MDRD

Phase III

The Modification of Diet in Renal Disease Study

Protocol

MDRD

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Protocol

Beck

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Phase III Protocol

Replacement Pages

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PHASE III PROTOCOL

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SECTION 1

INTRODUCTION

1.1 BACKGROUND

The Modification of Diet in Renal Disease (MDRD) Study is a multicenter cooperative clinical study designed to ascertain whether: i) restriction of dietary protein and phosphorus, and/or ii) reduction of blood pressure well below the currently accepted target of 140/90 will reduce the rate of progression of chronic renal disease irrespective of the nature of the primary underlying process.

Clinical observations have suggested that these dietary restrictions slow the rate of progression of chronic human renal disease. However, this conclusion must be regarded as unproven because (1) deterioration of renal function has not been determined by measures that were independent of changes in lean body mass, protein intake and/or renal tubular handling of clearance markers; (2) patients' compliance to dietary prescriptions has not been carefully assessed, (3) rigorous controls have not been utilized in most of the reported studies; and, (4) data on factors other than nutrition therapy have not been collected or statistically analyzed. Moreover, the impact of dietary restriction on overall health, nutritional status, and quality of life has not been adequately addressed in these reports.

The results of the limited Pilot Phase of the MDRD Study (Phase II) and several studies of diabetic renal disease have shown a positive correlation between blood pressure and the rate of progression. However, no study has evaluated the effect on renal disease of lowering blood pressure below a target less than 140/90 mmHg.

The MDRD Study is a prospective, randomized trial sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases and the Health Care Financing Administration.

1.2 HYPOTHESES

Chronic renal disease of diverse origins frequently follows a progressive course toward end-stage renal failure, even if the original disease process has become inactive. Why this occurs is not known. Several hypotheses have been advanced to explain the mechanisms by which this progression occurs. None of these mechanisms have been definitely established as the sole cause for this phenomenon. However, several of the proposed mechanisms and

past clinical experience suggest that low protein and low phosphorus diets may retard the rate of progression of renal failure. Trials of low protein and low phosphorus diets in rats with renal insufficiency indicate that these diets will retard progressive renal failure and lower the incidence and severity of progressive glomerular sclerosis and the quantity of calcium phosphate deposited in the kidney.

Clinical trials of low protein, low phosphorus diets in humans also suggest that such diets may slow the progression of kidney disease. However, these studies generally have suffered from deficiencies in experimental design. These deficiencies include lack of proper randomization procedures, inappropriate control populations, retrospective analysis of the data, inadequate methods for monitoring renal function, and poor information concerning the actual dietary intake of the study patients. Also, previous clinical trials have not documented that these low protein, low phosphorus diets will maintain good nutrition in patients with chronic renal failure.

If such dietary therapy can be shown to slow progression in patients with chronic renal disease, the potential benefits could be enormous, both in terms of reduction in human suffering and in cost savings to patients and to society.

Because the published literature provides suggestive data but does not prove that low protein, low phosphorus diets will retard progressive renal failure in patients with chronic renal disease and because these diets, if they are effective, would offer major benefits to the individual and to society, the National Institutes of Health has inaugurated a cooperative clinical trial to examine this question. This trial will test five primary hypotheses. The first three are:

1. That if patients with chronic kidney disease are prescribed and counseled to follow low protein, low phosphorus diets, this will retard their rates of progression of renal failure.
2. That such diets will not cause malnutrition.
3. That such diets are acceptable to patients for long-term use.

The benefits of lowering of blood pressures to levels less than 140/90 are universally recognized and include reduction of the incidence of congestive heart failure and stroke, as well as lowering the incidence of renal disease. In Type I diabetes, there is strong presumptive evidence (though no randomized trial) to suggest that lowering of blood pressures to levels less than 140/90 mmHg reduces proteinuria and slows the progression of renal insufficiency. Other studies have shown that Type II diabetic

patients with blood pressure less than 140/90 mmHg do not have progressive renal disease, whereas patients with higher levels of blood pressure may have these complications. Results of Phase II of the MDRD Study showed a significant positive correlation between mean arterial pressure (MAP) and the rate of decline in glomerular filtration rate. This correlation was observed even in patients whose mean arterial pressure was below 107 mmHg (equivalent to 140/90), suggesting that reduction of blood pressure below this widely accepted target might preserve renal function. However, these Phase II results were not the result of a randomized trial. It is equally possible that more rapidly progressive renal disease leads to higher blood pressures. Further, lowering of mean arterial pressures well below 107 mmHg may be associated with a significantly increased incidence of unacceptable treatment side effects and in some patients may even lead to reduction of glomerular filtration rate. Therefore, this trial will test the following two additional primary hypotheses:

4. That if patients with chronic renal disease are prescribed and counseled to follow a regimen to lower mean arterial pressure to a value at or below 92 mmHg, this will reduce their rates of progression.
5. This rigid blood pressure control (lowering mean arterial pressure $\leq$92 mmHg) will not be associated with an unacceptable increase in medication and/or hypotensive side effects.

Finally, the Health Care Financing Administration (HCFA) is responsible for conducting a cost-effectiveness component of the MDRD Study testing whether nutrition therapy for chronic renal disease is cost-effective and to determine whether this therapy might be made generally available as part of The Social Security Act. The following questions will be addressed in the cost analysis to be conducted by HCFA.

1. Is nutrition therapy cost-effective in the treatment of patients in the MDRD Study?
2. Is nutritional therapy less costly to HCFA than the current payment for dialysis and transplantation?
3. Is nutrition therapy under HCFA administratively feasible?
4. Can the therapy be effectively managed?
5. How might the therapy be effectively promulgated through HCFA policy?
6. To what degree should the therapy be subsidized by HCFA and other third party insurers?

1.3 STUDY TIMELINE

The MDRD Study Timeline consists of four Phases.

Phase I, September 1984-December 1985, was the time period in which the initial Protocol was developed and plans for Phase II were made.

Phase II, January 1986-February 1988, was a limited Pilot Study designed to document numbers of patients available and to test study procedures. Regular follow-up on Phase II patients concluded on February 29, 1988 with close-out and post-close-out visits continuing after that data.

Phase III, January 1989-December 1992, is a full-scale study with recruitment of patients with chronic progressive renal diseases who meet the entrance criteria. Phase III data will be used to accomplish the goals of the MDRD Study. Patient enrollment begins on January 1, 1989 and concludes March 31, 1991. Regular follow-up on Phase III patients concludes on December 31, 1992. Close Out is described in Section 12.12.

Phase IV, January-December 1993, will be used to complete the detailed final analysis of data generated in Phase III and to report the results of the study.

1.4 PURPOSE OF THE PROTOCOL

The purpose of this Protocol is to provide a summary of background, organization, and policy information for the MDRD Study, and to specify objectives and describe the designs of Studies A, B, C, F and G for Phase III.

1.5 MANUAL OF OPERATIONS

The MDRD Study also has a four-volume Manual of Operations. The Manual of Operations Volume I covers Clinical Center Procedures; Volume II includes all Data Collection Forms; Volume III includes Central Units and Administration; and Volume IV includes Patient Information. The purpose of the Manual of Operations is to provide detailed procedures for all aspects of the MDRD Study.

SECTION 2

OBJECTIVES AND DESIGN

2.1 OBJECTIVES

The goals of this study are:

1. To compare the effects of diets with various protein and phosphorus contents on the course of progressive renal disease.
2. To evaluate the nutritional safety and nutritional and other effects of various dietary interventions.
3. To determine patient acceptance of these dietary interventions.
4. To determine the cost-effectiveness of dietary interventions.
5. To compare the effects of maintenance of mean arterial blood pressure at usual vs. lower than usual therapeutic levels on the course of progressive renal disease.
6. To evaluate the safety of maintenance of mean arterial blood pressure at these two levels.
7. To determine the patient acceptance of antihypertensive regimens to achieve these two levels.

The primary outcome measure is:

1. Rate of change of Glomerular Filtration Rate (GFR).

Other major outcome measures are listed below:

2. Dialysis or transplantation.
3. Death.
4. Occurrence of serious medical conditions and intercurrent illnesses.
5. Nutritional status.
6. Achieved blood pressure and compliance with blood pressure regimens.
7. Complications related to high or low blood pressure.
8. Compliance and satisfaction with dietary regimens.
9. Symptoms.
10. Quality of well being.
11. Cost of care provided to patients, assessed from physician's time, dietitian's time, laboratory tests, and prescribed supplements.

2.2 DESIGN

The general research plan is a 2 by 2 factorial design. A 2 by 2 factorial design was selected in order to answer two

questions simultaneously: What are the effects of low protein and phosphorus diets and what are the effects of blood pressure control on the progression of chronic renal disease? No increase of sample size is necessary beyond what would be needed to address each question separately. The design may also produce more reliable estimates of progression (GFR slope) and enable one to detect smaller differences when only a single factor, such as diet, is examined. That is, it should restrict the variability of blood pressure within each diet group.

Study A: A comparison will be made of a moderate protein and phosphorus diet (M) and a low protein and phosphorus diet (L_2) for patients age 18-70 years with GFR 25 to 55 ml/min/1.73m^2 whose habitual dietary protein intake is $\geq$0.90 g/kg/day. Patients within each diet group will be assigned to a moderate mean arterial pressure goal or low mean arterial pressure goal. Patients in Study A who reach a GFR stop point may enter Study C, described below.

Study B: A comparison will be made of a low protein and phosphorus diet (L) and a very low protein and phosphorus diet supplemented with a mixture of essential amino acid and keto acid analogues (K) for patients with GFR 13-24 ml/min/1.73 m2. Patients within each diet group will be assigned to a moderate mean arterial pressure goal or low mean arterial pressure goal.

Study C: Study C is a within patient comparison in which patients in Study A who subsequently reach a GFR stop point are assigned a very low protein and phosphorus diet supplemented with a mixture of essential amino acids and keto acid analogues (K).

Study F: Follow-up every six months on patients who enter the Baseline Period in Study A or Study B, but who are excluded before randomization.

The protein and phosphorus composition of the Study diets is given in Table 2.1.

TABLE 2.1
Protein and Phosphorus Composition of Study Diets

Study	Diet	Protein g/kg/day	Phosphorus mg/kg/day	MDRD Keto Acid Supplements
A	Moderate (M)	1.30	16 -20	none
A, B	Low (L)	0.575	5 - 10	none
B, C	Very low (K)	0.28	4 - 9	mixture of essential amino acids and keto acid analogues 0.28 g/kg/day of SBW
F, G	Not Prescribed	-	-	-

TABLE 2.2
Mean Arterial Blood Pressure (MAP) Goals

Study	Age (years)	Moderate MAP Goal (mmHg)	Low MAP Goal (mmHg)
A, B, C	18 - 60	$\leq$ 107	$\leq$ 92
A, B, C	$\geq$ 61	$\leq$ 113	$\leq$ 98
F, G	Not Prescribed		

2.3 PROTOCOL FOR STUDIES A AND B

The protocol for patients enrolled in Studies A and B involves a three-month Baseline Period of observation, randomization to study diets and MAP goals, and a minimum of twenty months of follow-up after randomization. The specific objectives for each of these phases are described:

Objectives for the Baseline Period, prior to randomization, include:

- .Determination of baseline renal function
- .Determination of baseline nutritional status
- .Determination of usual diet
- .Baseline measures of diet acceptance
- .Determination of baseline blood pressure
- .Treatment of hypertension, if present
- .Establishment of supportive relationships between the patient and members of the Study Team
- .Education of the patient regarding
  - objectives of the study
  - his/her disease
  - nutrition and renal disease and nutrition in general
  - blood pressure and renal disease and blood pressure in general
  - keeping food records
  - measuring foods and estimating protein content of diet
  - following prescribed Baseline Period diet
  - collection of 24-hour urines
- .Involvement and education of the patient's family, if appropriate
- .Assessment of the patient's ability to comply with the prescribed protein-controlled diet, judging this by comparison of dietary protein prescription and estimated protein intake obtained from diet records and urine collections
- .Assessment of the patient's ability to comply with the antihypertensive regimen
- .Assessment of the patient's ability to comply with study procedures, such as recording of food records, keeping scheduled appointments, and collecting 24-hour urines

Objectives for the first three months of the Follow-Up Period include:

- .Implementation of antihypertensive regimen to achieve MAP goal
- .Design of an individualized diet by the patient and nutritionist that conforms to the MDRD diet prescription, including dietary alterations that are part of non-pharmacologic treatment of hypertension
- .Modification of the diet as necessary to help the patient adjust to the new diet
- .Confirmation that the diet does conform to the prescription by evaluation of the diet records by the Nutrition Coordinating Center
- .Assessment of patient's compliance with the diet, as documented by the results of 24-hour urine collections and diet records
- .Assessment of patient acceptance of the new diet

- Assessment of patient's compliance with nutritional supplements: keto acid, calcium, iron, vitamins, and blood pressure medications
- Assessment of blood pressure and side effects of antihypertensive regimen
- Assessment of patient acceptance of antihypertensive regimen

Objectives for the remaining Follow-Up Period include:

- Periodic assessment of renal function
- Assessment of degree of compliance with diet and drug prescription and nutritional supplements
- Remediation by education and counselling to improve compliance where needed
- Assessment of dietary acceptance
- Assessment of the nutritional status and overall medical condition
- Assessment of blood pressure and side effects of antihypertensive regimen
- Assessment of patient acceptance of antihypertensive regimen

2.4 TIME TABLE

The time table for the 48-month full scale trial (Phase III) will be as follows:

Recruitment	0 - 21 months
Baseline	3 months
Follow-up	up to 45 months

Hence, all patients will be followed potentially for a minimum of twenty months after randomization. Since the baseline period is three months, the maximum length of follow-up after randomization would be 45 months. It is expected that the length of time required for each center to identify and initiate the baseline period for all patients to be enrolled will take approximately 21 months.

