by the May 25th cut off date?*

A. By March 8th all participants assigned to doxazosin should be contacted and scheduled for a transition visit.

- If by May 1st you have not heard back from a participant then attempt to contact and conduct the transition visit by phone;
- If you CANNOT contact the participant after several attempts then file an AL07 lost or refused, as appropriate.

Remember, all transition paperwork must be received at CTC by May 25, 2000.

Q. Are there any patient assistance resources available for those participants who may need it?

A. Yes. The *Directory of Prescription Drug Patient Assistance Programs* is available on the Web at: www.pfdr.org/patients. If you do not have access to this then please contact your regional coordinator for a copy.

Q. I have more questions about the transition and changes in ALLHAT, who do I ask?

A. It is very important that you contact your regional coordinator with any questions or concerns. They are available and willing to assist you through this new EXCITING phase of ALLHAT!

SPECIAL CASES

1) Q. What do we do about participants in nursing homes, assisted living facilities or out of the area?

A. Your PI will send a letter to the medical director and inform him/her of the ALLHAT changes. The SC shall then contact the participant's primary nurse. It will be the SC's responsibility to provide all of the information and supplies needed to complete the transition.

2) Q. What do we do about participants who are scheduled in the clinic before the transition begins (2/18 - 3/8)?

A. There are several options:

- Reschedule the participant to come in during the transition period (after 3/8).
- See the participant as scheduled, but be sure to schedule another visit during transition and emphasize the importance of this visit to the participant.
- If the participant cannot reschedule the visit, and cannot come in later during the transition period, see the patient as scheduled--if absolutely necessary, the transition visit can be performed via telephone.

3) Q. What do we tell participants who ask about receiving open-label doxazosin for hypertension or other health problems?

A. Each physician prescribing open-label doxazosin must evaluate the specific benefits of this medicine for each individual participant. Doxazosin remains a FDA approved medication, which is effective for certain conditions. Urge the participant to

make an appointment to see the doctor who prescribed the doxazosin. Be sure to:

- Ask the participant for the name, address and phone number of the prescribing physician (if not the ALLHAT physician);
- Send to this physician the letter for "Other MD's Whose Participant is Assigned to Doxazosin" (this will be included in your second transition packet mailing from CTC).
- Have the ALLHAT PI call the physician to discuss the letter and the participant's concerns about remaining on doxazosin; and
- Let the participant know that you and his other physician(s) are working together to provide the best possible care.

REMEMBER!

- For participants not in the lipid-lowering trial, only *one* four month supply of open label chlorthalidone and/or ALLHAT step 2 or step 3 open-label medication will be provided. It is essential that you help these participants find a primary care physician to treat and monitor their blood pressure, if their ALLHAT physician is not their PCP.
- Changes in blood pressure medication require monitoring (e.g., with chlorthalidone potassium levels must be monitored). Other antihypertensive medications may differ from the doxazosin in side effects and in blood pressure control, all of which require monitoring by the physician and reassurances to the participants.

ALLHAT CLOSEOUT

**OCTOBER 2001 –
MARCH 2002**

ALLHAT CLOSEOUT KIT & INSTRUCTIONS

1

BEFORE YOU DO ANYTHING ELSE

The last page of this stapled set of materials is to be used as faxed acknowledgement to the CTC that you received this kit. Please complete your site number and investigators' name, and fax the confirmation to the CTC now.

As you know, ALLHAT Closeout Visits begin on October 1, 2001. The materials in this package contain everything that you need for closeout visits.

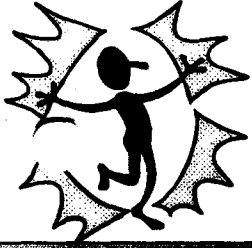
This package contains the following items, which are described more fully in the attached pages:

- 2 Closeout visit checklist (yellow cardstock) - English on 1 side, Spanish on the reverse side of the cardstock copy
- 1 Master list of participants so that you can keep track of who has been closed out and, if applicable, referred to another source of hypertension and/or lipid care
- 1 per patient For each participant: list of missing items, patient history, certificate of appreciation
- 50 Yellow envelopes for closeout materials (2 packs of 25) – order more from the CTC as you need them
- 50 ALLHAT Closeout Forms (AL22) (2 packs of 25) – order more from the CTC as you need them
- 2 Laminated response cards for Items #14 and #15 on the closeout form – English on 1 side, Spanish on the reverse side
- 2 Instructions for the closeout form
- 2 Sets of case study examples
- 25 Letters to non-ALLHAT physicians (1 tablet of 25 each) - order more from the CTC as you need them; these are also available from the CTC in Spanish
- 2 FAQ's for Regional and Study Coordinators
- 1 Guide to Pharmaceutical Patient Assistance Programs (GAP)
- 2 Closeout timeline (yellow cardstock)

ADDITIONAL QUANTITIES OF ANY OF THESE ITEMS MAY BE ORDERED FROM THE CTC

PLEASE NOTE: You should receive the *Health Matters* closeout newsletters for your participants (including FAQ's) under separate cover.

8/21/01



CLOSEOUT VISIT CHECKLIST

Participants not on the Step 1 medication still must have a Closeout Visit!
Please remember that the Closeout Visit will be the last ALLHAT visit.

FOR PARTICIPANTS ON ALLHAT STEP 1 MEDICATION

- Call the participant and remind them to bring their ALLHAT medications to the clinic.
- The first visit **on or after 10/1/2001** will be the closeout visit. **USE THE NEW FORM AL22. DO NOT FILE AN AL03 FOR ANY VISIT THAT TAKES PLACE ON OR AFTER 10/1/2001.**
- Use the list of missing items for the patient to determine what ECGs and laboratory tests must be done, if any, and complete those items:
 - ✓ The most recent required bloodwork
 - ✓ All of the required ECG's
 - ✓ All of the required event documentation
 - ✓ Release of information for documentation that you still need
 - ✓ Release of information to send participant's ALLHAT information to another physician, if required
 - ✓ Updated participant contact sheet
- Give the participant the following in an ALLHAT Closeout Folder:
 - ✓ A referral to another source of antihypertensive and lipid-lowering care, if needed
 - ✓ Closeout *Health Matters* newsletter
 - ✓ Certificate of appreciation
 - ✓ ALLHAT patient history, if desired by participant
- Provide antihypertensive and lipid-lowering medications as usual. The following medications will be provided by ALLHAT:
 - ✓ ALLHAT Step 1 blinded medication (until June 2002)
 - ✓ Open-label chlorthalidone, if needed, for participants originally assigned to doxazosin who are currently taking chlorthalidone (until June 2002)
 - ✓ ALLHAT Step 2 and Step 3 medications (until June 2002)
 - ✓ Potassium supplementation, as needed (until June 2002)
 - ✓ Pravastatin, as needed for those participants who were assigned to pravastatin in the lipid trial, if they are currently taking pravastatin (**1 bottle per participant only**)
- Complete:
 - ✓ All of the pending ALLHAT follow-up forms (AL03)
 - ✓ All of the pending ALLHAT Event Reporting forms (AL04), death certificates and discharge summaries
 - ✓ Any pending Serious Adverse Effect Forms (AL13)
 - ✓ All pending edits and corrections (routine edits, event edits, HCFA/VA event queries, AL09's)
 - ✓ The Closeout Form (AL22)

FOR PARTICIPANTS ON ALLHAT STEP 2 MEDICATION

- participants who are currently lost or refusing should contact you, complete a phone closeout or schedule a closeout visit in the clinic.
- You and your Regional Coordinator will work on the rest of these participants from January-March 2002.

Congratulations!

Congratulations for accomplishing the challenging task of following your ALLHAT participants up to the closeout phase of the study. The closeout phase of the study is extremely important considering both data collection and patient care. The contents of your closeout kit and this instruction packet will enable you to close ALLHAT successfully from both perspectives. Please contact your ALLHAT regional coordinator if you have any questions.

Best wishes as you plan and accomplish a successful closeout.

ALLHAT Closeout Calendar

About 9/15/01	Closeout kits Federal Expressed to the sites, including patient closeout newsletter
10/1/01	First closeout visit
1/31/02	Target for last closeout visit
2/02	Bulletin newsletter focusing on closeout issues
3/31/02	Last possible closeout visit
5/24/02	Last forms (all types, including AL04's) due at CTC
6/1/02	Unblinding kits to the sites
6/25/02	Last supporting event documentation due to CTC
7/25/02	Last changes due at CTC
8/15/02	Lock the data base – no further changes
Late 2002	Paper accepted for publication – Steering Committee meeting, Investigators' Meeting, press conference regarding ALLHAT results Bulletin & Health Matters special issues containing results and interpretation

Maintaining the blinding of the study medications during Closeout

After very careful consideration of issues related to the integrity and credibility of the trial, the ALLHAT Steering Committee has determined that to the extent consistent with good patient care, ALLHAT patients and their ALLHAT staff should not be unblinded as to their drug assignment until **June 2002**.

It is important for any trial (not only ALLHAT) to maintain the blinding of the study medications until all of the closeout visits, event forms and event documentation for **all** participants are complete. Therefore, although participants may complete their ALLHAT participation as early as October 1, 2001, unblinding of all bottle codes will not be done until **June 2002**. During the closeout period, the unblinding number will remain operational for medical emergencies.