SECTION 3

SAMPLE SIZE

3.1 SAMPLE SIZE CALCULATIONS

A critical question with any clinical study is whether there will be sufficient numbers of patients to demonstrate differences between the study groups, if such differences exist. This question has been examined with regard to the key outcome measurement: the rate of change in GFR (i.e., slope) starting at the Baseline Visit 3 GFR. There are two types of comparisons in this study: between diet groups (M vs. L in Study A and L vs. K in Study B) and between blood pressure control groups (moderate vs. low mean arterial blood pressure goals, see Table 2.2).

For patients on a standard diet meeting the eligibility requirements for this study, available data suggest that the GFR will decline on the average by approximately 12.0 ml/min/1.73m^2 over a two year period (slope = -0.5 ml/min/1.73m^2/month). A change of 30% or more in the GFR slope is considered clinically important for this study. Previous studies have suggested this magnitude of effect is feasible (Rossman, et al, 1984; Maschio, et al, 1982).

Sample sizes are determined so that if the GFR slopes differ by 30% or more between diets or between blood pressure groups, this study will have at least a 90% probability (power) of detecting such a difference. Specifically, ignoring blood pressure control, it is assumed that the mean slope in GFR in Study A is -0.50 ml/min/1.73m^2/month for Diet M and -0.35 ml/min/1.73m^2/month for Diet L. In Study B, it is assumed that the mean slope is -0.35 ml/min/1.73m^2/month in Diet L and -0.245 ml/min/1.73m^2/month in Diet K. It is likewise assumed that, ignoring diet, the moderate and low mean arterial blood pressure goal groups will have mean GFR slopes of -0.50 and -0.35 ml/min/1.73m^2/month, respectively, in Study A, and -0.35 and -0.245 ml/min/1.73m^2/month, respectively, in Study B. Based upon MDRD Phase II data, these GFR slope differences are equivalent to a mean difference of mean arterial blood pressure between the moderate and low goal groups of 5 mmHg in Study A and 8 mmHg in Study B.

In order to calculate the required sample size, it is necessary to specify the standard deviation of the individual GFR slopes, which is a function of the number and time-spacing of GFR measurements, the variability among the true slopes of individuals, and the variability of individual GFR measurements about each subject's regression line (Schlesselman, 1973).

Actual data on GFR slopes and their variability for diabetics (Mogensen, 1976; Parving, et al, 1981; and Viberti et al, 1983) indicate that almost all the variability in estimated slopes is from the variability between the true slopes of individuals, and less is due to variability about the regression line for a single person. This has been observed in the MDRD Phase II data as well even with the limited follow-up experience. Given the planned duration of follow-up, the number of follow-up points has small impact upon the ability to accurately estimate the standard deviation of the slopes in a group of persons. For example, increasing the number of annual GFR measurements from 3 to 4 would reduce the standard deviation of an individual GFR slope by about 10%.

Using MDRD Phase II data, restricted maximum likelihood estimates (Laird and Ware, 1982) were obtained for the two components of variance needed; i.e., the between-person variance of true slopes and the residual variance about an individual patient's regression line, separately for Studies A and B. These estimates were used along with the Phase III study design of GFR being measured at Baseline Visit 3, 2 months, 4 months and every 4 months thereafter (and assuming an average of 3 years of follow-up in Study A and 2 years in Study B) to obtain an adjusted slope standard deviation for each study. These adjusted standard deviations are used in the sample size calculations: 0.49 ml/min/1.73m^2/month for Baseline GFR 25-55 and 0.20 ml/min/1.73m^2/month for Baseline GFR 13-24. Data from Phase II of the MDRD Study also indicate it is reasonable to assume a normal distribution of slopes in both studies A and B. Recent data in 18 non-diabetic patients (Walser, 1986, private communication) also support this.

For sample size calculations, the following formula (Snedecor and Cochran, 1980) was used, assuming a two-sided Type I error rate (significance level) of 0.05 and a statistical power of 90%:

$$n = \frac{2\sigma^2(Z_{\alpha/2} + Z_{1-\beta})^2}{\Delta^2}$$

where n = sample size for each diet or blood pressure group

σ = the adjusted standard deviation of GFR slopes

$Z_{0.025} = 1.96$

$Z_{0.100} = 1.28$

Δ = the difference between the mean GFR slopes for the two diet or blood pressure control groups: 0.15 ml/min/1.73m^2/month in Study A and 0.105 ml/min/1.73m^2/month in Study B.

The nominal 5% significance level has been assumed for testing both the diet and blood pressure effects in each study without making any adjustment for the multiple comparisons being made.

Table 3.1 below gives the required number of randomized persons in each diet or blood pressure control group for the two studies under various size differences between mean slopes.

TABLE 3.1

Sample Size Per Diet or Blood Pressure Group for Different Mean Slope Differences (Δ)

	Δ ml/min/1.73m^2/mo	Δ%	Number per group
Study A			
(B3 GFR 25 to 55)	.25	50%	82
	.15	**30%**	**227**
	.125	25%	327
	.100	20%	510
	.075	15%	907
Study B			
(B3 GFR 13 to 24)	.25	71%	13
	.15	43%	36
	.125	36%	52
	.105	**30%**	**74**
	.075	21%	144

At randomization, a total of 454 and 148 persons in the two GFR ranges, respectively, will be required for a total of 602 randomized individuals. However, note that administratively, the Phase III Study has been designed to include 800 randomized persons. This implies that a total of 604 and 196 persons will be randomized in Study A and Study B, respectively. In Study A, 151 would be randomly assigned to each of the four treatment combinations (302 per diet group) and in Study B, 49 would be so assigned (98 per diet group).

This increased number of randomized persons will enable the study to detect changes in GFR slope of about 26% between diet or blood pressure control groups with 90% power. Based upon Phase II data, this large a difference in GFR slopes could exist if the

25.8% A
26.6% B

mean difference of mean arterial pressure between the moderate and low goal groups was 4 mmHg in Study A and 7 mmHg in Study B. With the increased sample sizes, a 30% difference in mean GFR slopes could be detected with 96% power. If there is an interaction between diet and blood pressure control, the two diets can be compared within each blood pressure group separately. Each of these comparisons, in Study A or Study B, has an 80% power of detecting a mean GFR slope difference of 32%. The power for detecting an interaction effect is the same as for a main effect for a specified effect size. However, the 30% difference we expect to see for a main effect may be unrealistic to expect for an interaction effect.

Since the GFR slope will be used as the primary outcome, an individual will have an estimated slope if there are two or more GFR measurements. Hence, the number of persons with a missing outcome measurement should be very small and is assumed to be zero since everyone should have both a Baseline Visit 3 and a two-month follow-up GFR measurement. More importantly, dropouts during Baseline result in fewer persons available at randomization. Based upon MDRD Phase II data, 32% of persons with Baseline GFRs 25-55 and 22% of those with GFRs 13-24 drop out or are excluded prior to randomization. Therefore, the numbers of persons enrolled at Baseline need to be 48% and 28% larger in Studies A and B, respectively, than the number of randomized subjects. Therefore, to detect a 30% mean difference of slopes in two diet or blood pressure control groups in each study, 894 and 251 persons in Studies A and B, respectively, need to be enrolled at Baseline.

Centers will each have designated enrollment goals. For example, if 15 centers participate in Phase III of the MDRD Study, each center will be expected to enroll 77 patients into Baseline, 60 in Study A and 17 in Study B. Each center would be expected to randomize 40 patients into Study A and 13 patients into Study B. Once a center has met its goals for randomized patients for both studies, that center may be allowed to enroll additional patients. However, the center will only be allowed to enroll additional patients into the study which is under projected figures overall, and this can only be done with the concurrence of NIH and the Data Coordinating Center.

3.2 SAMPLE SIZE FOR STUDY C

Patients reaching only a GFR stop point in Study A are assigned to Diet K (Study C). The number of randomized patients in Study A is expected to be over 550. Assuming that less than 5% of patients will drop out and approximately 10% of patients will reach a renal function stop point, it is estimated that about 30 to 80 patients will be eligible to enter Study C. The primary analysis will be within diet comparisons before and after the

change in diet. Hence, the rate of change in GFR before the change in diet will be compared to the rate of change in GFR after the change in diet. The mean difference will be examined by a two-sided paired t-test at the 0.05 significance level for Diets L and M separately. If the mean difference in the rate of change in GFR is equal to the standard deviation of the differences in the rate of change in GFR, then there is approximately a 90% chance of detecting such a difference in the diets with 11 patients. With the expected 15 to 40 patients in this study for each of the two diets, a mean difference as small as 50-85% of the standard deviation of the differences in the GFR slopes could be detected with 90% power.

SECTION 4

PATIENT SELECTION

4.1 ELIGIBILITY AND EXCLUSION CRITERIA

Investigators at each participating clinical center will enroll patients into Study A and Study B. Except for level of GFR and usual dietary protein intake, eligibility for and exclusion from Study A and Study B are based on the same criteria. It is anticipated that patients selected for the study will be highly motivated. Selection of patients will be conducted in two periods: a Screening Period for initial determination of eligibility and exclusions, and a Baseline Period (3 months) to train patients in study procedures, to assess GFR, dietary protein intake and compliance, to control blood pressure according to study antihypertensive regimen, and to assign patients to Study A or B. Following this, patients are randomly assigned to the study diets and blood pressure goals and the Follow-up Period begins.

Tables 4.1 and 4.2 contain a summary of eligibility and exclusion criteria for Study A and Study B. The criteria employed during the Screening Period are described in Section 7 (Screening Evaluation). The criteria employed during the Baseline Period are described in Section 6 (Baseline Evaluation).

4.2 USE OF ERYTHROPOIETIN

At the time this Protocol was approved by the Steering Committee, FDA had not released recombinant human erythropoietin (r-HuEPO) for treatment of anemia in humans, including anemia associated with end-stage renal disease. Analysis of Phase II data revealed that 3% of patients in Study A and 25% of patients in Study B had hematocrit less than 25%. Based on these findings, it appeared likely that use of r-HuEPO for treatment of anemia would be infrequent in patients eligible for the MDRD Study even after its release by the FDA. Only anecdotal information (from small, uncontrolled studies) was available concerning the effect of r-HuEPO treatment or of raising the hematocrit on GFR or on the progression of renal disease in humans who had not yet developed end-stage renal disease.

The following principles were adopted:

1. Until its release by the FDA, patients treated with r-HuEPO are excluded from enrollment in the MDRD Study (as are other patients treated with investigational new drugs, Section 7.5).

2. After its release, patients treated with r-HuEPO are not excluded from participation. Specifically,
   a. Patients treated with r-HuEPO during Screening are eligible to enter the Baseline and Follow-Up Periods. Dosage should be adjusted to maintain target hematocrit.
   b. Patients not initially treated with r-HuEPO should not be subsequently treated unless necessary. If treatment is necessary, the patient is not excluded from continuing in the Baseline and Follow-Up Periods. The dosage should be adjusted to maintain target hematocrit.

3. After its release, the guidelines in #2 will be re-evaluated periodically and as new information becomes available.

TABLE 4.1
SUMMARY OF ELIGIBILITY CRITERIA

Eligibility Criteria	SCREENING Required for Entry into Baseline Period (Section 7)	BASELINE 3 VISIT Required for Randomization (Section 9)
1. Age 18-70 years	Section 7.4	NA
2. Increased Serum Creatinine or other objective evidence of kidney disease Men: 1.4-7.0 mg/dl Women: 1.2-7.0 mg/dl Other objective evidence of kidney disease is defined as endogenous creatinine clearance <70 ml/min/1.73m^2 B.S.N. and, an abnormal kidney biopsy, an abnormal kidney size or configuration, an abnormal urinalysis or a history of kidney disease.	Section 7.4	NA
3. Blood Pressure (mmHg) Mean Arterial Pressure (MAP) ≤125 mmHg	Section 7.4	Section 9.11
4. GFR (ml/min/1.73m^2) 13-55	NA*	Section 9.12
5. Urinary Protein Excretion < 10g/day	NA*	Section 9.13
6. Protein Intake (g/kg/day) GFR 25-55: ≥0.90 GFR 13-24: any value	NA*	Section 9.14

* **WARNING: GFR, dietary protein intake, and urinary protein excretion need not be measured prior to entry into Baseline Period. However, patients whose GFR, dietary protein intake, or urinary protein excretion are out of range at the conclusion of the Baseline Period are excluded from randomization. Investigators are advised not to enter patients into Baseline if it appears likely that they will not be permitted to be randomized.**

TABLE 4.2

SUMMARY OF EXCLUSION CRITERIA

Exclusion Criteria	Exclusion from Entry into Baseline Period (Section 7)	Exclusion from Randomization (Section 9)
1. Pregnancy	Section 7.5	Section 9.16
2. Poor or Doubtful Compliance	Section 7.5	Section 9.16
3. Relative Body Weight		
<80% or	Section 7.5	Section 9.16
>160%	Section 7.5	NA
4. Serum Albumin <3.0 g/dl	Section 7.5	Section 9.16
5. Selected Renal Disorders (if known)	Section 7.5	Section 9.16
Renal Artery Stenosis as the cause of Renal Insufficiency		
Upper Urinary Tract Obstruction		
Staghorn Calculi		
Kidney Transplant		
Cystinuria		
6. Bladder Outlet Obstruction	Section 7.5	Section 9.16
7. Medical Conditions	Section 7.5	Section 9.16
Diabetes requiring insulin		
Malignancy within 1 year		
Heart Failure (Class 3, 4)		
Lung Disease (cor pulmonale)		
Liver Disease		
Gastrointestinal Disease		
Systemic Infections		
Collagen-Vascular Diseases		
Frequent hospitalizations		
8. Drugs	Section 7.5	Section 9.16
9. Allergy to iodine	Section 7.5	Section 9.16
10. Inability or unwillingness to consent	Section 7.5	Section 9.16

SECTION 5

INFORMED CONSENT

5.1 GENERAL PRINCIPLES

In order to be eligible for the study, each participant must be willing to sign a statement of informed consent prior to the Baseline Period as well as a second statement of informed consent prior to randomization. This will document the agreement of the subject to participate in the study activities. Copies of signed Informed Consent Forms will be kept at the Data Coordinating Center. These will be stored apart from the other study forms since they contain confidential information, i.e., the patients' names.

5.2 PARTICIPATION IN OTHER STUDIES

Participation in the MDRD Study is expected to be quite time consuming, and additional patient obligations beyond those required for the MDRD Study may adversely affect compliance. Therefore, patients will not be asked by MDRD Study personnel to participate in any other research studies during their participation in the MDRD Study unless the request is reviewed by the Publication, Ancillary Studies and Recruitment Committee and approved by the Steering Committee.

In addition, patients agreeing to participate in the MDRD Study will be advised not to volunteer for other studies during their participation in the MDRD Study. It is recognized, however, that the decision to participate or not to participate in any study is a right of the patient which cannot be abrogated by the MDRD Study.

5.3 SEQUENCE OF PROCEDURES

It is recognized that Clinical Center Institutional Review Boards have official responsibility for determining informed consent procedures. Prototype informed consent forms have been developed for the study, and each Clinical Center's IRB-approved consent form will be reviewed to make sure the essential material is included. The following description is intended as a guideline that most centers could follow.

A three-stage consent is planned for the MDRD Study. 1) Consent will be obtained prior to or at the time of the Screening Visit (Screening Period Consent Form), and will include description of the interaction with members of the study team, measurement of height, weight, elbow breadth, limited physical

examination, blood and urine tests. 2) Consent will be obtained after it is determined that the patient is eligible to enter the Baseline Period (Baseline Period Consent Form) and will include consent to interact with members of the study team; where needed, control of blood pressure to the conventional target; assessment of GFR, nutrition history, and diet intake and compliance; compliance with study procedures and diet prescription; and intention to agree later to follow the study diet selected by random assignment. 3) Consent to enter the Follow-Up Period (Follow-Up Period Consent Form) will be requested at the end of the Baseline Period, just prior to randomization, and will include in addition to the above, specific consent to be randomized to a study diet, and consent to randomization to one of two blood pressure target ranges.

Study C will require a separate consent form (Study C Consent Form) which will be signed at the time of entry into Study C.

Obtaining follow-up data on patients who are not eligible to enter the Follow-Up Period (Study F) will generally not require a separate consent form. Each Clinical Center should contact the Institutional Review Board to determine if consent forms are necessary for Study F, which is described in Section 15 of this Protocol. Otherwise, informed consent for Study F will be part of the Baseline Consent.

5.4 PRIVACY

At the beginning of the study, each participant will be assigned an identification number and a name code. Participants are identified only by number in any individual tabulations, and it is expected that only group data will be published. If individual patient data are published, no identifying information will be included. The medical records of patients participating in the MDRD Study will be confidential. Specific study related information may be made available to the Food and Drug Administration and the study sponsors, National Institutes of Health and the Health Care Financing Administration.

All patients will include their social security numbers on the Economic Information Form and provide their phone numbers to the Data Coordinating Center for the QWB phone interviews. The social security numbers and phone numbers will be treated as confidential information. Any questionnaire (besides the QWB) which involves phoning patients and collecting data will be considered an Ancillary Study and require the approval of the Ancillary Studies Committee and the Steering Committee.

SECTION 6

CLINICAL CENTER MEASUREMENTS AND PROCEDURES DURING SCREENING, BASELINE AND FOLLOW-UP PERIODS

6.1 GENERAL PRINCIPLES

This section describes procedures for measurements that are obtained in the Clinical Centers during the Screening, Baseline and Follow-Up Period evaluations. Times at which these measurements are done during Screening, Baseline and Follow-Up are given in Protocol Chapters 7, 9 and 12. Additional details are included in the Clinical Center Manual of Operations. Procedures performed by the Data Coordinating Center, Nutrition Coordinating Center, Central Laboratories and Facilities are described in their respective Manuals of Operations. Quality control procedures are described in Section 18.

6.2 GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) is assessed by the urinary clearance of ^{125}I-iothalamate (35 microcuries) after subcutaneous injection. Ideally, GFR procedures are performed in the morning, in the sitting or supine position, during oral water loading after an 8-hour fast. If the patient cannot tolerate an 8-hour fast, or if the procedure must be performed in the afternoon or evening, the procedure may be modified as follows: the procedure is performed after a 2-hour fast. During the two hours prior to the 2-hour fast, the patient should not drink caffeinated beverages, but may eat a light meal, containing < 2 g protein, as described in the Manual of Operations. This exception to the GFR procedure is obtained by notification of the Centeral GFR Laboratory. Subsequent GFR procedures should be performed under the same conditions, that is at the same time in the day and after the same duration of fasting.

Prior to each GFR procedure, menstruating women who have not been surgically sterilized have an HCG-RIA or an approved on-site, within-visit serum pregnancy test. Non-steroidal anti-inflammatory agents aspirin, cimetidine, ranitidine, trimethoprim/sulfa, and trimethoprim are withheld for at least 48 hours prior to the GFR procedure. (Usual diuretic and antihypertensive agents are not withheld.) Prior to administration of ^{125}I-iothalamate, a saturated solution of potassium iodide (SSKI) (five drops) is given orally to block thyroidal iodine uptake.

^{125}I-iothalamate is administered without epinephrine. Following a 1-hour equilibration period, four clearance measurements are performed. Urine is collected by voluntary voiding. Serum specimens are obtained by venipuncture. Serum and urine radioactivity are measured at the Central GFR

Laboratory. Clearance is calculated as the time-weighted mean of the four clearance measurements. Clearance values are reported (during Baseline) to the nearest .1 ml/min/1.73m^2. For purposes of eligibility and study assignment, GFRs with 5 in the tenth's place will be rounded to the nearest even whole number. For example, GFR 12.5 is rounded down to 12, 24.5 is rounded down to 24, and 55.5 rounded up to 56. Clinical Center personnel remain "blinded" to the results of Follow-Up Period GFR results. During Baseline, both the GFR result and variability data are reported. During Follow-Up, only variability data are reported.

Additional details of the GFR procedure included in the Manual of Operations, Chapter 3. If ^{125}I-iothalamate is unavailable, another filtration marker (as yet unspecified) will be used.

6.3 24-HOUR URINE COLLECTIONS

24-hour urine samples are collected in containers containing 250 ml of 5% acetic acid as a preservative to prevent bacterial breakdown of urea. Patients are given the container at the clinic visit prior to the visit at which it is to be returned. Ideally, the urine sample should be collected the day before the visit at which it is to be returned and carried to the clinic. Pyridium, cephalothin, and cefoxitin are withheld for 48 hours prior to the beginning of a 24-hour urine collection. The urine must be received at the Central Biochemistry Laboratory within seven days of its collection. Details on 24-hour urine collection are given in Chapter 5, The MDRD Technicians Chapter, of the Manual of Operations.

6.4 DIETARY DATA

6.4.1 3-Day Food Records. Food records are assigned at the time of the visit and must be completed and, if possible, mailed to the dietitian prior to the visit at which they are to be reviewed and documented.

6.4.2 1-Day Food Recall. A 24-hour recall is completed with the dietitian at the first Baseline visit.

6.5 ESTIMATED PROTEIN INTAKE (EPI)

6.5.1 UNA is calculated by the DCC from results of 24-hour urine collection analyzed by the Central Biochemistry Laboratory and the patient's standard body weight, according to the following formula (Maroni, Steinman, Mitch, 1985): EPI from UNA = 6.25 x [UUN + (0.031 x SBW)] + UProt where UUN is urine urea nitrogen (g/day), 0.031 is the constant value of urinary non-urea nitrogen losses and non-urinary nitrogen losses (g N/kg SBW/day), SBW is standard body weight (kg), and UProt (g/day) is the 24-hour urine protein excretion in excess of 5 g/day. (Note: The possible contribution to UNA from changes in serum urea nitrogen

concentration or in total body water are ignored by this calculation. These changes from day to day are expected to be small.)

The normalized EPI is the EPI formula in grams per day divided by the patient's standard body weight in kilograms.

6.5.2 EPI From Dietary Data

EPI is calculated by the NCC from 3-day food records and 1-day food recalls. At defined times, EPI is calculated by Clinical Center dietitians using the Computerized Diet Design Tool (CDDT).

6.6 ESTIMATED PHOSPHORUS INTAKE

Phosphorus intake is estimated by the NCC from dietary data. At defined times, phosphorus intake is estimated by Clinical Center dietitians using the CDDT.

6.7 ARTERIAL BLOOD PRESSURE

6.7.1 Measurement Devices

Standardized Hawksley random-zero sphygmomanometers are used for all visits.

6.7.2 Measurement Technique

Measurement technique is adopted from the JNC Report (1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure):

1. Patients should be seated with their arm bared, supported and positioned at heart level. They should not have smoked or ingested caffeine within 30 minutes prior to measurement.
2. Measurement should begin after 5 minutes quiet rest.
3. The appropriate cuff size must be used to ensure an accurate measurement. The rubber bladder should encircle at least two-thirds of the arm. Several sizes of cuffs (e.g., adult, large adult) should be available.
4. Both the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) should be recorded, as well as the random zero value. The disappearance of sound (Phase V) should be used as the diastolic reading.
5. SBP and DBP are measured three times in the same arm without changing positions. For each

measurement, the random zero value is subtracted to calculate the actual blood pressure measurements.

6.7.3 Recording Technique

1. Results of all three measurements are recorded.
2. Mean arterial pressure (MAP) is calculated and recorded for the final two actual blood pressure measurements according to the formula below:
   MAP = DBP + 1/3(SBP-DBP)
3. Average MAP for the last two recordings is calculated and reported on the MDRD Patient Data Flow Sheet.