Closeout Visit Checklist - yellow cardstock tip card

The yellow cardstock tip card should be posted NOW where ALLHAT staff may refer to it during closeout visits. This card will help you to remember what to do for each participant. The help card is the same as the Closeout Visit Checklist included in this packet.



Master list



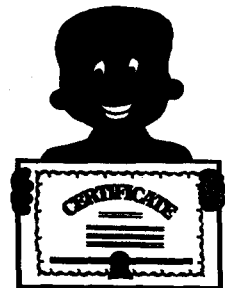
This list is in alphabetic order by your participants' names. The list provides the date of the last AL03 and the participant's status as of the beginning of August. You should use this list to keep track of who has had a closeout visit. If any visits, ECGs, labs, or edits were missing at the time the listing was generated, an "X" will appear in the appropriate space. There is also space for you to indicate when you saw the patient for their closeout visit, space for you and your regional coordinator to make extra notes about postcards, and the date that everything was completed.

Patients reported as dead as of the August 2001 reports are excluded from the lists, but patients who are reported as lost or refused are included and flagged.

Patient-specific Items

The following are included for every participant not reported as deceased:

1. A list of missing items such as the most recent blood work, any missing ECGs, missing events or documentation, and some edits – On your master list, any item flagged by an "X" for a participant will be specifically listed here. Use this to guide you in preparation for and during the participant's closeout visit. Be sure to schedule enough time for missing ECGs, labs and event clarification during the visit.



If you have sent several items in that are still listed as missing, please send them just one more time! Please feel free to call the CTC or your Regional Coordinator about specific items at any time.

2. Participant history - This contains information on blood pressure, antihypertensive and lipid-lowering medications, labs and other items during the time the participant was in ALLHAT. If the participant will be referred to another source of care for hypertension and lipid lowering, this may be provided to the patient and/or his/her other health care provider. You may make additional copies as you need them, but be sure to keep the original for your files. **If you will be mailing this to another physician, please obtain a release of information from the participant, if you are required to do so.**
3. Certificate of Appreciation – Scan through these certificates as soon as possible. If any certificates were damaged in shipping, are missing, or have names spelled incorrectly please let the CTC know as soon as possible so that they may be reprinted for you. At the end of the closeout visit, provide this certificate to the participant. These can be mailed to participants who cannot come to the clinic during closeout.

Closeout *Health Matters* Newsletters – coming to you under separate cover



You will be getting questions from participants, their families, and from other physicians about ALLHAT's closeout. This edition of the *Health Matters* Newsletter includes questions that will probably be among the most frequently asked, along with appropriate responses. This edition of the newsletter is also available in Spanish. Please order more from the CTC as needed.

Envelopes for Closeout Materials

The participants will be taking home some very important information. To keep it organized, bright yellow envelopes are provided. Please put everything that you are giving the participant into one of these envelopes. Order more from the CTC as you need them.



TIP: Use these envelopes to collect materials in preparation for the visit!

ALLHAT Closeout Forms, Instructions and Laminated Response Cards

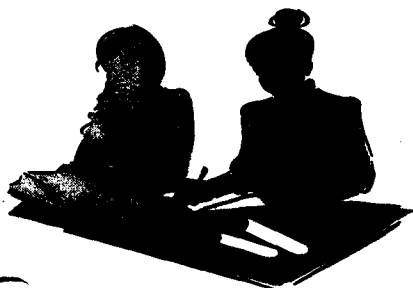


Beginning **October 1, 2001**, every ALLHAT participant who you see in the clinic will have his or her closeout visit using the new Closeout Form (AL22). Because of the nature of these visits, clinic visits are preferred. If you cannot accomplish a clinic visit in time to meet the **March 31, 2002** deadline, home visits are encouraged. Only when you exhaust those two possibilities should you consider a telephone visit. All closeout visits must be finished by **March 31, 2002**.

Enough closeout forms are included for your first 50 closeout visits. Please order additional AL22's if you need them using the regular supplies order process. The enclosed instructions tell you how to use the form.

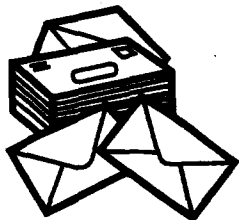
Along with the instructions and the forms, you will find two laminated response cards - English on one side and Spanish on the other side. These are to be used with Items #14 and #15 on the closeout form (AL22), which asks if there are any reasons why the participant might not have taken the ALLHAT medicine or otherwise did not participate fully in ALLHAT.

Case studies



Several case studies used for the closeout training in Kansas City are enclosed. You may find these helpful. If you did not attend the Kansas City training, please review these case studies prior to the first closeout visit.

Letters to Non-ALLHAT Physicians



For participants who are being referred to other non-ALLHAT physicians for continuing antihypertensive and/or lipid-lowering treatment and follow-up, form letters are provided so that you can inform them that ALLHAT is ending and how that affects their patient's treatment. Fill in the blanks in the letter with the participant's current treatment (blinded medication, pravastatin, other antihypertensive and lipid-lowering medications, potassium supplementation doses and dates first prescribed), recent blood pressure values and dates, and other comments regarding the participant. The letter also describes the timing for bottle code unblinding and release of study results. Be sure to sign the letter and provide your contact information. **BE AWARE THAT THIS LETTER IS DOUBLE-SIDED!** Additional tablets of these letters, as well as a Spanish translation of the letter, are available from the CTC.

Closeout Medications

If the participant is on the Step 1 (blinded) study medication, it may be continued until unblinding in **June 2002**. Other ALLHAT medications (open-label chlorthalidone, Step 2, Step 3 and/or potassium supplementation) may also be continued until that time. The open-label chlorthalidone may continue to be used for participants originally assigned to doxazosin who are currently taking chlorthalidone.



Keep in mind that there will not be another official ALLHAT visit to replenish the ALLHAT medications. If you decide to provide a four-month supply, you may need to see the participant prior the unblinding in **June 2002** if more medication is required, or you may decide to mail additional supplies to the participant. If local medical care customs allow, you may provide the participant with enough medication to last until **June 2002** (up to 8 months, for participants whose closeout visits are in **October 2001**). If you decide to provide enough medication to last until **June 2002**, the chart below may be helpful in determining how many bottles to dispense:

Month of closeout visit	# bottles to last until June 2002	
	Dose 1 or 2	Dose 3
October 2001	2	4
November 2001	2	4
December 2001	2	4
January 2002	2	4
February 2002	1	2
March 2002	1	2

ALLHAT pravastatin is available for those participants who were assigned to pravastatin in the lipid trial, if they are currently taking pravastatin (**1 bottle per participant only**). You may also prescribe other antihypertensive and/or lipid-lowering medication(s) at the participant's expense.

If you need to order more ALLHAT medications, please use the ALLHAT Drug Order Form (AL10 - purple border) to do so. **The last date that study medication will be shipped from the DDC will be Thursday, May 30, 2002.** Drug orders will not be accepted after that date.

Significant adverse effects after the closeout visit

Significant adverse effects (SAEs) due to the blinded study medication are very uncommon. However, if you believe that a participant has had a SAE due to the blinded study medication, and it occurs after the closeout visit, please report it in the usual way on an AL13.

Pharmaceutical patient assistance programs

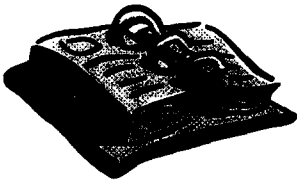
ALLHAT has put together a reference binder, called the Guide to Assistance Programs (GAP), which contains information on various patient pharmaceutical assistance programs. Usually, the patient has to have a limited annual household income and have no health insurance to qualify. Some of the tools in this binder include:

- A handy alphabetical and comprehensive listing of the common antihypertensive and lipid lowering medications and the manufacturer for each of these drugs.
- A copy of the PhRMA Patient Assistance Program Directory that lists individual pharmaceutical companies and their contact numbers.
- Copies of the actual applications from the different companies that provide free drugs are included for your use.
- Some patients may not qualify for the free medication programs. A list of programs that provide medication assistance for a processing fee is provided.

Frequently Asked Questions (FAQ's) for Regional and Study Coordinators

The enclosed FAQ's provide additional detail and rationale about the closeout timeline and procedures.

Closeout Timeline



Closing down a study requires a tremendous amount of work to be done in a relatively short time. To help you keep track of all of the tasks, a timetable is included on yellow cardstock for you to post in your clinic. The most important dates are listed below:

- Closeout visits begin on **October 1, 2001.**
- All closeout visits must be completed no later than **March 31, 2002.**
- All forms (all types) must be received at the CTC by **Friday, May 24, 2002** (the May 2002 mail cutoff).
- All remaining event documentation must be received at the CTC by **Tuesday, June 25, 2002** (the June 2002 mail cutoff).
- The last changes (AL09's and edits) are due at the CTC by **Thursday, July 25, 2002** (the July 2002 mail cutoff).

Please review this timeline carefully and schedule your clinic activities accordingly.

The routine closeout visit, and instructions for the Closeout Form (AL22)

The first visit on or after **October 1, 2001** is the closeout visit for that patient. Because of the nature of these visits, clinic visits are preferred. If you cannot accomplish a clinic visit in time to meet the **March 31, 2002** deadline, home visits are encouraged. Only when you exhaust those two possibilities should you consider a telephone visit.

Scheduling the closeout visit:

The last line of a sample visit schedule might look something like this, although the visit number and the window might be different:

Visit 26	7 yr 4 mo	27-Sep-2001 - 26-Jan-2002
----------	-----------	---------------------------

You can see that October 1, 2001 is in the window for this visit.