6.8 ANTHROPOMETRY

6.8.1 Weight is measured on a calibrated scale. Patient is weighed in light clothing, without shoes.

6.8.2 Height is measured on a standard stadiometer. Patient is measured without shoes.

6.8.3 Frame size is derived from measurement of elbow breadth (Frisancho, A. Roberto, Ann Arbor, MI: Health Products, 1988). Elbow breadth is measured using a Bicondylor Vernier caliper.

6.8.4 Standard body weight (SBW) is calculated from measurement of height and frame size, according to tables compiled by A. Roberto Frisancho, Ph.D. (Ann Arbor, MI: Health Products, 1988) from NHANES I and II weight, height and frame size data.

6.8.5 Skinfolds are measured using calibrated Holtain calipers, and arm circumference is measured using a flexible steel tape measure. Biceps, triceps, subscapular skin fold and arm circumference are measured two times by a single observer on each occasion. If the values reported differ by less than 5% from each other, the second measurement will be reported. If the values differ by more than 5%, the measurements will be repeated until two consecutive measurements differ by less than 5% and the final measurement will be reported.

For details on anthropometry, see Manual of Operations, Volume I, Chapter 1.

6.9 BLOOD TESTS

Blood tests are required at intervals as stated in subsequent sections in the Protocol. Special instructions, such as fasting conditions, withholding of medications, and site of measurement (Central Laboratories vs. local Clinical Center Laboratories) are specified.

6.10 ELECTROCARDIOGRAM (EKG)

12-lead EKGs are performed by Clinical Center personnel according to usual techniques and read by the Central EKG Lab to check for evidence of arrhythmias, conduction defects, myocardial infarction, left ventricular hypertrophy, P wave abnormalities, QRS complex abnormalities, and T wave abnormalities.

6.11 QUESTIONNAIRES

Questionnaires used during the study to assess satisfaction with dietary regimens, symptoms and overall quality of life include the following:

Form 26 - Patient Symptom Form
Form 27 - Quality of Well-Being
Form 28 - Symptom Check List (SCL-90-R)
Form 48 - Physical Activity Questionnaire
Form 74 - Dietary Satisfaction

The Dietary Satisfaction Questionnaire, Patient Symptom Form, Symptom Check List, and Physical Activity Questionnaire are self-administered and completed by the patient during the visit. The Quality of Well Being Questionnaire is administered to the patient over the phone by an interviewer from the Data Coordinating Center at a time which has been previously scheduled with the patient.

SECTION 7

SCREENING PERIOD EVALUATION

7.1 GENERAL PRINCIPLES

Patients may be screened at any time during the 21 month recruitment period. As described below, screening includes a combination of chart reviews and clinic screening visits. All screening requirements must be met before entry into Baseline and patients must be entered into the Baseline Period within two months of the date of the measurement of serum creatinine that is used for determination of eligibility. After two months, patients cannot enter the Baseline Period unless the procedure below is repeated.

7.2 SCREENING PERIOD ELIGIBILITY REQUIREMENTS

Screening eligibility criteria are listed below.

1. Age 18-70 years.
2. Most recent serum creatinine during the past one year within the limits below:
   a. 1.4-7.0 mg/dl (men)
   b. 1.2-7.0 mg/dl (women)
3. Not taking insulin.
4. Not a kidney transplant recipient.

Patients who meet the above criteria are eligible for further chart review and visits, as described below. Patients who were enrolled in the MDRD Pilot Phase are not eligible for enrollment in Phase III.

7.3 SCREENING PROCEDURE

Patients who meet the screening eligibility requirements are derived from one of two sources: 1) Systematic review of records or laboratory results, and 2) Referrals, including patients referred by their physicians or self-referred for entry into the MDRD Study. Screening procedures for patients from both sources are described below:

1. All patients derived from systematic review. Complete Screening Chart Review (Form #01). Go to #3.
2. Patient is referred from physician or self-referred. Complete Screening Chart Review only if the patient is eligible for a Screening Visit. Go to #3.
3. Patient is eligible for Screening Visit.
   No. Do Not Continue.
   Yes. Invite patient for Screening Visit, then go to #4.

4. Patient attends Screening Visit.
   No. Complete Form #02. Do Not Continue.
   Yes. Go to #5.
5. Patient is eligible to enter Baseline.
   No. Do Not Continue. (Patients found to be ineligible may be rescreened at a later date.)
   Yes. Invite patient to enter Baseline, then go to #6.
6. Patient consents to enter Baseline (see Section 5).
   No. Complete Form #03.
   Yes. Complete Form #03. Conduct Baseline Visit 0 within 2 months of the date of serum creatinine determination. Eligible patients who cannot enter Baseline Period within this interval should be screened again at a later date.

7.4 ELIGIBILITY CRITERIA FOR ENTERING BASELINE

1. Age 18-70 years.

2. Increased Serum Creatinine or other objective evidence of kidney disease:
   Men: 1.4-7.0 mg/dl
   Women: 1.2-7.0 mg/dl
   Measurements of serum creatinine should not be made within 48 hours of ingestion of non-steroidal anti-inflammatory agents, inhibitors of tubular secretion of creatinine (e.g., cimetidine, trimethoprim), or agents which interfere with chemical determination of creatinine (e.g., cephalosporins).
   Other objective evidence of kidney disease is defined as either endogenous creatinine clearance <70 ml/min/1.73m^2 B.S.N. or inulin, DTPA or iothalamate clearance $\leq$ 55 ml/min/1.73m^2 and an abnormal kidney biopsy, an abnormal kidney size or configuration, an abnormal urinalysis or a history of kidney disease.

   If creatinine clearance is used to define other objective evidence of renal disease, this should be specified on the Form 51. If inulin, DTPA, or iothalamate clearance is used, the clinical center should notify the DCC in writing.

3. Blood Pressure:
   Mean Arterial Pressure $\leq$125 mmHg on most recent measurement.

7.5 EXCLUSION CRITERIA FOR ENTERING BASELINE

Patients with any of the following criteria are excluded from entry into the Baseline Period. More detailed explanations of the criteria are included in the Manual of Operations, Volume II.

1. Lactating or pregnant women or women planning to become pregnant within 2-4 years.

2. Patients in whom compliance is doubtful.
   a. Drug abuse.
   b. Alcohol abuse.
   c. Psychiatric illness.
   d. Poor understanding of the study.
   e. Limited motivation.
   f. Unusual diet preferences.
   g. Transient residence.
   h. Unsuitable home environment.
   i. History of frequent missed appointments.
   j. Unable to read food labels or study instructions.
   k. Unable to write food records.
   l. Lack of access to a phone.
   m. Poor compliance in other clinical trials.

3. Relative body weight.
   Body weight <80% or >160% of standard weight for height adjusted for frame size (as judged from tables compliled by A. Roberto Frisancho, Ph.D. (Ann Arbor, MI: Health Products, 1988) from NHANES I and II weight, height and frame size data. (See Manual of Operations, Volume I, Chapter 1.)

4. Reduced serum albumin.
   Serum albumin <3.0 g/dl on most recent measurement within the past three months.

5. Selected renal disorders, if known, including:
   a. Urinary tract obstruction
   b. Renal artery stenosis as the cause of renal insufficiency
   c. Branched or staghorn calculi
   d. Kidney transplant recipients
   e. Cystinuria

6. Inability to empty the bladder, if known.
   Patients with symptoms of bladder outlet obstruction must have a post-void bladder ultrasound and/or other study to evaluate bladder emptying. Patients with urinary retention are excluded.

7. Chronic serious medical conditions affecting dietary protein prescription, nutritional status, renal function or compliance with study protocols. Patients with the conditions listed below are excluded:
   a. Diabetes mellitus (patients taking insulin, or patients with fasting serum glucose >200 mg/dl).

b. Malignancy initially diagnosed or known to be recurrent within the past year.
c. Heart failure (class 3 or 4 NY Heart Association).
d. Lung diseases causing cor pulmonale.
e. Liver diseases.
f. Gastrointestinal diseases causing anorexia or frequent episodes of nausea, vomiting or diarrhea (unless related to renal disease).
g. Chronic systemic infections (including AIDS and ARC).
h. Collagen vascular diseases (SLE and vasculitis).
i. Frequent hospitalizations or disability. Any condition (other than renal disease) leading to more than 3 hospitalizations or more than 60 days of hospitalization within the past year. Any disabling condition that prevents adherence to study procedures.

8. Drugs.
   a. Immunosuppressive agents
   b. Corticosteroids in excess of replacement dosage for $\geq$2 months/year
   c. Gold or penicillamine within the past month
   d. Salicylates, more than 20 tablets per week
   e. Other non-steroidal anti-inflammatory agents, more than three times per week during the past two months. (See Table in Manual of Operations, Volume II.)
   f. Investigational new drugs.

9. Allergy to iothalamate or iodine, if known.

10. Inability or unwillingness to consent to enter the Baseline Period.

SECTION 8

ANTI-HYPERTENSIVE REGIMENS

8.1 INTRODUCTION

This section describes the goals and procedures for the treatment of high blood pressure during the Baseline and Follow-Up Periods. Goals for blood pressure during the Baseline Period are expressed as mean arterial pressure (MAP) and are given in the Table 8.1. MAP goals are the upper limits for acceptable range of MAP. There is no lower limit, provided that symptoms or findings of low blood pressure do not occur.

In the Baseline Period, MAP goal is determined only by the patient's age. In the Follow-Up Period, MAP goal is determined by the patient's age and random assignment to either the moderate MAP goal or low MAP goal. Anti-hypertensive regimens to achieve MAP goals are similar during both the Baseline and Follow-Up Periods and for both the moderate and low MAP goals and are described later.

TABLE 8.1

BLOOD PRESSURE (MAP) GOALS FOR BASELINE AND FOLLOW-UP PERIODS*

Baseline Period

Age (Years)	MAP Goal (mmHg)
18-60	$\leq$ 107
$\geq$ 61	$\leq$ 113

Follow-Up Period

Age (Years)	Moderate MAP Goal (mmHg)	Low MAP Goal (mmHg)
18-60	$\leq$ 107	$\leq$ 92
$\geq$ 61	$\leq$ 113	$\leq$ 98

*MAP is defined as DBP + 1/3 (SBP-DBP). For example,
BP 140/90 mmHg is equivalent to MAP 107 mmHg,
BP 160/90 mmHg is equivalent to MAP 113 mmHg,
BP 125/75 mmHg is equivalent to MAP 92 mmHg, and
BP 145/75 mmHg is equivalent to MAP 98 mmHg.

8.2 GENERAL PRINCIPLES

In general, in order to enhance compliance, efforts should be directed at recommending the most simple anti-hypertensive regimen that is effective in maintaining the MAP goal and that is tolerated without side effects.

8.2.1 Management of Patients With MAP Above Goal

An anti-hypertensive regimen, as described in this Chapter, should be initiated or adjusted to lower MAP by lowering either SBP, DBP or both. During Follow-Up, if MAP exceeds the goal on two consecutive visits, a High Blood Pressure Action Item is identified (Section 13.3). However, if symptoms of low blood pressure arise, despite MAP above the goal, a Symptoms of Low Blood Pressure Action Item is identified, and MAP goal is increased (Section 13.3).

8.2.2 Management of Patients With MAP At or Below Goal

An anti-hypertensive regimen should not be initiated in patients with MAP at or below goal. For patients receiving an anti-hypertensive regimen, it is preferable, but not required, that the regimen be adjusted to allow MAP to rise to a higher level that is still at or below the MAP goal, especially if such adjustments simplify the anti-hypertensive regimen and lead to enhanced compliance. Examples of medically necessary reasons for maintaining MAP below goal include concomitant effects of anti-anginal or diuretic therapy.

8.3 ASSESSMENT OF MAP

The procedure for measuring and recording blood pressure is described in Section 6.7. Clinic blood pressure results are the only measurements that are recorded and are the basis for determining whether the patient has reached the MAP goal.

Measurement and recording of blood pressure at home or at work is encouraged for self-monitoring and for aiding compliance. Frequent calibration of home or work blood pressure measuring devices is necessary to assure accuracy of results. Results of home or work blood pressure measurements are not entered on the forms or in the database and are not used to determine whether the patient has reached MAP goal.