If Visit 26 is prior to October 1, 2001 and in the visit window:

- Complete an AL03 for the visit.
- Schedule another visit between October 1, 2001 and January 31, 2002 for the study closeout visit.
- If another visit cannot be scheduled by January 31, 2002, then schedule the visit on or before March 31, 2002.

If Visit 26 is on or after October 1, 2001 and in the visit window:

- This will be the closeout visit.
- Do not complete an AL03.
- Complete the ALLHAT Closeout Form (AL22) and procedures.

If a visit cannot take place until after the visit window:

- Schedule a visit prior to January 31, 2002 for the study closeout visit.
- If a visit cannot be scheduled by January 31, 2002, then schedule the visit on or before March 31, 2002.

If a visit cannot be scheduled in the clinic, by phone or at home by March 31, 2002:

- This will include losses to follow-up, refusals and non-responders.
- Your Regional Coordinator will be working with you to report these starting January 2002.

Plan on accomplishing the following at a closeout visit:

- ✓ Provide antihypertensive medication, potassium supplementation, and/or pravastatin as needed
 - See the information on pharmaceutical patient assistance programs if needed
- ✓ Obtain most recent ECG and bloodwork if missed
- ✓ Have the participant sign a release of information to send information to outside physician, if necessary
- ✓ Release of information for event documentation, if needed

- ✓ Update the participant contact sheet
- ✓ Refer the participant to another source of care, if needed
- ✓ Provide the participant with
 - The closeout *Health Matters* newsletter
 - Patient certificate of appreciation
 - Patient history, if desired by the participant
- ✓ Plan for pending AL03's, AL04's & documentation, AL13's, edits and corrections
 - Release of information for event documentation

What's Familiar

- Two seated blood pressure measurements
- Provision of antihypertensive medication, potassium supplementation and pravastatin as needed
- Study events assessment
- Quality of life questions

What's New

- Reasons participant might have had a problem with the study medication or problems attending clinic
- Assessment of participant's drug assignment

Specific instructions for the form are included in this closeout kit. After reviewing them carefully, please insert them at the end of your ALLHAT Manual of Operations, Chapter 3. Also, there is a laminated card to use with Items #14 and #15 on the form. Keep this laminated card handy during your closeout visits.

Closeout Activities for Losses to Follow-up, Refusals and Other Nonresponders

It is still very important for ALLHAT to know the vital status on or after **October 1, 2001** for every participant. The CTC has submitted identifying information to a search firm for all participants whose vital status remains unknown as of July 2001, even if they were not classified as lost or refused. You have received these results already, and should be using this information to try again to contact these participants. Document all of your attempts in your progress notes. If you are able to contact these participants, complete a closeout visit in the clinic, at the participant's home or by telephone on or after October 1, 2001.



In **January 2002**, your Regional Coordinator will work with you to complete closeout requirements for participants who still remain as lost, refusing, or who are still not responding as of that time. But don't wait until then to try to locate these participants – it is important to **START NOW!**

Returning study drugs to the ALLHAT DDC



In **June 2002**, you should return or destroy locally all of the Step 1 bottles from your inventory as well as partial bottles returned to you by your ALLHAT participants. At the same time, return or destroy unused open-label chlorthalidone, Step 2 and Step 3 medications, unused potassium supplement, and unused pravastatin. **Reserpine** must be returned to the DDC; do not destroy it locally. You will receive specific drug return instructions from the DDC in **June 2002**.

Study events

All study events occurring up to and including the date of the closeout visit must be reported on AL04's, regardless of when you find out about them. Do not report events that occur after that date. File an AL04 as soon as the event is known. File any documentation you have at the same time – it *may* be sufficient. If you have to request documentation, do it right away!



In some cases, alternate documentation is acceptable:

- For **non-hospitalized revascularization procedures**, the procedure reports or operative notes are usually adequate.
- For **cancer diagnoses**, the pathology reports of the initial diagnosis are best. Subsequent hospitalizations or treatment reports often do not give the date of initial diagnosis.
- For **nonfatal accidents (resulting in hospitalization)**, any documentation that describes the injury or treatment is sufficient.
- For the **initiation of chronic kidney dialysis**, progress notes or records documenting the dialysis are acceptable.

For the filing of fatal event reports:

- Deaths that occurred outside of the hospital do not need a hospital summary.
- Deaths occurred (or were "called") in the ER need an ER report.
- All deaths need a death certificate.
- If the **place of death** (home vs. ER or inpatient) on the death certificate differs from the investigator's impression of the place of death, the investigator must send in a correction form (AL09) changing the location of death question (#7a) on the AL04 or explaining the discrepancy. We will assume the death certificate to be correct (for location of death) unless told otherwise. NOTE: This error results in a large volume of AL09's!

- If the **cause of death** on the AL04 does not correspond to the death summary or, if none, the death certificate, the site will receive an AL09 querying their response to AL04 #4. **IT IS IMPERATIVE THAT THE SITE PI REVIEW ALL DOCUMENTATION**, and send in AL09's to correct the cause of death should it be necessary.
- For **deaths in which the CTC is to retrieve the death certificate**, the site must first complete all edits and AL09s, and submit all other required documentation. A request from the Regional Coordinator is then required for the CTC to close the case and request the death certificate.

Endpoint quality control (QC):

- All **incomplete quality control documentation** is listed on the monthly monitoring report. A site that has no incomplete event reports may still have incomplete quality control cases.
- The **requested QC documentation** must be submitted with the signed AL12 (the form requesting the documentation). If any documents are not available, that should be stated in the comment area (#9) on the AL12.
- Because of the time it takes to process and evaluate the QC endpoint results, it is absolutely imperative that this documentation be submitted to the CTC as soon as possible!

ALLHAT EVENT REPORTING FORM - VERSION 3

Attach hospital discharge summary and, if applicable, death certificate. For cancers diagnosed out of hospital, please attach pathology report.

Place ID label here
Patient name: _____

- 1. Today's date: ___ - ___ - ___
2. Date of event: ___ - ___ - ___
3. Type of event: Death [] 1
Non-fatal event [] 2

For all deaths - Complete items #4 - 10. Attach death certificate and, if applicable, discharge summary.

- 4. Cause of death (check only one) ... Definite MI [] 1
Definite CHD [] 2
Possible CHD [] 3
Stroke [] 4
CHF [] 5
Other cardiovascular disease [] 6
Cancer (list primary site in item #6) [] 7
Kidney disease [] 11
Accident, suicide, homicide [] 8
Other noncardiovascular disease [] 9
Unknown cause [] 10
5. If or definite or possible CHD, did death occur within 24 hours of symptoms? ... Yes [] 1
No [] 2
DK [] 3
6. If cancer, give primary site ... Lung [] 1
Colon [] 2
Breast [] 3
Prostate [] 4
Bladder [] 5
Other (specify) _____ [] 6
DK [] 7
7. a. Was patient hospitalized, or taken to a hospital, during fatal event? ... Yes [] 1
No (go to #8) [] 2
DK (go to #8) [] 3
b. If yes, is discharge summary attached? ... Yes [] 1
No [] 2
c. If hospitalized or taken to a hospital, what other events occurred during this hospitalization, other than the cause of death checked in #4?
a. None [] 1
b. Acute myocardial infarction (including evolving MI with thrombolysis) [] 1
c. Stroke (not TIA or "ministroke") [] 1
d. Cancer (a new primary diagnosis; excluding non-melanoma skin cancer) [] 1
e. Congestive heart failure [] 1
f. Angina pectoris (actual episode of chest pain) [] 1
g. Lower extremity arterial disease [] 1
h. Accident or attempted suicide [] 1
i. Kidney transplant [] 1
j. Start of chronic kidney dialysis [] 1
k. Coronary artery bypass graft (CABG) [] 1
l. Coronary PTCA (angioplasty), stent or atherectomy [] 1
m. Lower extremity peripheral revascularization/bypass/angioplasty [] 1

3. Is death certificate attached? Yes 1
 No 2
3. Death certificate or discharge summary is not attached, give primary reason Pending 1
 Patient/family refusal 2
 Unable to locate records 3
 Other (specify in comments) 4

For all nonfatal events, complete items #10 - 13. Attach discharge summary.

10. Type of nonfatal event (check all that apply)
- a. Hospitalized for acute myocardial infarction (including evolving MI with thrombolysis) 1
 - b. Hospitalized for stroke (not TIA or "ministroke") 1
 - c. Cancer (a new primary diagnosis; excluding non-melanoma skin cancer) 1
 - d. Hospitalized for congestive heart failure 1
 - e. Hospitalized for angina pectoris (actual episode of chest pain) 1
 - f. Hospitalized for lower extremity arterial disease 1
 - g. Hospitalized for accident or attempted suicide 1
 - h. Kidney transplant 1
 - i. Start of chronic kidney dialysis 1
 - j. Coronary artery bypass graft (CABG) 1
 - k. Coronary PTCA (angioplasty), stent or atherectomy 1
 - l. Lower extremity peripheral revascularization/bypass/angioplasty 1

11. If cancer, give primary site
- Lung 1
 - Colon 2
 - Breast 3
 - Prostate 4
 - Bladder 5
 - Other (specify) _____ 6
 - DK 7

12. a. Was patient hospitalized? Yes 1
 No 2
 DK 3
- b. If yes, is discharge summary attached? Yes 1
 No 2

13. If discharge summary is not attached, give primary reason Pending 1
 Patient/family refusal 2
 Unable to locate records 3
 Other (specify in comments) 4

For all events, please describe symptoms and your assessment/diagnosis

Place ID label here

Patient name: _____

14. Comments: _____

15. Initials of person completing this form
16. Signature of person completing this form _____
17. Signature of investigator _____

ALLHAT CORRECTION REQUEST

Place ID Label Here

Also place on Yellow and Pink copies.