8.4 STEPPED CARE APPROACH

Selection of an anti-hypertensive regimen should proceed according to principles of the JNC Report (Joint National Committee, 1988; included in the Appendix). This approach includes non-pharmacologic therapy as the first step, including

dietary modifications, weight loss, reduction in alcohol intake, and other life-style changes. Pharmacologic therapy is the second step and various agents may be selected, including diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium channel inhibitors. For the MDRD Study, the approach is modified as discussed below:

1. The potential difficulties are recognized in initiating dietary and life-style changes as part of non-pharmacologic therapy for hypertension in patients who are simultaneously altering dietary protein and phosphorus. Non-pharmacologic therapy is de-emphasized if it conflicts with compliance to protein and phosphorus prescription in study diets during the Baseline and Follow-Up Periods.

2. In order to reduce variability in anti-hypertensive regimens, ACE and calcium channel inhibitors (with or without diuretics), are encouraged as agents of first choice and second choice, respectively, in initiating or changing pharmacologic therapy, if medically appropriate.

8.4.1 Non-Pharmacologic Therapy

Although non-pharmacologic therapy is encouraged as the first step in the design of the anti-hypertensive regimen, the dietary and life-style modifications may conflict with the objectives of the Baseline and Follow-Up Periods (see Section 2). Because of the different objectives during the Baseline and Follow-Up Periods, different approaches are recommended:

8.4.1.1 Non-Pharmacologic Therapy During the Baseline Period.

Because dietary changes may conflict with determination of usual eating pattern, education of the patient regarding protein content of the diet, and compliance with the Baseline Period diet, additional dietary changes should be minimized. If they are necessary, such additional changes should be implemented at the time of the Baseline diet prescription (Baseline Visit 1).

8.4.1.2 Non-Pharmacologic Therapy During the Follow-Up Period.

Dietary changes may also conflict with objectives of the Follow-Up Period. However, the potential for conflict is less than during the Baseline Period because data obtained during the Baseline Period can be used to construct the Follow-Up diet

and dietary changes can be made at the same time as assignment of the Follow-Up diet, and because a longer interval is available for counseling and assessing compliance.

8.4.2 Pharmacologic Therapy

The preferred first and second step pharmacologic agents for initiating or changing therapy are ACE and calcium channel inhibitors, respectively. Concomitant treatment with diuretics may be included, as appropriate. The strategy for initiating and changing pharmacologic therapy is as follows:

1. Patients on pharmacologic agents with MAP at or below goal and without side effects: No changes in antihypertensive agents are necessary.

2. Patients on pharmacologic agents with MAP at or below goal but with side effects: Substitute ACE or calcium channel inhibitors, as appropriate.

3. Patients on pharmacologic agents with MAP above goal and without side effects: Increase dosages of current medications, as appropriate, or add ACE or calcium channel inhibitors.

4. Patients on pharmacologic agents with MAP above goal and with side effects: Add ACE or calcium channel inhibitors.

SECTION 9

BASELINE PERIOD EVALUATION

9.1 GENERAL PRINCIPLES

The Baseline Period is three months long. Section 20 summarizes the schedule of measurements and procedures that will be performed at each Baseline Visit. During the first month patients will undergo assessment of GFR, BP, urinary protein excretion, usual protein intake on an unmodified eating pattern, dietary history, nutritional status, medical history, physical examination and laboratory evaluation. During the second and third months, patients will be prescribed an eating pattern with a defined protein level. Dietary protein intake, compliance with study procedures, and urinary protein excretion will be assessed. At the end of the three-month Baseline Period, assessment of GFR, BP, urinary protein excretion, and dietary protein intake will be repeated. Target dates for all Baseline visits, records, and examinations are given in Table 9.1. All efforts should be made to adhere to this schedule. Missed visits, records and events should be made up as soon as possible within the window. Allowable intervals during Baseline Period are also shown in Table 9.1. This schedule insures that patients will have a minimum of two months instruction in the Baseline Diet and procedures.

TABLE 9.1
Target Dates and Allowable Intervals for Baseline Visits
Target Dates for Baseline Visits and Randomization

Visit #	Target Date
0	0
0A	2 weeks
1	5 weeks
1A	1-1/2 months
2	2 months
3	3 months
Randomization	3-1/2 months

Allowable Intervals Between Baseline Visits

Interval	Target	Allowable Range
B0 - B1	5 weeks	3 months
B1 - B3	2 months	2 - 4 months
B0 - B3	3 months	5 months
B3 - Randomization	2 weeks	6 weeks

A summary of eligibility and exclusion criteria for randomization is given in Tables 4.1 and 4.2. Patients who are eligible to enter the Follow-up Period will be assigned to Study A or Study B and must be randomized within 6 weeks of their Baseline 3 Visit. Patients who drop out or are excluded during the Baseline Period or who are not randomized within 6 weeks of their Baseline 3 Visit are not eligible to enter the Follow-up Period and should be entered in Study F. At a later date still in the MDRD recruitment time period and at least one month after being excluded, patients may be rescreened and re-entered in the Baseline Period (Section 9.19).

9.2 GLOMERULAR FILTRATION RATE

GFR will be measured at Baseline Visit 0 and at Baseline Visit 3. It is recommended that GFR be measured at every Baseline 0 Visit. However, if a patient who previously completed the entire Baseline period is repeating Baseline following the provisions of Section 9.19, then that patient's previous Baseline 3 GFR may be used as the new Baseline 0 GFR, as long as the new Baseline 0 Visit falls within two months of the date of the previous Baseline 3 GFR. The purpose of Baseline Visit 0 GFR is to determine Baseline diet prescription. The purpose of Baseline Visit 3 GFR is to determine eligibility for entry in Study A and Study B.

9.3 LABORATORY TESTS

9.3.1 Schedule for laboratory tests is given in Table 9.2. Laboratory tests are not repeated except as specified in the protocol or as necessary for usual medical care. The Central Laboratory will not accept repeat specimens for measurement unless an error in shipping or laboratory procedure has occurred. In the event that an error in procedure has occurred in the local laboratory, the value for the report measurement should be submitted on the Data Change Form (Form #25).

9.3.2 24-Hour Urine Collections
Patients will collect a 24-hour urine for Baseline Visits 0, 1, 2, and 3 (See Table 9.2). At the conclusion of the Screening Visit and each Baseline Visit, patients will be given a container for the urine collection to be submitted at the next visit, as described in Section 6.3. Urine should not be collected during a short term illness.

TABLE 9.2.
FREQUENCY AND LOCATION OF BASELINE LABORATORY TESTING FOR PHASE III

TESTS	Baseline Consent 0++	Month # 1	2	Follow-Up Consent 3++	
Glucose	L			L	R
Sodium	L			L	
Chloride	L			L	
Potassium	L			L	
Bicarbonate	L			L	A
CBC	L			L	
WBC					
Hgb					
Hct					N
Iron	L			L	
Magnesium	L			L	
Phosphorus	C			C	
Calcium	L			L	D
SUN	C			C	
Creatinine	C			C	
					O
Albumin	C			C	
Transferrin	C			C	
LDH				C	
SGOT				C	M
Bilirubin				C	
Uric Acid				C	
Standard Lipid Profile	C			C	
Total, HDL, LDL Cholesterol, Triglycerides					I
Complete Lipid Profile				C	
HDL2, HDL3, Apo-lipoproteins A1 and B					Z
Hemoglobin A_{1c}				C	
					A
Amino Acids				C	
Plasma "After Thought"				C	
24 Hr Urine					T
pH	C	C	C	C	
Protein	C	C	C	C	
Urea Nitrogen	C	C	C	C	
Creatinine	C	C	C	C	I
Phosphorus	C	C	C	C	
Sodium	C	C	C	C	
Potassium	C	C	C	C	
"After Thought"				C	O
GFR	C			C	
Electrocardiogram			C		
					N

L = Local Laboratory Determination C = Central Laboratory Determination
++ = 12-Hour Fasting Measurement

excretion is to determine Baseline Diet Prescription (Section 9.10), Urine Protein Excretion at B3 (Section 9.13), Mean Baseline Estimated Protein Intake (Section 9.14) and protein content of assigned diet for patients who enter the Follow-Up Period (Section 12).

9.3.3 Blood Tests

Blood tests are required at Baseline Visits 0 and 3. (See Table 9.2.) Measurements are made after a 12-hour fast at the Baseline 0 Visit and after a 12-hour fast at the Baseline 3 Visit. The following medications should not be administered for 48 hours prior to the measurement: Non-steroidal anti-inflammatory agents, inhibitors of tubular creatinine secretion (e.g., cimetidine, trimethoprim), or agents which interfere with clinical determination of creatinine (e.g., cephalosporins).

9.3.4 Electrocardiogram

Electrocardiogram (EKG) is performed at Baseline Visit 2.

9.4 DIETARY DATA

Dietary data will be collected using 3-day food records. Dietary data will be collected during the Baseline Period according to the following schedule in Table 9.3.

TABLE 9.3
COLLECTION OF DIETARY DATA DURING BASELINE PERIOD

Baseline Visit	Dietary Data	Identifier
0A	3-Day Record	B0A 3-Day Record*
B3	3-Day Record	B3 3-Day Record*

*Analyzed by NCC

Note: Additional food records and recalls may be requested by Clinical Center Dietitians as necessary for counseling.

9.4.1 Additional instructions for food records

The BO-A 3-Day Record is to be kept within the week following Baseline Visit 0. Thereafter, records will be completed on days during the intervals between visits as selected by the dietitians. BO-A 3-Day Record will be analyzed by the NCC and may be analyzed locally using the CBORD Professional Diet Analyzer

system. The results of the NCC analysis will be used in the calculation of usual protein intake.

In addition to dietary data collected as indicated in Table 9.3, patients will self-monitor protein intake for Baseline Visits 1 and 2 and for the F1 Visit (see Manual of Operations).

9.5 MEDICINES

Medicines taken by the patient during the Baseline Period will be recorded on the monthly visit forms.

9.6 PHYSICAL EXAMINATION

9.6.1 Blood Pressure

Blood pressure will be measured at each clinic visit.

9.6.2 Anthropometry

Measurement of height and frame size will be repeated at Baseline Visit 0 for calculation of standard body weight. The average of the standard body weight values obtained at Screening Visit and Baseline Visit 0 will be considered the patient's standard body weight throughout the MDRD Study.

Weight is measured at the Baseline 0, 0-A, 1, 2 and 3 visits. Triceps, biceps, and subscapular skinfolds and upper arm circumference are measured at Baseline Visits 0-A and 2.

9.7 PATIENT QUESTIONNAIRES

The following questionnaires will be administered during the Baseline Period as indicated below:

Dietary Satisfaction Form 74 - B0
Patient Symptom Form 26 - B0, B1, B2, B3
Quality of Well-Being Form 27 - Between B2 and B3
Symptom Checklist (SCL-90-R) Form 28 - B3
Physical Activity Questionnaire Form 48 - B1, B3

9.8 ASSESSMENT OF GFR AT B0

The purpose of B0 GFR is to determine Baseline Diet Prescription (see Section 9.10 below).

Note: **B0 GFR provides an estimate of the likely GFR at B3. Allowable range for GFR at B3 is 13-55 ml/min/1.73m^2. Patients whose GFR is out of range at B3 are excluded from randomization. Investigators are advised not to continue patients after Baseline Visit 0 if it appears likely that the GFR will be out of range at Baseline Visit 3.**

9.9 ASSESSMENT OF USUAL PROTEIN INTAKE AT BO-A

The purpose of assessment of usual protein intake at BO-A is to determine Baseline Diet Prescription (see Section 9.10 below). Assessment of usual protein intake is based on the average of 1) estimated protein intake (EPI) from B0 24-hour urine collection and 2) BO-A 3-Day Food Record.

9.10 BASELINE DIET PRESCRIPTION

Baseline Diet Prescription is assigned at Baseline Visit 1. Baseline Visit 1 is scheduled to occur within one month of Baseline Visit 0 and must take place within 3 months of Baseline Visit 0 in order for the patient to have a minimum of two months of counseling in the Baseline diet. Patients who do not have a Baseline Visit 1 within 3 months of Baseline Visit 0 are excludedfrom randomization and are included in Study F.

Protein prescription will be determined according to results of GFR at Baseline Visit 0 and results of assessment of usual protein intake, as described in Table 9.4 below. Energy intake and other components of the diet are prescribed according to the patient's medical condition and usual dietary practice.

TABLE 9.4
Baseline Diet Prescription

GFR (ml/min/1.73m^2)	Usual Protein Intake (g/kg/day)	Protein Prescription (g/kg/day)
≥25	≥0.90	0.90 - 1.30
	<0.90	0.90 - 1.30*
≤24	0.90 - 1.30	0.90 - 1.30
	≥.60 - <0.90	0.60 - 0.90
	<0.60	0.60

*Prescription for those patients applies only if 1) the protein intake has recently been restricted because of renal disease or temporary change in eating habits, and if 2) the patient and the physician are willing to accept a dietary protein prescription of 0.9 - 1.3 g/kg/day. Otherwise, the patient should be excluded from further participation in Baseline since the patient is unlikely to be a candidate for randomization. A Secondary Screening Form (Form #8) must be submitted to the Data Coordinating Center indicating that the patient has been discontinued at this point in the Baseline period because of low protein intake.

9.11 TREATMENT OF HYPERTENSION DURING BASELINE PERIOD AND ASSESSMENT OF BLOOD PRESSURE AT B3

Strict control of blood pressure is required. An antihypertensive regimen should be prescribed as described in Section 8. If the mean arterial pressure (MAP) is >125 mmHg at B3, the measurement may be repeated once within one month. If the MAP remains >125 mmHg, the patient is excluded from randomization and included in Study F (see Section 9.18). (Note: The six-week limit between the Baseline Visit 3 and randomization is not extended if the blood pressure measurement must be repeated.)

9.12 ASSESSMENT OF GFR AT B3

The purpose of B3 GFR is to determine eligibility for randomization and entry into the Follow-Up Period.

Allowable limits of GFR at Baseline Visit 3:

Study A: GFR 25-55 ml/min/1.73m^2
Study B: GFR 13-24 ml/min/1.73m^2

Patients whose GFR falls outside this range are excluded from randomization and included in Study F (see Section 9.18).

9.13 ASSESSMENT OF URINARY PROTEIN EXCRETION AT B3

Urine protein excretion must be ≤10.0 g per day on the two most recent measurements during Baseline. Patients whose values for protein excretion exceed this value are excluded from randomization and included in Study F (see Section 9.18).

9.14 ASSESSMENT OF MEAN BASELINE ESTIMATED PROTEIN INTAKE

Mean baseline dietary protein intake is calculated from the average of results of EPI in the two most recent 24-hour urine collections.

Allowable limit for mean baseline EPI

Baseline 3 GFR ($ml/min/1.73m^2$)	EPI (g/kg/day)
25 - 55	≥0.90
13 - 24	any value

Patients with Baseline 3 GFR between 25-55 and whose value for Mean Baseline EPI is less <0.90 g/kg/day are excluded from randomization. Excluded patients are included in Study F (see Section 9.18).

9.15 ASSESSMENT OF COMPLIANCE TO STUDY PROTOCOL

Patients will be judged to be meeting the standards of performance of the Study Protocol if they meet the following performance standards.

1. Completion of Baseline Visit 1 within 3 months.
2. Completion of Baseline Visits 0, 1, 2, and 3 within 5 months.
3. Completion of GFR measurement at Baseline Visit 0 and 3.
4. Completion of three 24-hour urine collections.
5. Return both the BO-A and B3 food records.
6. Randomization within 6 weeks of Baseline 3 Visit.

If a patient does not meet these criteria, he or she will be excluded.

9.16 ADDITIONAL ASSESSMENTS AND EXCLUSIONS DURING THE BASELINE PERIOD

Patients with the following items at Baseline Visit 3 are excluded from randomization and included in Study F.

1. Poor or doubtful compliance based on unusual diet preferences, e.g., some vegetarians (see Manual of Operations).
2. Actual body weight less than 80% of standard body weight at Baseline 3 Visit.
3. Low serum albumin. If serum albumin <3.0 g/dl at Baseline Visit 3, the measurement may be repeated once within one month. If the repeat measurement is <3.0 g/dl, patient is excluded. (Note: The six week limit between the Baseline Visit 3 and randomization is not extended if the serum albumin must be repeated.)
4. If the CV of the GFR at BV3 exceeds 35%, this value cannot be used for randomization. Under these circumstances, the GFR determination may be repeated once within one month. If the repeat GFR determination has a CV exceeding 35%, the patient is excluded. (Note: The six week limit between the Baseline Visit 3 and randomization is not extended if the GFR must be repeated.)
5. Refusal to consent to random assignment to study diets and participation in Follow-up Period protocols (Follow-Up Consent Form).

9.17 SUMMARY OF EXCLUSIONS DURING BASELINE PERIOD

1. Baseline diet prescription does not apply (for patients with GFR $\geq$25) (Section 9.10).
2. High blood pressure at B3 (Section 9.11).
3. GFR out of range at Baseline 3 Visit (Section 9.12).
4. Urinary protein excretion out of range at B3 (Section 9.13).
5. Mean Baseline estimated protein intake out of range at conclusion of Baseline Period (Section 9.14).
6. Poor or doubtful compliance based on failure to meet the performance standards (Section 9.15).
7. Poor or doubtful compliance based on unusual diet preference (Section 9.16).
8. Relative body weight out of range at B3 (Section 9.16).
9. Serum albumin out of range at B3 (Section 9.16).
10. New medical, psychiatric, nuritional or social condition (Section 9.16).
11. Refusal to sign Follow-Up Consent Form (Section 9.16).

9.18 CRITERIA FOR ENTRY INTO STUDY A AND STUDY B

Patients not excluded during the Baseline Period are eligible for entry into Study A or Study B. Based on Baseline Visit 3 GFR and assessment of mean baseline EPI, the following study assignments will be made:

Study A
1. GFR 25-55 ml/min/1.73m^2.
2. EPI $\geq$0.90 g/kg/day.

Study B
1. GFR 13 - 24 ml/min/1.73m^2.
2. EPI: any value

Patients eligible for Study A and Study B proceed to randomization. Patients who drop out during the course of the Baseline period or who are not eligible for randomization at the end of Baseline enter Study F. The purpose of Study F is to obtain follow-up every six months on patients who do not enter the Follow-Up Period (see Section 15). During recruitment, patients in Study F may be seen at more frequent intervals to determine if they become eligible to enter Study A or Study B. If any patients in Study F appear to no longer meet the exclusion criteria that put them in Study F, they may be re-screened, and re-enter Baseline one month or more after being excluded from randomization.

9.19 Reentry Into Baseline

When a previously excluded patient is re-entered into Baseline, there are three special mechanisms in place to make things easier. Details on procedures are given in the Manual of Operations Study Coordinator's Chapter.

9.19.1 B0-A Visit Optional

To streamline reentry into Baseline, the B0A visit may be considered optional for any patients who previously completed Baseline and are reeentering Baseline within two months from their previous B3 visit. To facilitate this process, the dietitian should assess whether the patient's skills would be compromised if the B0A Visit is not held. Patients whom the dietitian determines should not miss the visit or those who are reentering Baseline more than 2 months after the last B3 visit should follow the usual visit schedule and attend the B0A Visit.

The food record normally documented at the B0A visit may be documented at the B0 visit. If the B0A visit is not held and the record is documented at the B0 visit, the food record should be mailed to the patient before the visit with instructions that it is to be completed and returned at the B0 Visit.

Patients entering Baseline a second time may have the anthropometry measurements usually taken at the B0A Visit taken at the B0 visit. If a GFR is scheduled at the B0 visit, the measurements should be taken at Baseline Visit 1 instead.

9.19.2 Using the B3 GFR as a B0 GFR

If a patient who previously completed the entire Baseline period is repeating Baseline following the provisions of Section 9.19, then that patient's previous Baseline 3 GFR may be used as the new Baseline 0 GFR, as long as the new Baseline 0 Visit falls within two months of the date of the previous Baseline 3 GFR.

9.19.3 Eliminating the B0 Visit altogether

The following procedure may be applied for patients re-entering within two months of a prior B3.

New Screening Visit Form 3 is not required.
The B0 and B0A visits are not required.
The 3-day food record can be mailed to the patient to return to be documented at the B1 visit.
The DCC substitute, the B3 GFR for B0 GFR, the B3 BP for B0 BP, B3 serum and urine results for B0 results, and B0 24-hour recall for new B0 recall.
The old B2 EKG becomes the new B2 EKG, and the old B2 anthropometry results become the new B0A anthropometry.

Maximum interval until the new B3 is 5 months from date of prior B3. Complete details on re-entering excluded patients are given in the Study Coordinator's Chapter of the Manaul of Operations.

SECTION 10

RANDOMIZATION

10.1 PROCEDURE

Treatment assignments for the MDRD Study will be made using separate randomization schedules for each of the participating Clinical Centers. Within each Clinical Center, Study A patients will be stratified into four subgroups. Patients will be grouped according to the rate of decline of the screening reciprocal serum creatinine (>-0.0030 dl/mg/mo and $\leq$-0.0030 dl/mg/mo), and any patient without a defined screening creatinine slope will be placed in the >-0.0030 dl/mg/mo group. Patients will also be grouped according to the average mean arterial blood pressure during the Baseline Period adjusted for age (high MAP and low MAP). The "high MAP" stratum is defined as average baseline MAP greater than 107 for ages less than 61 or average baseline MAP greater than 113 for ages 61 or older. Within each Clinical Center, patients entering Study B will be stratified into two groups based on age-adjusted Baseline 3 mean arterial pressure, using the same stratum definitions as in Study A. Based on the analysis of Phase II data, it is anticipated that about 50 percent of the Study B patients, and about 25 percent of the Study A patients will fall in the higher age-adjusted mean arterial pressure stratum and that approximately 50 percent of the Study A patients will have inverse serum creatinine slopes greater than -.0030 dl/mg/mo. As described in Chapter 2, each patient will be randomized to a dietary regimen and a blood pressure control regimen.

The randomization schedules will be prepared by the Data Coordinating Center prior to the start of patient recruitment. Allocation to treatment groups will be equal. The specific allocation procedure will be a stratified block randomization procedure. Block randomization is used to help balance numbers of subjects assigned to each group. It guarantees that at no time during randomization will the subjects in the individual groups be grossly unequal. The size of each block will be determined in a random fashion. Random selection of the block size makes it very difficult for Clinical Center Staff members to determine where blocks start and stop.

The randomization process will be centrally administered. All randomization schedules will remain confidential and known only by members of the Data Coordinating Center staff. Once all Baseline period studies have been completed and the forms corresponding to these studies have been received by the Data Coordinating Center, the patient has signed the consent forms, and

it has been determined that the patient meets all eligibility requirements (including an acceptable level of compliance with study procedures), the Principal Investigator or the study coordinator shall telephone the Data Coordinating Center. The staff of the Data Coordinating Center will verify through a defined set of questions that the patient is ready to be randomized, and give the Clinical Center a randomized treatment assignment for that patient based upon his or her stratum. After receiving the treatment assignment, the Clinical Center will complete a form indicating that assignment. These forms will be cross-checked with the randomization assignment given by the Data Coordinating Center when received at the Data Coordinating Center. No phone randomization will be allowed at night (between 4:30 p.m. and 8:00 a.m. Eastern Time) or during weekends.

Randomization of the patient to his or her dietary and blood pressure control intervention plans marks the patient's official and irrevocable entry into the Follow-Up Period. Once a patient has been randomized, efforts will be made to conduct all evaluations irrespective of the patient's compliance to the assigned dietary or blood pressure control regimen and protocol procedures. These efforts should continue until termination of the Follow-Up Period.

SECTION 11

DIETARY REGIMENS

11.1 INTRODUCTION

Based on the outcome of randomization, one of three diets is prescribed at Follow-Up Visit 1: a moderate protein diet (M), a low protein diet (L), and a very low protein diet supplemented with a mixture of keto acids and amino acids (K). (See Table 11.1)

In all diets, the quantity of protein, ketoacids (where applicable), and phosphorus to be prescribed will be determined according to the patient's Standard Body Weight (SBW) as calulated from tables compiled by A. Roberto Frisancho, Ph.D. (Ann Arbor, MI: Health Products, 1988) utilizing height and frame size.

Table 11.1 contains guidelines for nutrient composition of the various diet regimens. Adjustments to the initial diet prescription and rationale for selected features of the diet are given in this chapter. While there may be indications for the inclusion of dietary modifications to support blood pressure or lipid lowering protocols, it should be emphasized that the primary nutrients for modification in the MDRD Study are protein and phosphorus. Modifications in nutrients other than these can be considered whenever possible providing they do not compromise adherence to protein and/or phosphorus recommendations. Assessment of compliance to the prescribed diet during the Follow-up Period is described in Section 12. Assessment of nutritional status during the Follow-up Period is described in Section 12. Occurrence of defined clinical events (Intercurrent Illness, Action Items, and Stop Points) is a signal for modification of the initial diet prescription, vitamin and mineral prescription or frequency of measurements. A detailed description of these events is contained in Section 13.