1. Today's Date: - -
 MM DD YY

2.a. Form AL

2.b. Form Date: - -
 MM DD YY

3. Is form being:

Deleted

Reason: _____

Replaced

Reason: _____

Corrected



4.a. Item Number(s)

Description of Error(s)

4.b. Item Number(s)

Corrections

5.a. Correction is to the participant's Name/Acrostic

b. Participant's CURRENT Name appears as: _____

c. Participant's CORRECT Name is: _____

The Coordinating Center will automatically update the participant's ACROSTIC if applicable.

6.a. Correction requested by: Clinic Coordinating Center

b. By: _____

7. Date corrected on form: - - By: _____
 MM DD YY

For Coordinating Center Use Only:

8. Date correction made to the master file: - -
 MM DD YY

By: _____

WHITE - CTC Copy

YELLOW - Clinic Copy

PINK - File Copy

AL09 1/1
Version 2 - 11/96

ALLHAT ENDPOINT QUALITY CONTROL SELECTION AND DOCUMENTATION

The event listed below has been selected as part of ALLHAT's endpoint quality control documentation. Please obtain the records requested and send them with this cover sheet to the Clinical Trials Center with your regular shipment of study forms.

PLEASE KEEP A PHOTOCOPY OF THIS FORM FOR YOUR FILES.

- 1. Date this request generated: 04-15-99
Sequence Number: 1
- 2. Patient ID:
- 3. Site code: A
- 4. Acrostic: BERSO
- 5. Event date from ALO4 (mm-dd-yy): 12-14-98
- 6. Event type:
 - a. MI death X
 - b. Definite CHD death
 - c. Possible CHD death
 - d. Stroke death
 - e. Nonfatal MI
 - f. Nonfatal stroke
- 7. The following additional documents are requested:
 - a. ECGs X
 - b. Enzymes X
 - c. Reports of CT or MRI scans
 - d. Lumbar puncture results
 - e. Reports from neurologists
 - f. Discharge summary X

For clinical site use: Label all additional records with patient ID, acrostic and event date

- 8. The following additional records are enclosed:
 - a. None (explain) —
 - b. ECGs —
 - c. Enzymes —
 - d. Reports of CT or MRI scans —
 - e. Lumbar puncture results —
 - f. Reports from neurologists —
 - g. Discharge summary —

9. Comments: _____

10. Initials of clinical site staff person completing form: _____

11. Signature: _____

Clinical Trials Center Use Only:

12. Date additional documentation received: _____

13. Date completed: _____

14. Initials of CTC monitor: _____

15. Signature of CTC monitor: _____

COMPLETE LIST OF ALLHAT AL04 EVENTS

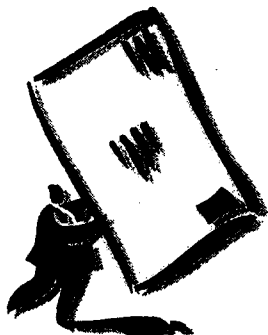
Report date: 05-06-01 14:17:36 Project: AL3170 RECR_SUM1
 Randomizations as of Wednesday, 05-02-01

Center number: Region

ID Number	Acrostic	Transfer Status	Event Type	Date of AL04	Date of Event	Missing Disch sum	Missing Death cert	Missing Yes	Missing Requires	Quality Control	
										Enzymes	Discharge summary
Incomplete	AVIAN		Cancer	02/10/1997	11/20/1996						
	AVIAN		Unknown Death	02/16/2001	07/15/2000					X	
			AWAIT DOCUMENTATION & CAUSE								
	VILTOO		CHF Death	02/20/1997	08/27/1995						
Incomplete	BERSO		Def MI Death	12/14/1998	12/14/1998					X	ECG
	VILAN		CHF	03/18/1998	01/19/1998						
	CUREL		Kidney dialysis	01/06/1999	09/30/1998						
	CASJUS		Oth NonCVD Dth	07/17/2000	12/24/1998						
	STOLAL		Oth NonCVD Dth	01/14/1999	08/20/1998						
Incomplete	ARTERE		Angina Pectoris	06/08/1999	02/09/1999						
	ARTERE		Angina Pectoris	05/17/1999	03/01/1999						
	ARTERE		CABG	06/15/2000	05/17/1999						
	DAVBEE		MI	04/23/1997	03/08/1997						
	ALCMA		Stroke	09/24/1997	07/21/1997						

Pending response to AL09 & AL04 MI 02/99

Unblinding in June 2002



You will receive a package in **June 2002** revealing each participant's blinded study medication. In that package, you will find:

- IRB packet
- Unblinding letters for participants, including a copy of each letter for your files
- Postage-paid envelopes for the letters
- Return address labels for your site
- An updated calendar for study results
- More ALLHAT Q&A

The letters to the participants must be mailed as soon as possible after you receive the kit in **June 2002**. Be aware that when the participants receive the letters, some may call for more information about what they should do about their blood pressure or lipid-lowering medicine. Since the study results will not be known until several months later, the most prudent advice seems to be to tell them that they should stay on their current medication until the study results are available in late 2002, unless they are having problems with their current medicines or a change in their health requires a prescription change.

The other items – an updated study calendar and more ALLHAT Q&A - will update you on what is happening with the plans for releasing the study results.

leaning up loose ends

Before ALLHAT can close out completely it must have no loose ends. In order for the results of ALLHAT to be taken seriously by the scientific community, the data must be complete and "clean." And, we must have as much information as possible about every patient ever enrolled in ALLHAT.



How can we be sure that we know the vital status of all ALLHAT patients? How can we get the maximum number of ECGs and blood work done on patients? How can we track down lost and refused patients? **By setting a comprehensive plan and sticking to it!**

Think ahead—develop a time table

It is not too early to have a plan—keep in mind the study dates below think about a possible time line that you may be want to be working on. *ALLHAT closeout is a process.* There are a lot of steps you will take to get it all done.

Important dates:

October 1, 2001
 January 31, 2002
 March 31, 2002
 May 24, 2002
 June 25, 2002
 July 25, 2002
 August 15, 2002

ALLHAT closeout visits begin
 Desired date to complete closeout visits
 Last date for all closeout visits
 Final forms are due the CTC
 Last event documentation due
 Last changes (including any type of edits) due
 Database is "locked"

Make a “to do list” of all the things your site needs to do to complete ALLHAT closeout

Keep this motto in mind: **“No plan = no progress.”**

Be honest with yourself—figure out which parts of ALLHAT you need to concentrate on, and then formulate a plan that will help to get started. The more you do now and the more organized you are as closeout begins, the easier it will be for you. Work with your Regional Coordinator to develop the best plan for your site.

This is the time to eliminate paperwork backlogs!

- This includes uncompleted forms for visits, events, serious adverse effects, losses and refusals, and ECGs.

Obtain and file event documentation:

- This includes death certificates and hospital discharge summaries
- Remember to obtain records for QC events (CHD and stroke)

Edit tips:

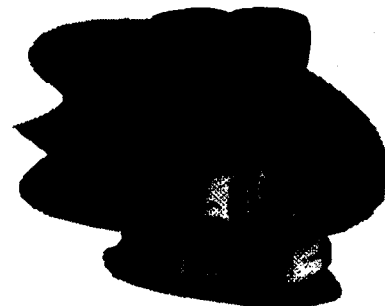
- Don't let edits pile up.
 - Be aware of what causes “edits” in the first place—incomplete or contradictory information that shows up on the form.
- When you fix an edit make sure it won't create new problems on the form. If it will create new edits, also be sure to fix those problems when the original correction is sent to the CTC.
- Pay special attention to question #7 on the AL03. For example, if you change from a blank to “none” this will cause questions #8 and #9 to kick in.
 - On the AL03, if you indicate there was an event in question #5 then you must complete an AL04. If there is no matching AL04, you will get an “event edit”.

Missing events reported by HCFA or the VA:

- These reports of possible missed MI's, deaths, and selected other events are from hospitalizations reported to Medicare or the VA.
- Submit AL04, if you find that the event actually did occur.

Storage of records

Federal regulations mandate that study records must be maintained for three years after the study is over. For ALLHAT, this will be **August 15, 2005**. Your IRB may have additional regulations. The University of Texas IRB does not have additional regulations, and IRB's in Canada do not have additional regulations. Records may be stored, but must be retrievable for that period of time. **DO NOT SEND YOUR RECORDS TO STORAGE UNTIL ALL EDITS ARE COMPLETED!**



This is a list of all things you need to keep:

- Patient charts
 - Case report forms (AL forms)
 - Signed and witnessed informed consent forms
 - Central laboratory reports
 - ECGs submitted as study data
 - Event documentation
 - Accompanying progress notes & visit schedule
- All versions of the protocol
- Study document binder, including approvals
- Drug Accountability Records
- Manual of Operations

You do not need to keep:

- Leftover patient labels or lab supplies
- Unused study forms
- Leftover mailing labels
- Monthly reports, newsletters, other correspondence

You don't have to keep these, but you might want them for future reference:

- ASK (Adherence Survival Kit)
- GAP (Guide to Assistance Programs)

Keep a supply of blank AL13's (Report of Serious Adverse Event) in case you need to report a SAE possibly due to the study drug, for participants continuing on the drug until unblinding.