11.2 INITIAL DIET PRESCRIPTION

A meal pattern will be prepared by the dietitian within the first two months after randomization. The meal pattern must provide 3-7 days of sample menus which

a. follow guidelines of nutrient composition of the diet prescription (Table 11.1).
b. include other nutritional modifications as necessary, and
c. reflect the patient's own eating style and food preferences.

The primary determinants of the eating pattern will reflect the central nutrition variables of the study, i.e., protein, phosphorus and energy. However, other nutritional

TABLE 11.1 Nutrient Composition of Diets[a]

	Moderate Protein Diet	Low Protein Diet	Very Low Protein (Keto acid) Diet
Total Protein (g/kg/day)[b]	1.30	0.575	0.28
High Biologic Value Protein (g/kg/day)	No upper or lower limit[c]	≥0.35	No upper or lower limit
Low Biologic Value Protein (g/kg/day)	No upper or lower limit[c]	≤0.25	No upper or lower limit
Energy (kcal/kg/day)	Adequate to maintain or promote standard weight		
Calcium (mg/day)[f]	1300 - 1700	1300 - 1700	1300 - 1700
Phosphorus (mg/kg/day)	16 - 20	5 - 10	4 - 9
Magnesium (mg/day)	≥300 - 350[d]	≥300 - 350[d]	≥300 - 350[d]
Sodium (mg/day)	≥1200[j]	≥1200[j]	≥1200[j]
Potassium (mEq/day)	50 - 150	50 - 150	50 - 150
Iron (mg/day)	≥10 - 18[e]	≥10 - 18	≥10 - 18
Zinc (mg/day)[f]	15 - 20	15 - 20	15 - 20
Vitamin A (IU/day)[g]	5000	5000	5000
Vitamin D (ug/day)[h]	5.0 - 7.5[i]	5.0 - 7.5[i]	5.0 - 7.5[i]

[a] See text for further discussion of nutrient composition of diet.

[b] Add one gram of high quality protein for each gram of daily urine protein loss during Baseline up to a maximum of eight grams.

[c] The patient can eat any combination of high and low biological value protein as long as 1) total protein intake remains at the prescribed level, and 2) the dietitian indicates that the patient ingests the minimum recommended safe intake of essential amino acids.

[d] ≥350 mg/day for males; ≥300 mg/day for females.

[e] ≥10 mg/day for males and nonmenstruating females; ≥18 mg/day for menstruating females.

[f] Including supplements.

[g] The monthly average of Vitamin A intake from foods should be at least 5000 IU/day but this will not be a requirement of the dietary prescription. If the average of Vitamin A intake is less than 300 IU/day, a supplement of 5000 IU/day of Vitamin A will be given; otherwise, no Vitamin A supplement will be administered to the patient.

[h - i] Given as cholecalciferol or ergocalciferol. 5.0 ug/day for men and women ages 23 to 74 years old; 7.5 ug/day for men and women ages 19 to 22 years old.

[j] Level adjusted to 2000 mg/day as non-pharmacologic therapy of hypertension.

considerations such as sodium, alcohol, as well as type and amount of dietary fat and dietary cholesterol may need to be included depending on the blood pressure and/or lipid levels which were measured during the Baseline Period. While the model meal pattern will be constructed to support multiple dietary interventions, if necessary, the time frame for the implementation of these various interventions will be tailored for each individual patient. The primary determinants of the menu plan are the protein, phosphorus and energy prescription. Dietitians will analyze three to seven days of sample menus using the CDDT Professional Diet Analyzer to determine the protein, phosphorus, energy, calcium, sodium and potassium content of the diet. Modification of the meal plan and prescription of calcium carbonate supplements is based on these analyses.

11.3 Keto Acids and Urinary Protein Excretion Adjustment

11.3.1 Keto Acids

The composition of the essential amino acid and keto acid analogues is shown in Table 11.3. The MDRD Keto Acid Mixture is a mixture of ornithine, lysine and histidine salts of branched chain keto acids (keto-analogues of leucine, valine, and isoleucine), and the calcium salt of the hydroxy-analogue of methionine, threonine, tyrosine, and tryptophan. It does not contain phenylalanine in any form. It is administered

at a daily dose of 2.8 g per 10 kg of standard body weight in three divided doses in conjunction with Diet K. For calculation of keto acid dose, the patient's standard body weight is rounded to the nearest 10 kg.

11.3.2 Dietary Protein Adjustment Based On Urinary Protein Excretion

Dietary protein prescription will be increased by 1 g (or fraction thereof) high biologic value protein for each 1 g (or fraction thereof) urinary protein excreted per day up to a total of 8 g per day. Increase in dietary protein prescription is rounded to the nearest 0.1 g. Determination of the value for urinary protein excretion is based on measurements during the Baseline Period and is defined as the average of urinary protein excretion during Baseline Visits 0-3. The prescription is not altered during the Follow-up Period for subsequent changes in proteinuria.

TABLE 11.3
Composition of the MDRD Keto Acid-Amino Acid Supplement Used in Diet K

	mmol/day/64 kg ideal wt.
Tyrosine	20
Threonine	15
Calcium (D,L-) α-hydroxy-γ-methylthiobutyrate	2
Tryptophan	0.25

plus a mixture of basic amino acid salts of branched-chain keto acids containing the following components:

	mmol/day/64 kg ideal wt.		mmol/day/64 kg ideal wt.
Ornithine	21	α-ketoisocaproate	18
Lysine	21	α-ketoisovalerate	14
Histidine	4	α-keto-β-methylvalerate	14
Total	46		46

11.4 ENERGY

The patient's usual energy intake will be assessed from diet records during the Baseline period in order to determine energy prescription. The goal of the energy prescription is to maintain a desirable body weight: if the patient's weight is stable, the

ATTN: Jennifer Gassman

FROM: David B Cockram, MS, RD
PHONE: 614 624 7580
FAX: 614 627 7580

DATE: 10-Oct-1994
SUBJECT:

Ross Products Division Abbott Laboratories
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MEMO:.....

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10 October 1994

Jennifer Gassman
Dept of Biostatistics and Epidemiology
Desk P88
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195-5196

Dear Jennifer:
Hi! Well, your reviewer was, in fact, correct and the table in the protocol was in error! The table below includes our label claims in both mmol/kg and mmol/64 kg doses (columns 2 and 3, respectively). Since they obviously didn't concur with the formulation in your table (column 4), I went to the literature and tracked down Mitch W *et al: NEJM*;311:623-629 to find out the formulations for the Walser "EE" and "FF" formulations. These are located in the last two columns of the table. The formulation listed in your table is that for "EE".

Hope this helps. Kudos to your reviewer for his sharp eye!

Regards,

David B Cockram, MS, RD
Senior Clinical Research Associate
Medical Nutrition Research and Development

COMPOSITION OF KETOANALOGUE SUPPLEMENTS					
Component	ROSS RKAP (mmol/kg)	ROSS RKAP (mmol/64 kg)	NIH Table* (mmol/64 kg)	Walser "EE"** (mmol/d)	Walser "FF"** (mmol/d)
KMV***	0.240	15	14	14	8
KIC	0.310	20	18	18	16
KIV	0.260	17	14	14	22
HMTB	0.300	19	–	–	–
Orn	0.490	31	21	21	21
Lys	0.240	15	21	21	21
His	0.700	45	4	4	4
Trp	0.040	3	0	0	0
Tyr	0.270	17	20	20	20
Thr	0.120	8	15	15	7
Ca	0.017	1	–	–	–
CaHMTB	–	–	2	2	2
Serine	–	–	–	–	5

patient will not be required to increase or decrease dietary energy intake. If a patient indicates a desire to gain weight, then energy intake can be increased so as to promote weight gain. If the patient is obese, then the patient will be encouraged to reduce the energy intake to accomplish weight reduction. All hypertensive or obese patients will be encouraged to lose at least 5% of their body weight in order to enhance blood pressure response. However, energy intake will not be reduced unless the patient agrees. Recommendations to change energy intake must take into consideration the patient's self image, willingness to change body weight, and the potential negative impact on compliance with other aspects of the diet prescription.

11.4.1 Ratio Of Carbohydrate to Fat Calories

The ratio of calories derived from carbohydrate and fat are based on the patient's individual preferences in order to enhance compliance with the protein and phosphorous restriction, except as indicated below.

11.4.2 Patients With Non-Insulin Dependent Diabetes Mellitus

In patients with Non-Insulin Dependent Diabetes Mellitus (fasting serum glucose levels greater than 140 mg/dl at B0 and Baseline 3 Visits are indicated on Form 4), 45-60% of total daily energy intake should come from carbohydrate and not more than 45% of daily energy intake should be from fat; the ratio of carbohydrate to fat calories should exceed 1.0. The amount of dietary energy that will be derived from protein will be determined from the patient's dietary protein prescription. If a diabetic patient weighs more than 115% of standard weight, a reduced energy intake will be prescribed to cause weight reduction to within 10% of standard weight.

11.4.3 Patients With Hyperlipidemia

Lipid profile is measured at B0 and B3. Desired range for serum lipids (based on the average of B0 and B3 values) is as follows: total cholesterol, $\leq$240 mg/dl; LDL cholesterol, $\leq$160 mg/dl; and triglycerides, $\leq$600 mg/dl. Patients with values that exceed these ranges or with a previous diagnosis of hypercholesterolemia or hypertriglyceridemia will be provided with an eating pattern and additional materials which support the incorporation of lipid lowering principles in accordance with the National Cholesterol Education Program (Expert Panel, 1988), as specified in the Manual of Operations, providing it does not conflict with protein and phosphorous prescription.

11.4.4 Alcohol Levels in Diet

Alcohol intake will be controlled in two situations. In the first case, alcohol intake will be monitored to control caloric intake. In this case, alcohol may be increased to support an adequate caloric intake or decreased to result in a lower caloric intake. In the second case, alcohol intake would be reduced to assist in the reduction of blood pressure. The goal for the latter case would be to reduce consumption to equal or less than the equivalent of two drinks per day as defined in the 1988 JNC Report (Joint National Committee, 1988).

11.5 MINERAL AND VITAMIN SUPPLEMENTS

In order to prevent deficiencies in minerals and vitamins during the Follow-up Period, supplements of calcium carbonate, iron, zinc, and vitamins are prescribed. Calcium is given to all patients. The list of allowable calcium supplements is included in the Manual of Operations. Iron is given to patients on Diets K and L. Allowable iron supplements are ferrous sulfate or ferrous fumerate containing 60 to 70 mg of elemental iron. Zinc and vitamins are given to all patients in the MDRD Multi-Vite. Composition of the MDRD Multivite is shown in Table 11.4.

TABLE 11.4
Composition of MDRD Multi-Vite Tablets to be Used for Vitamin Supplementation

Vitamin	MDRD Study Vitamin[a,b]	RDA[c]
Thiamine (mg)	1.5	1.5
Riboflavin (mg)	1.7	1.7
Niacinamide (mg)	20	19.0
Pyridoxine HCL (mg)[d]	10	2.2
Pantothenic Acid (mg)	10	---
Vitamin B_{12}) g)	6	3.0
Biotin (g)	300	---
Ascorbic Acid (mg)	60	60
Folic Acid (g)	1000	400
Cholecalciferol (g)	5.0	7.5
Zinc (mg)	8	15.0
Vitamin E (mg)	6	10.0

[a] Dose per tablet.
[b] Distributed by Tishcon Corporation of Westbury, New York.
[c] RDA - Recommended Dietary Allowance for healthy non-pregnant, non-lactating adults proposed by the Food and Nutrition Board, National Research Council/National Academy of Sciences (1). The values shown are the maximum for any age and sex group included in the study.
[d] Indicates quantity of pyrodixine hydrochloride which is 81.2% pyridoxine.

11.5.1 Calcium

Total dietary calcium intake will range between 1300 and 1700 mg/day. Calcium supplementation should be given in sufficient amounts to achieve that target, but only if the patient's serum phosphorus is within the normal range. (When calculating the prescribed total daily calcium intake, the approximately 30 to 50 mg of calcium contained in the keto acid preparation should be ignored.)

To attain the recommended quantity of calcium intake, it will be necessary to provide calcium carbonate supplements. A list of acceptable preparations is contained in the Manual of Operations, Volume II with the Diet Prescription Form. The clinical centers provide their own calcium supplements from the accepted list in the Manual of Operations, Volume II.