Plans for dissemination of results

Of course, you will be fully informed of the study results and what they mean for you and your patients:

- In **late 2002**, the ALLHAT Steering Committee will be notified of the results at a face-to-face meeting.
- There will also be a meeting in which you will be shown the results.
- The results will be published in a major medical journal.
- There will be a press conference.
- After the results are published, there will be a special newsletter for ALLHAT staff and one for the participants. You should plan to mail these to your participants who are no longer in your practice at that time.
- We hope to present the results at a major scientific meeting early in 2003.



You will be kept informed as plans are finalized.

As always, if you have any questions, please call your Regional Study Coordinator as soon as possible.

Revised 8/13/01



CLOSEOUT TIMELINE

- | | |
|--------------------|---|
| By 9/31/01 | Receive your closeout kit for your site |
| 10/1/01 | First closeout visit |
| 1/1/02 | Begin working with your Regional Coordinator on closeouts for remaining losses, refusals and other missing participants |
| 1/31/02 | Target for last closeout visit |
| 3/31/02 | Last possible closeout visit |
| 5/24/02 | May 2002 mail cutoff - last forms (all types, including AL04's) due at CTC |
| Early 6/02 | Receive your unblinding kit; mail letters to participants; schedule visits as desired |
| During 6/02 | Respond to final drug recall from the ALLHAT DDC |
| 6/25/02 | June 2002 mail cutoff - last event documentation due to CTC |
| 7/25/02 | July 2002 mail cutoff - last changes due at CTC |
| Late 2002 | Paper accepted for publication – Steering Committee meeting, Investigators' Meeting, press conference, workshop on dissemination of results |
| | <i>Bulletin & Health Matters</i> special issues containing results and interpretation |



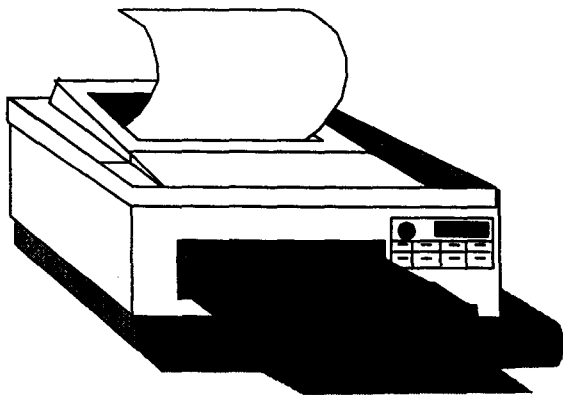
CLOSEOUT KIT CONFIRMATION

Center # and site code: _ _ _ _ _

Investigator: _____

To confirm that you received this package, write your center number and investigator's name at the top of this page and **fax this page back to the CTC BY Friday, 9/28/01.**

CTC FAX NUMBER: 713-500-9530
Attention: Judy Bettencourt



ALLHAT CLOSEOUT - LIST OF MISSING ITEMS

Report date: 08-06-01 14:59:15 Project: AL3421 CLOSEOUT
Data as of Wednesday, 08-01-01

Clinic: 001A

Name: [REDACTED]
ID & Acrostic: 001-003-001 YUHRID

Patient status as of 08/01/01: Known alive

Date of death and source:

Recent missed visits:

Visit # 23 05/17/2000 - 09/16/2000

ECGs:

Dates of all ECGs on file: 03/08/1994 07/10/2001

Please review your charts for these missed ECGs:

Year 2 01/17/1996 - 01/16/1998

Year 4 01/17/1998 - 01/16/2000

Labs:

Missed last required lab - please draw at closeout visit or sooner:

Visit #22, Panel ALL09

Forms in edit - please refer to your monthly edits:

No forms in edit as of 08/01/01 - please respond to future edits ASAP.

Incomplete events, including quality control events:

No incomplete events as of 08/01/01 - please complete future events ASAP.

HCFA/VA edits:

No outstanding HCFA/VA edits - please respond to future requests ASAP.

END OF LISTING FOR (001-003-001 YUHRID)

ALLHAT CLOSEOUT FORM

**To be completed between October 1, 2001 and March 31, 2002
and received at the CTC by May 24, 2002**

<p>Place ID label here</p> <hr/> <p>Patient name</p>	<p>1. Date this form is completed (mm-dd-yyyy): ____ - ____ - ____</p>
--	--

2. a. Has participant moved outside the United States, Canada, Puerto Rico or the U.S. Virgin Islands? Yes 1
No 2
Don't know 3

b. Type of visit (check one):
1 ALLHAT clinic
2 Home
3 Phone

c. Date of visit: ____ - ____ - ____ (mmddyyyy) (SKIP TO #3)

OR

4 Lost to follow-up
5 Refusal
6 Otherwise unable to contact

d. Date last known alive: ____ - ____ - ____ (mmddyyyy) (SKIP TO #16)

3. a. Seated blood pressure readings (mmHg) (use 999 for telephone visits) ____ / ____

Patient should be seated for 5 minutes without smoking, feet flat on the floor, in an erect comfortable position.

Average: ____ / ____

b. Initials of person performing blood pressure measurements (use 999 for telephone visits)

4. What dose of the ALLHAT Step 1 (blinded) medication is the patient being advised to take? Dose 1 1
Dose 2 2
Dose 3 3
None 4

5. Which of the following medications is the patient being advised to take? a. None of the below 1

This refers to any open-label antihypertensive or lipid-lowering medication, and potassium supplementation, including medications provided by ALLHAT or from another source, and regardless of reasons for prescription. CHECK ALL THAT APPLY.

- b. Diuretic 1-2 times per week 1
- c. Diuretic 3 or more times per week 1
- d. Calcium-channel blocker 1
- e. ACE inhibitor 1
- f. Alpha blocker 1
- g. Atenolol 1
- h. Clonidine 1
- i. Reserpine 1
- j. Hydralazine 1
- k. Other antihypertensive medication, regardless of indication 1
- l. HMG CoA reductase inhibitor (including ALLHAT pravastatin) 1
- m. Other lipid-lowering medication 1
- n. Potassium supplement 1
- o. Information not available 1

i. Number of overnight hospitalizations since the patient's last ALLHAT visit (none = 00, unknown = 99)

7. Number of visits to any doctor's office or clinic since the patient's last ALLHAT visit (none = 00, unknown = 99)... ____
 (Includes interim visits to ALLHAT clinic for blood pressure measurements and/or drug titration.)
8. Since the last ALLHAT visit, has the participant experienced any new occurrence of the following:
 Please check one for each of the items #8a-k.)

	<u>Hospitalized</u>	<u>Diagnosis Only</u>	<u>Treatment Only</u>	<u>No</u>
a. Acute myocardial infarction (including evolving MI with thrombolysis)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
b. Stroke (not TIA or "ministroke")	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
c. Cancer (a new <i>primary</i> diagnosis; excluding non-melanoma skin cancer).....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
d. Congestive heart failure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
e. Angina pectoris (actual episode of chest pain)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
f. Lower extremity peripheral arterial disease	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
g. Accident or attempted suicide.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

Any of the following procedures?

	<u>Yes</u>	<u>No</u>
h. Kidney transplant or start of chronic dialysis	<input type="checkbox"/> 1	<input type="checkbox"/> 2
i. Coronary artery bypass graft (CABG) or transmyocardial laser revascularization	<input type="checkbox"/> 1	<input type="checkbox"/> 2
j. Coronary PTCA (angioplasty), stent or atherectomy	<input type="checkbox"/> 1	<input type="checkbox"/> 2
k. Lower extremity peripheral revascularization/bypass/angioplasty.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2

Complete an Event Reporting Form (EDR) to all boxes on this form.

9. In general, would you say your health is:
- Excellent 1
 - Very good 2
 - Good 3
 - Fair 4
 - Poor 5
 - No answer/unknown 6
10. If you were to rate your current health on a scale of 0 to 100, with 100 being perfect health and 0 being death, what number would you rate yourself today? (Unknown = 999)
11. Have you ever smoked cigarettes?
- Current smoker (past 30 days) 1
 - Past smoker (100+ cigarettes) 2
 - Never smoked 3
 - Unknown 4
12. Are you currently taking aspirin regularly?.....
- Yes 1
 - No 2
 - Don't know 3
13. *For women only:* Are you currently prescribed an estrogen supplement?.....
- Yes 1
 - No 2
 - Don't know 3

Place ID label here

Patient name

14. a. Were there any reasons that kept you from taking your ALLHAT medicine (the black and blue capsules) ?..... Yes 1
No (skip to #15) 2

What were the reasons? b. Size or taste of pills was a problem 1

Show the participant the laminated response card for #14 and let them tell you their response(s). CHECK ALL THAT APPLY.

- c. Too many pills 1
- d. I didn't like not knowing what the medicine was 1
- e. It was hard to remember to take the medicine 1
- f. I didn't think that I needed the medicine 1
- g. I didn't understand how to take the medicine 1
- h. I had a bad reaction to the medicine 1
- i. I was worried about the health effects of the study medicine 1
- j. Living in nursing home 1
- k. Lack of support from family/friends 1
- l. Another doctor told me to stop 1
- m. My insurance changed 1
- n. Other reason _____ 1
- o. No reason given 1
- p. Information not available 1

15. a. Were there any reasons that kept you from coming to the clinic? Yes 1
No (skip to #16) 2

What were the reasons? b. I didn't want to be in the study 1

Show the participant the laminated response card for #15 and let them tell you their response(s). CHECK ALL THAT APPLY.

- c. I didn't want to come to the clinic 1
- d. It was not convenient to attend clinic 1
- e. I didn't like the clinic 1
- f. I didn't like the visits 1
- g. Transportation problems 1
- h. Living in nursing home 1
- i. Lack of support from family/friends 1
- j. Another doctor told me to stop 1
- k. My insurance changed 1
- l. Other reason _____ 1
- m. No reason given 1
- n. Information not available 1



16. a. Initials of the person assessing drug assignment..... _____

b. The person in #16a is (check the first that applies): Principal Investigator 1
Other physician 2
Study coordinator 3
Other staff member 4

Place ID label here

Patient name

17. To which medicine would you guess the participant was assigned in ALLHAT? Diuretic (chlorthalidone) 1
 Calcium-channel blocker (amlodipine) 2
 ACE inhibitor (lisinopril) 3
 Not applicable - participant was assigned to doxazosin (**skip to #19**) 4

Do not leave item #17 blank – please guess!

18. On which of the following do you base your guess? (Check all that apply.) a. Drug code unblinded 1
 b. Laboratory findings 1
 c. Symptoms 1
 d. Blood pressure control 1
 e. Other reason _____ 1
 f. No reason 1

19. Signature and initials of person completing this form: _____

******* ALLHAT CLOSEOUT VISIT REMINDERS *******

Do you have all of the following? (Check the list of missing items for this patient.)

- The most recent required bloodwork?
- All of the required ECG's?
- All of the required event documentation?
- Release of information for documentation that you still need?
- Release of information to send participant's ALLHAT information to another physician, if required
- Updated participant contact sheet?

Give the participant:

- A referral to another source of antihypertensive and lipid-lowering care, if needed
- Closeout *Health Matters* newsletter
- ALLHAT antihypertensive medication and potassium supplementation, if prescribed
- Pravastatin, as needed for those participants who were assigned to pravastatin in the lipid trial, if they are currently taking pravastatin (**1 bottle per participant only**)
- Other prescription, if necessary
- Certificate of appreciation
- ALLHAT patient history, if desired by the participant

Have you completed:

- All of the pending ALLHAT follow-up forms (AL03)?
- All of the pending ALLHAT Event Reporting forms (AL04)?
- Any pending Serious Adverse Effect Forms (AL13)?
- All of the pending edits (routine edits, event edits, HCFA/VA event queries, AL09's)

Place ID label here

Patient name

INSTRUCTIONS FOR ALLHAT CLOSEOUT FORM (AL22)

Please insert these instructions at the back of your Manual of Operations (MOO) Chapter 3

- The ALLHAT Closeout Form (AL22) is required for all patients enrolled in ALLHAT and not known to be dead (except the doxazosin patients who were already closed out).
- Closeout visits begin on October 1, 2001. All visits on or after this date are considered closeout visits.
- Use an AL22 for all visits done on or after October 1, 2001. Do NOT use an AL03 for any visit after this date.
- For additional details, consult your closeout materials or contact your Regional Coordinator.

General information: The ALLHAT Closeout Form (AL22) is a four (4) page NCR form. As with other forms, the completed white (original) portion is sent to the CTC and the yellow copy is for your files. The closeout form is designed to be very comprehensive. It should be thought of as a tool to gather very important information about your participants before you close them out of ALLHAT forever.

Preparing for the visit: Prior to each participant's visit, please take the time to review what each person may be missing (e.g. visits, lab work) so you can get that task completed while the patient is in the office.

Clinic, home or phone: Because of the nature of these visits, clinic visits are preferred. If you cannot accomplish a clinic visit in time to meet the March 31, 2002 deadline, home visits are encouraged. Only when you exhaust those two possibilities should you consider a telephone visit.

Participants who are lost to follow-up or refusing: It will be difficult to complete closeout visits for participants who are reported as lost or refusing, but forms still must be filed for those participants (see additional instructions in closeout kit). Also, there will be a few participants for whom contact is impossible for a variety of reasons - for example, participants who are out of town for long periods of time and for whom out-of-town contact information is not correct.

Checklist: The last page of the form is a checklist designed to help you with two important aspects of closing out each ALLHAT patient. First, do you have everything complete for the patient? Look to see if anything still needs to be done, for example, do you need to complete ECGs, blood work, release forms, etc. Secondly, have you given the patient everything they are entitled to? This includes a new prescription (if necessary), their certificate of appreciation, patient history, and *Health Matters* newsletter.

Progress notes: Just like other ALLHAT visits, you should keep separate progress notes to document all information on the AL22.

DIRECTIONS FOR ALLHAT CLOSEOUT FORM (AL22) ARE BELOW.

As with the AL03, incorrectly completed forms will receive an "edit" and will not be paid until completed correctly.

ID label: Affix participant's ID label in the spaces provided. Be sure to put a label on the yellow copy or print the participant's name to show through on the yellow copy.

Item #1—Date this form is completed: Fill in the date you are completing the form. In most cases this will be the same as the date of this visit.

Item #2a—Has the participant moved: Check "yes" if you *know for certain* that the participant no longer lives in the U.S., Canada, Puerto Rico or the U.S. Virgin Islands. Check "don't know" if your participant is lost, but you don't know for certain whether they have moved out of the countries/territories where ALLHAT is being conducted. All other patients should be marked as "no."

Item #2b—Type of visit: *If you complete the visit*, check one box to indicate if the visit was done either at the clinic, the patient's home, or over the phone. *If you are unable to complete the visit*, check the box which best describes the patients' circumstance: lost to follow up, a refusal or if you are otherwise unable to contact the patient. **DO NOT CHECK MORE THAN ONE BOX.**

Item #2c—Date of visit: If you complete the visit in the clinic, at the participant's home or by phone, fill out the date (month-day-year) of the visit with the patient.

Item #2d - date last known alive: If the visit does not take place because the participant is lost, refusing or otherwise unable to contact, please insert the last date that the participant was last known (by you) to be alive. Be sure that you have supporting documentation for that date, such as a progress note regarding seeing or speaking to the participant (circumstances and date), or receipt of reliable information from a third party (such as a relative or friend). If the information is from a third party, your notes should include the relationship of the third party to the participant and your degree of certainty regarding the reliability of the information. **IF YOU ARE UNCERTAIN REGARDING THE RELIABILITY OF THIRD-PARTY INFORMATION, DO NOT USE IT!**

Item #3a - Seated blood pressure readings: Take two blood pressure readings as you would for a normal follow-up visit. The same BP measurement procedures apply. Be sure to read to the nearest even digit, use leading zeros as necessary, and check your arithmetic on the average. If you completed the visit by telephone, complete all six BP spaces with 999.

Item #3b - Initials of person performing blood pressure measurements: The person performing the blood pressure measurements should PRINT their initials in #3b. Use 999 for telephone visits.

Item #4 - Dose of ALLHAT Step 1 (blinded) antihypertensive prescription at this visit: In Item #4, indicate which dose of the Step 1 (blinded) medication you are advising the participant to take at this visit -- either "Dose 1", "Dose 2", "Dose 3", or "None". Do not leave this item blank. Check only one box, please.

Item #5 - Open-label medication prescription: This question is asking about any open-label antihypertensive or lipid-lowering medication, including medications provided by ALLHAT or from another source, and regardless of reasons for prescription. For example, if a participant is on atenolol for angina, please mark "atenolol" even though this is not prescribed for blood pressure.

Please refer to the four pages at the end of the Manual of Operations, Chapter 3 for a complete list of antihypertensive medications (generic and trade names). This list indicates which box to check for each medication. **The question number is different than on the AL03, but the letter is correct.**

Sometimes two boxes are required for combination medications. Please mark all that apply.

If the participant is not on any open-label medications, put an "X" in the box indicating "None", and skip to Item #6. If for any reason the information is not available, mark "o" (Information not available).

NOTE: Items #6, #7 and #8a-k appear here exactly as they appear on the AL03 (ALLHAT Follow-up Form).

Item #6 - Number of overnight hospitalizations: This item asks for information on the number of *overnight hospital admissions* (not emergency room visits or overnight observations when the participant was not actually admitted) since the participant's last ALLHAT visit. (*Be sure to distinguish between the last non-ALLHAT office visit and the last ALLHAT office visit.*) Do not provide the number of days the participant was in the hospital, but the total number of admissions. If the participant has had none, please complete the item as "00" - do not leave this item blank.

Item #7 - Number of visits to doctor's office or clinic: We are interested in the number of visits to a doctor's office or clinic since the last ALLHAT visit. (*Be sure to distinguish between the last non-ALLHAT office visit and the last ALLHAT office visit.*) This should include all interim visits to your office as well as other physicians' offices or clinics, and should include interim drug titration visits for ALLHAT. **DO NOT INCLUDE VISITS TO A CHIROPRACTOR OR ACUPUNCTURIST (UNLESS THE ACUPUNCTURIST IS A PHYSICIAN.)** Again, if the participant had no interim visits to either your office or another office, complete the item as "00" - do not leave this item blank.

Item #8 - New occurrences of study events: Review this item very carefully. For each possible study event listed, a response is expected - "Hospitalized", "Diagnosis only", "Treatment only", or "No". You should use your clinical judgment plus guidance provided in Chapter 5 of the Manual of Operations in determining the proper response to each of these:

- 8a) acute myocardial infarction, including evolving MI with thrombolysis - do not report apparent "silent" MIs ascertained on the basis of definitive ECG changes; these will be ascertained centrally.
- 8b) stroke (not a TIA or "ministroke"),
- 8c) a new primary diagnosis of cancer (do not report recurring overnight hospitalizations for chemotherapy or other cancer treatment, and do not report non-melanoma skin cancers or recurrent or metastatic/secondary cancers.) - note that this is the only event for which a "diagnosis only" (e.g., out-patient biopsy) is reportable via AL04
- 8d) congestive heart failure - acute episode only
- 8e) angina pectoris - acute episode only
- 8f) lower extremity peripheral arterial disease - does not include carotid disease, renal artery disease or aortic aneurysms
- 8g) accident or attempted suicide
- 8h) kidney transplant or start of chronic dialysis
- 8i) Coronary artery bypass graft (CABG)
- 8j) Coronary PTCA (angioplasty), stent or atherectomy
- 8k) Lower extremity peripheral revascularization / bypass / angioplasty

"Acute episodes" are those that bring the patient to medical attention or cause some change or addition to their daily treatment or routine.

Take special note of all events that are enclosed in the boxes on the form. For each of these events, the investigator will also obtain and submit a copy of the hospital discharge summary upon which the diagnosis is based. (For "diagnosis only" cancers, a pathology report is sufficient.) Form AL04 should be completed (one for each of these events; please refer to Chapter 5 for instructions).

We do not collect information via AL04 on non-hospitalized MI's or strokes. Both should still be checked on the AL22 as "treatment only," if treatment occurred. Do not report "silent" MI's discovered on the basis of definitive ECG changes; these will be ascertained as part of the central ECG coding of ALLHAT biennial ECGs.

Note—Items 9 - 13 are the same questions asked on the AL03 at the years 2, 4, and 6 visits. You must ask these questions of ALL patients during the closeout visit, even if it is not a year 2, 4, or 6 visit.

Items #9 and #10 - Quality of life: Items #9 and #10 are questions that must be asked of the patient. Both of these items are indicators of quality of life. The first, Item #9, is relatively straightforward. Repeat the question to the patient exactly as worded, and verbally list the response categories. Record the patient's response. If the patient is really unsure, refuses to respond, or if you cannot otherwise ascertain the proper response, check "No answer/unknown".

The second quality of life item, Item #10, might be a little harder for the patient to understand. Use language that you think might make the questions clearer for the patient. *If the patient is having trouble thinking of a 0-100 scale, you may use a 0-10 scale for clarification, but be sure to multiply the response by 10.* If the patient just cannot answer this question, code this question as "999".

Item #11 - Cigarette smoking: In Item #11, indicate whether the patient is a current smoker (in past 30 days) or past smoker (not a current smoker, but > 100 cigarettes in his or her lifetime), or has never smoked cigarettes. Item #11 refers only to cigarettes, not cigars or pipes. For example, a patient who previously smoked > 100 cigarettes but in the last 30 days has smoked only a pipe would be classified as a "past smoker".

Item #12 - Regular use of aspirin: Regular use of *aspirin* (Item #12) may alter the patient's risk of cardiovascular events. Indicate here whether the patient is currently taking regular doses of aspirin (not non-aspirin pain relievers). Medications that contain aspirin have been discussed on page 2-16 of the Manual of Operations.

Item #13 - Current use of estrogen (oral or patch): *For women only,* Item #13 requests information regarding current use of estrogen (oral or patch). This includes any estrogen preparation that might include or be taken with other hormones. Again, clarify with the patient if you are not clear on the proper response to this question. *Do not answer this item if the patient is male!*

Item #14a—reasons for not taking ALLHAT meds: If the participant answers "no" to this question, then skip to the next question (Q #15). If the participant answers "yes" to this question, you are to hand them a copy of the laminated card that lists all the possible responses. Mark all the reasons the patients tell you that kept them from taking their ALLHAT medicine(s).

If you complete the closeout visit over the phone, then you should follow the instructions provided for phone visits on the laminated cards for these items.

Item #15a—reasons for not coming to the clinic: If the participant answers “no” to this question, then skip to the next question (Q #16). If the participant answers “yes” to this question, you are to hand them a copy of the laminated card that lists all the possible responses. Mark all the reasons the patients tell you that kept them from coming to the clinic.

If you complete the closeout visit over the phone then you should follow the instructions provided for phone visits on the laminated cards for these items.

The purpose of Items #16, #17, and #18 is to get an idea of what drugs clinicians thought their patients were assigned to. Therefore, these questions are to be completed by the clinician most familiar with the patient.

Item #16a—initials of person assessing drug assignment: The clinician most familiar with the patient should print their initials in blanks. This person also needs to answer questions #16b, #17 and #18.

Item #16b—role of person who completed #16a: Check the title that best describes your job on ALLHAT. Check only one response.

Item #17—which medicine would you guess patient was assigned to? Choose only one response. Since the purpose of this question is to assess how well the study medication blinding was maintained, guessing is appropriate for this item. If this patient was assigned to doxazosin, mark “not applicable” and skip to question #19.

Item #18—basis for your guess: Please mark as many of the responses that apply to what you witnessed with this patient.

Item #19—Signature and initials: The person completing this form needs to both sign and initial the form. The person completing the majority of this form should sign it, even though another person may be completing items #16 - #18.

ALLHAT Closeout Visit Reminders: Carefully review this list for each patient to make sure there is nothing missing for this patient, and that you have given the patient everything they need.



Response card for AL22 #14 and #15

CHECK ALL THAT APPLY

THIS SECTION FOR CLINIC USE ONLY

For telephone interviews: Ask the leading questions (#14a and #15a) as stated on the form. If the participant indicates a problem, then say, *"Since you said 'Yes', I am going to read you some possible reasons. Please tell me whether you agree or disagree with each of the reasons."* You may state this in a way that is conversationally comfortable for you. Then read each reason from the list exactly as it is written – do not rephrase or try to explain the reasons. Check all reasons that the participant agrees were reasons for not taking the medicine or not visiting the clinic.

14. Possible reasons that kept you from taking your ALLHAT medicine:

- b. Size or taste of pills was a problem
- c. Too many pills
- d. I didn't like not knowing what the medicine was
- e. It was hard to remember to take the medicine
- f. I didn't think that I needed the medicine
- g. I didn't understand how to take the medicine
- h. I had a bad reaction to the medicine
- i. I was worried about the health effects of the study medicine
- j. Living in nursing home
- k. Lack of support from family/friends
- l. Another doctor told me to stop
- m. My insurance changed
- n. Other reason (please explain)
- o. No reason

15. Possible reasons that kept you from coming to the clinic:

- b. I didn't want to be in the study
- c. I didn't want to come to the clinic
- d. It was not convenient to attend clinic
- e. I didn't like the clinic
- f. I didn't like the visits
- g. Transportation problems
- h. Living in nursing home
- i. Lack of support from family/friends
- j. Another doctor told me to stop
- k. My insurance changed
- l. Other reason (please explain)
- m. No reason



Date: _____

Dear Dr. _____:

Your patient, _____, has been participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). I am writing to let you know that ALLHAT is completing follow-up for this patient.

The hypertension component of ALLHAT was designed to compare the ability of three newer antihypertensive medications - a calcium antagonist (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), and an α -adrenergic blocker (doxazosin) - with that of a diuretic (chlorthalidone) to reduce the risk of coronary heart disease (primary endpoint), as well as stroke, all major cardiovascular disease events (CVD) and all-cause mortality (secondary endpoints) when these drugs are used as first-line treatment of hypertension. The purpose of the cholesterol-lowering trial component is to determine whether lowering serum cholesterol in moderately hypercholesterolemic hypertensive men and women with the HMG CoA reductase inhibitor (pravastatin) will reduce all-cause mortality as compared to a control group receiving "usual care".

When your patient joined ALLHAT, he/she was assigned by chance to take one of the four blood pressure medicines and, if he/she qualified and agreed, to receive pravastatin or not. The safety of ALLHAT participants has been monitored closely throughout the study by an independent panel of experts. During a review in January 2000, it was determined that one of the ALLHAT medicines (doxazosin) appears to be less effective than the diuretic (chlorthalidone) in preventing CVD, especially heart failure, and study medication was discontinued for assigned participants. In late 2002, we will know the ALLHAT results regarding the other antihypertensive medications and pravastatin.

The participant named in the first paragraph is currently taking the following medications:

- Step 1, Dose __, prescribed since _____. It is important for any trial (not just ALLHAT) to maintain the blinding of the study medications until all of the data for all participants are complete. Therefore, the trial participants will be informed of the actual medication in June 2002. The possible medications are:

Step 1 Agent	Dose 1	Dose 2	Dose 3
Chlorthalidone	12.5 mg	12.5 mg	25 mg
Amlodipine	2.5 mg	5 mg	10 mg
Lisinopril	10 mg	20 mg	40 mg

- Pravastatin ____ mg/day, prescribed since _____.
- Other antihypertensive and lipid-lowering medications and potassium supplementation, doses, and dates first prescribed:
- Recent blood pressure values and dates for this patient - the ALLHAT blood pressure goal is less than 140 mmHg systolic and less than 90 mmHg diastolic:
- Other comments regarding this patient:

I am sure that you will want to review this medication regimen, particularly for recent changes in medication, and plan your own follow-up accordingly.

The ALLHAT study is providing blinded medication until June 2002 (when unblinding will take place) for participants who elect to continue this under the supervision of their private physicians. atenolol, clonidine, reserpine, hydralazine and potassium supplementation are also provided, if needed, until June 2002. Open-label chlorthalidone is available until June 2002 for participants originally assigned to doxazosin who were also participating in the lipid-lowering part of ALLHAT. If your patient requires an additional supply of these medications to last until June 2002, they may be obtained from my office.

A final 90-day supply of pravastatin has already been provided to patients who participated in the lipid trial, were assigned to pravastatin and who are currently taking pravastatin

I would be happy to consult with you regarding antihypertensive and/or lipid-lowering therapy for your patient during this transition phase. If you have any questions or concerns regarding the study medication, please do not hesitate to contact me.

All of us who are conducting ALLHAT greatly appreciate your patient's participation, which will help us to answer important questions regarding the comparative effects of antihypertensive medications, as well as the effect of lipid-lowering therapy in hypertensive patients with moderate hypercholesterolemia.

Sincerely,

Telephone:

Frequently Asked Questions (FAQs)

For Principal Investigators, Study Coordinators and Regional Coordinators

Getting ready for closeout

1. What should I do to get ready for closeout visits?

It is important to consider the following two things as soon as possible to ensure a smooth transition for the participants to non-ALLHAT hypertension and lipid-lowering treatment:

- ✓ What blood pressure and lipid-lowering therapy you will recommend at the closeout visit?
- ✓ If needed, how you will refer the participant to another source of antihypertensive and lipid-lowering care?

Other things you can do to position you and the rest of your clinic's staff for a well-organized and successful study closeout include:

- ✓ Filing AL03's for visits not yet submitted to the CTC;
- ✓ Filing AL04's for events not yet reported to the CTC, including any MI's or deaths reported from the HCFA or VA databases;
- ✓ Obtaining and submitting outstanding event documentation;
- ✓ Responding to all outstanding edits;
- ✓ Working on locating lost participants, reinstate as many refusing and nonresponding participants as you can.

You and your Regional Coordinator will be discussing a plan for your site.

Visits

2. What are the first and last dates for closeout?

Participant closeout visits will begin **October 1, 2001**. Every participant, even lost, refusing, or otherwise not responding, must have a closeout visit form on or after October 1, 2001. A participant's first visit on or after October 1, 2001 is that participant's closeout visit, and a special form (the ALLHAT Closeout Form, AL22) is required. **No AL03 visits should take place on or after October 1, 2001.**

Closeout visits **must be completed** for all participants **no later than March 31, 2002.**

Recommendation: Although you should always be working on losses, refusals and nonresponders, try to complete closeout for all of your active participants by January 31, 2002. You will then have two months to obtain vital status on your lost, refusing and nonresponding participants.

3. How do we close out participants who are lost or refusing for the final closeout visit?

Knowledge of vital status for all **ALLHAT** participants is critical to the trial. Attempts to contact all participants whether lost, refusing or otherwise previously unable to contact must be made.

Further instructions for closeout of losses, refusals and non-responders will be sent to the clinics in January 2002.

- ✓ There was a final search for contact information for ALL participants whose vital status was uncertain as of July 1, 2001. This contact information was sent in mid August.
- ✓ You should already be using the results from that search to contact your lost and refusing participants. If you are able to contact any of these participants, you should complete a closeout visit (AL22) in the clinic, at the participant's home or by telephone.
- ✓ Beginning in January 2002, your regional coordinator will be working with you to close out any lost, refusing or non-responding participants you are still not able to get in touch.

4. What do we do about participants who are in nursing homes (NH), assisted living (AL) facilities, or are out of the area?

Making arrangements

- ✓ The PI should pave the way by contacting the medical director by phone or in person or, in the case of a patient in a non-ALLHAT area, telephoning the patient's new primary care provider. It is a good idea to follow-up by putting the agreed plan in writing to the medical director or other health care provider.

Obtaining closeout information

- ✓ SC calls and speaks with the nurse who has primary responsibility for that patient. That information is used to complete the AL22. All information obtained by telephone must be documented in the ALLHAT progress notes, as well as who provided the information.
- ✓ SC speaks with the patient directly, or a family member, to collect information.
- ✓ AL22 forms may be completed from progress notes obtained from NH, AL or home health care or other health care provider.

5. Do we need to obtain blood work and/or an ECG at the closeout visit?

- ✓ For each participant not already reported to the CTC as deceased, there will be a list of missing items to be addressed at the closeout visit. These items are: the most recent missing lab work; missing ECGs; missing or incomplete event documentation;

and missing visits. Every effort should be made by the clinics to obtain and/or complete the missing items.

You should also plan to obtain an ECG and/or blood work if the patient's closeout visit is in a window for an ECG or lab and they have not already been done in the window.

Unblinding

6. When will we find out what blinded medicine our patients were taking during the study?

In **June 2002**, you will receive a package that reveals each participants' blinded study medication. You will need to notify your participants. Detailed instructions will be provided by the CTC at that time.

Medications

7. What medications will we provide to the participants until their next appointment with their primary provider?

The following will be available:

- ✓ ALLHAT Step 1 blinded medication (until June 2002)
- ✓ Open-label chlorthalidone, if needed, for participants originally assigned to doxazosin who are currently taking chlorthalidone (until June 2002)
- ✓ ALLHAT Step 2 and 3 medication (atenolol, clonidine, reserpine and/or hydralazine) (until June 2002)
REMINDER: atenolol is one of the generally recommended first-step drugs
- ✓ Potassium supplementation, as needed (until June 2002)
- ✓ Pravastatin, as needed for those participants who were assigned pravastatin in the lipid trial, if they are currently taking pravastatin (1 bottle per participant)
- ✓ If it is necessary, provide a prescription for other medication

You may use any of the above medications, if clinically indicated for your participant.

Remember, it is important that you assist your participant in finding another physician (if the ALLHAT physician is not their primary care physician) **BEFORE** this medication runs out, so they can be transitioned from the ALLHAT medication to a new treatment plan in the safest way possible.

8. What sources of free or low cost medicines are available to refer our ALLHAT participants to after closeout?

ALLHAT has put together a reference binder called the *Guide to Patient Assistance Programs* (GAP) containing information on various patient assistance programs.

Usually, the patient has to have a limited annual household income and have no health insurance to qualify. Some of the tools in this binder include:

- ✓ A handy alphabetical and comprehensive listing of the common antihypertensive, lipid lowering medications, and the manufacturer for each of these drugs.
- ✓ A copy of the PhRMA Patient Assistance Program Directory that lists individual pharmaceutical companies and their contact numbers.
- ✓ Copies of the actual applications from the different companies that provide free medications.
- ✓ Some patients may not qualify for the free medication programs. A list of programs that provide medication assistance for a processing fee is provided.

Events

9. An ALLHAT patient has an event after they are closed out. Should this be reported?

No, events occurring after a participant's closeout visit will not be reported. However, if you hear of a lost or refused patient's death occurring after closeout, this is beneficial information because it shows the vital status of the patient (i.e., whether they were alive or deceased) at the time of closeout. You do not need to submit an ALO4, but you can amend the date last known alive on the closeout form, AL22, until July 25, 2002.

10. Which ALLHAT events should be reported?

All events occurring on or before the date of the patient's closeout visit must be reported on an ALO4. If you uncover an event that occurred at any time during the study, please submit an ALO4 and supporting documentation immediately.

Data cleanup

11. What does our site need to do to be "officially" completed with our work for ALLHAT?

Closeout work for ALLHAT will essentially be in two parts—the first is to get completed forms submitted for all of your patients.

- ✓ Part one begins on **October 1, 2001**, when closeout visits begin.
- ✓ Part two will occur in 2002, when you will need to notify patients of what medicines they were on, and disseminate the results of the trial to them.

Not only do you need to have a completed closeout form filed for each patient, but you will need to complete any other forms that may be incomplete. For example, this

means all of your edits need to be completed and documentation for events needs to be submitted.

Closeout will be a busy time. Plan ahead to stay on top of all the work you have to do. We know there is a lot of work, but completing it **fully and accurately** is critical to the success of ALLHAT. It is your site's ethical and legal obligation to make sure there are no "loose ends" at your site, per your initial written agreement with the CTC or VA.

Please refer to the "cleaning up data" section of your closeout materials for additional information.

Results

12. How and when will the sites and participants be notified of the results?

After the drug codes are unblinded to you and the participants in **June 2002**, it will be several months before the results are available. The following timeline applies:

- In **late 2002**, the ALLHAT Steering Committee will be notified of the results at a face-to-face meeting.
- There will also be a meeting in which you will be shown the results.
- The results will be published in a major medical journal.
- There will be a press conference.
- After the results are published, there will be a special newsletter for ALLHAT staff and one for the participants. You should plan to mail these to your participants who are no longer in your practice at that time.
- We hope to present the results at a major scientific meeting early in 2003.

You will be kept informed as plans are finalized.

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