11.5.2 Other Minerals

The suggested magnesium, iron and zinc intakes are equal to those published in the recommended dietary allowances for normal adults. It is recognized that the actual magnesium, iron and zinc intakes for the diets will be less than the Recommended Dietary Allowances and the intakes may be particularly low with Diet K.

An iron supplement of 60 mg/day or more is prescribed for all subjects assigned to Diet L and Diet K. The iron content of various iron supplements is listed in the Manual of Operations. Iron supplements are provided by the local clinical center, not the Drug Distribution Center.

Serum magnesium concentration will be monitored during Follow-Up to detect magnesium deficiency. Magnesium supplements will be prescribed only if deficiency arises.

The zinc content of study diets is estimated to be very low, ranging from an average of 2.5 mg/day with Diet K, 5-8 mg/day with Diet L, to 5-9 mg/day with Diet M. For this reason, a supplement of 8 mg/day is added to the vitamin pill.

11.5.3 Sodium and Potassium

If necessary, the sodium and potassium content of the eating pattern will be prescribed at levels to maintain acceptable blood pressure, fluid volume, and serum potassium. The goal for sodium reduction will be to decrease sodium intake by at least 30% of the baseline value as calculated from the mean urine sodium obtained from the B0, B1, B2, and B3 Visits. The goal of sodium intake will not be lower than 1200 mg/day.

11.5.4 Fat Soluble Vitamins

Diets L and K are estimated to provide about 1.0-2.5)g/day of vitamin D. Diet M may provide more vitamin D, if dairy products are ingested. Since patients are to follow these diets for extended periods of time, vitamin D (Cholecalciferol of 5.0)g/day) is added to the vitamin pill.

Patients with advanced renal failure have increased serum total and free vitamin A concentrations and appear to have intolerance to vitamin A supplements. Therefore, patients will not routinely be prescribed vitamin A supplements. Vitamin A intake with all three diets should be

sufficient to prevent vitamin A deficiency; thus, supplementary vitamin A will be prescribed only if vitamin A intake, as measured by analyses of diet records, are below the RDA.

The multi-vitamin supplement prescribed for all patients in Study A and Study B contains two-thirds of the RDA for vitamin E (6 mg/day). Therefore, no additional supplement for vitamin E will be necessary.

11.5.5 Water Soluble Vitamins

Patients with renal insufficiency may develop deficiency of water soluble vitamins if they do not receive vitamin supplements. The MDRD Multi-Vite supplements listed in Table 11.4 are designed specifically to prevent or correct deficiencies of water soluble vitamins.

11.6 GENERAL PRINCIPLES TO MAXIMIZE ADHERENCE TO PROTOCOL.

Compliance is likely to prove a limiting factor in this study, but can be significantly improved by the approaches taken by the study team. The following factors have a substantial effect on the degree of compliance of patients to their prescribed dietary and drug regimen:

.stability of the relationship of the patient with the study team
.frequency and quality of the communication of the patient with the study team
.pleasant surroundings and absence of delays in clinic visits
.high quality nutrition intervention on a continuing basis to establish, maintain and enhance compliance
.recognition that the educational process is gradual and needs periodic testing and reinforcement
.encouragement in the patient of a sense of personal responsibility for his/her diet and control over his/her future
.individualization of the eating pattern to the extent possible
.encouragement of a home environment supportive of compliance
.regular feedback to the patient on his or her progress

Guidelines to improve adherence and compliance are discussed in the Manual of Operations, Volume I, Chapters 1 and 2.

SECTION 12

FOLLOW-UP PERIOD EVALUATION

12.1 GENERAL PRINCIPLES

During the Follow-Up Period, routine visits will be held monthly. Table 12.1 and Section 20 summarize the laboratory measurements and procedures that will be performed at each Follow-Up Visit. Target dates for Follow-Up Visits are one calendar month apart, starting at the F1 visit which is scheduled one month after Baseline Visit 3. Follow-up visits are to occur within 15 days of their target dates. Windows for follow-up measurements are listed below. Visits and laboratory tests at more frequent intervals may be required for clinical management or to encourage compliance with assigned diet and anti-hypertensive regimen.

As discussed in Section 11.2, the study diet and MAP goal are assigned at Follow-Up Visit 1. In addition to the subsequent monthly visits, visits will be held 2 weeks after Follow-Up Visit 1 (Follow-Up Visit 1A) and 2 weeks after Follow-Up Visit 2 (Follow-Up Visit 2A) for the purpose of dietary counseling and adjustment of the anti-hypertensive regimen.

12.2 GLOMERULAR FILTRATION RATE

GFR will be measured at Follow-Up Visits 2, 4, and every four months thereafter. Window for GFR measurements is within + 1 month of the target visit date. An additional GFR measurement will also be obtained within one week after reaching a stop point other than a GFR stop point (before diet is changed or dialysis begins).

12.3 LABORATORY TESTS

12.3.1 Schedule for laboratory tests is given in Table 12.1. Note that 9 differential counts will be done every fourth month (at F4, F8, F12, etc.) for patients randomized to Diet K. However, the differential count data will be stored locally and will not be transmitted to the Data Coordinating Center. Laboratory tests are not repeated except as specified in the protocol or as necessary for usual medical care. The Central Laboratory will not accept repeat specimens for measurement unless an error in shipping or laboratory procedure has occurred. In the event that an error in procedure has occurred in the local laboratory, the value for the correct measurement should be submitted on the Data Change Form (Form #25).

12.3.2 24-hour urine collections brought to each monthly clinic visit will be used to assess compliance with dietary prescription for protein and phosphorus. At the conclusion of each visit, patients will be given a container to replace

TABLE 12.1 FREQUENCY AND LOCATION OF FOLLOW-UP LABORATORY TESTING FOR PHASE III

TESTS		Month #																							
		1	2+	3	4+	5	6	7	8+	9	10	11	12+	13	14	15	16+	17	18	19	20+	21	22	23	24+,1
Glucose	R		L		L		L		L		L		L		L		L		L		L		L		L
Sodium			L		L		L		L		L		L		L		L		L		L		L		L
Chloride			L		L		L		L		L		L		L		L		L		L		L		L
Potassium			L		L		L		L		L		L		L		L		L		L		L		L
Bicarbonate			L		L		L		L		L		L		L		L		L		L		L		L
CBC	A		L		L		L		L		L		L		L		L		L		L		L		L
WBC																									
Hgb																									
Hct	B																								
Differential Count*					L				L				L				L				L				L
Iron					L				L				L				L				L				L
Magnesium					L				L				L				L				L				L
Phosphorus	D		C		C		C		C		C		C		C		C		C		C		C		C
Calcium			L		L		L		L		L		L		L		L		L		L		L		L
SUN			C		C		L		C		L		C		L		C		L		C		L		C
Creatinine	O		C		C		L		C		L		C		L		C		L		C		L		C
Albumin			C		C		C		C		C		C		C		C		C		C		C		C
Transferrin			C		C		C		C		C		C		C		C		C		C		C		C
LDH	H								C								C								C
SGOT									C								C								C
Bilirubin									C								C								C
Uric Acid									C								C								C
Standard Lipid Profile	I				C				C				C				C				C				C
Total, HDL, LDL Cholesterol Triglycerides																									
Complete Lipid Profile	Z												C												C
HDL2, HDL3, Apo-lipoproteins A1 and B																									
Hemoglobin A_{1c}	A				C				C				C				C				C				C
Amino Acids*									C								C								C
Amino Acids			C		C				C				C				C				C				C
Plasma "After Thought"	T												C												C
24 Hr Urine		C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Protein		C	C	C	C	C	C	C	C				C				C				C				C
Urea Nitrogen	I	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Phosphorus		C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Sodium		C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Potassium	O	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
"After Thought"													C												C
GFR			C		C				C				C				C				C				C
Electrocardiogram	H					C						C						C						C	

*Diet K Patients

[1]Follow-up beyond two years will follow a similar pattern. +Fasting Measurements (12 hour fast, except for F2 which requires an 8 hour fast.

L = Local Laboratory Determination C = Central Laboratory Determination

that used in the previous month. Ideally, the urine should be collected the day before the next clinic visit and carried to that visit. The window for 24-hour urine collection is within ± 15 days of target date. If the patient has a short-term illness (defined in Section 13.2.2) during the entire 30-day window for collection, the urine should not be collected. Allowable ranges for urea nitrogen and phosphorus excretion are discussed in Section 12.8, Assessment of Dietary Compliance.

12.3.3 Blood tests are measured at Follow-Up Visit 2 and every two months thereafter as indicated in Table 9.1. Patients are to be fasting for 12 hours prior to Follow-Up Visits 4, 8, and every four months thereafter, and for 8 hours prior to Follow-Up Visit 2. Windows for blood tests are within ± 15 days of the target visit date. The following medications should not be administered for 48 hours prior to the measurement: Non-steroidal anti-inflammatory agents, inhibitors of tubular creatinine secretion (e.g., cimetidine, trimethorprim), or agents which interfere with chemical determination of creatinine (e.g., cephalosporins).

12.3.4 Electrocardiogram

An electrocardiogram will be obtained at Follow-Up Visit 11 and every twelve months thereafter. The window for obtaining an EKG is within ± 1 month of target date.

12.4 DIETARY DATA

The analyses of the dietary data provide estimates of the protein and phosphorus intake as well as estimates of other nutrients in the participant's eating pattern. They also provide estimates of group intake in order to compare the randomized study groups.

12.4.1 Frequency Of Food Records and Recalls.

Prescribed diet is assigned at Follow-Up Visit 1. Counseling to reach diet goal begins at Follow-Up Visit 1, using information regarding adherence to Baseline Diet as a guide.

12.4.1.1 Prior to Follow-Up Visit 1

Between Baseline Visit 3 and Follow-Up Visit 1, patients will self-monitor food intake. A minimum of 3 days should be used. More days may be assigned as judged necessary by the dietitian. The purpose of keeping these records is to reinforce diet recording techniques. They will not be analyzed by the NCC.

12.4.1.2 Food Records After Follow-Up Visit 1

After Follow-Up Visit 1, a three-day food record will be completed at F2, F4 and every two months thereafter and will be reviewed and documented at the following Follow-Up Visits. The NCC will analyze three-day food records from F2, F4 and all subsequent even numbered visits. Food records will be identified by the visit at which they were reviewed (e.g., the food record assigned at F1 and reviewed at F2 is identified as the F2 3-day record).

12.4.2 Intake of Prescribed Supplements

Intake of keto acid supplements will be assessed by pill or packet counts of supplements brought to each monthly clinic visit. All supplements will be recorded on food records.

12.5 OTHER MEDICINES

Other medicines taken by the patient during the Follow-Up Period will be recorded on the monthly visit forms.

12.6 PHYSICAL EXAMINATION

12.6.1 Blood Pressure

Blood pressure will be measured monthly. Additional blood pressure measurements may be required in order to achieve goal blood pressure. Standing blood pressure will be measured at the annual visit.

12.6.2 Anthropometry

Weight is measured monthly. Triceps, biceps and subscapular skin folds and upper arm circumference are measured at Follow-Up Visit 6 and every four months thereafter. Height is measured annually at the F12, F24 and F36 Visits.

12.7 PATIENT QUESTIONNAIRES

1. The Dietary Satisfaction Questionnaire (Form 74) is completed at Follow-Up Visit 6 and every six months thereafter.
2. The Quality of Well-Being Questionnaire (Form 27) is completed at an interview over the phone near the time of Follow-Up Visit 6 and every 6 months thereafter.
3. The Symptom Check List (SCL-90-R) (Form 28) is completed at Follow-Up Visit 4 and every four months thereafter.
4. The Patient Symptom Form (Form 26) is completed at each monthly visit.
5. The Physical Activity Questionnaire (Form 48) is completed at Follow-Up Visit 10 and annually thereafter.

12.8 ASSESSMENT OF DIETARY COMPLIANCE

It is expected that patients will be adhering to the assigned study diet by Follow-Up Visit 4 or sooner. Adherence to the prescribed diet will be assessed each month by analysis of 24-hour urine collections, dietary data, measurement of plasma alloisoleucine, and intake of prescribed supplements.

Calculation of estimated protein intake (EPI) from 24-hour urine samples will be performed by the DCC each month and transmitted to the Clinical Center. Calculation of protein, phosphorus, and energy intake from 3-day food records will be performed by NCC every other month and transmitted to the Clinical Center. Clinical Center dietitians are encouraged to use CDDT to analyze 3-day food records if results are needed for immediate counseling. Intake of prescribed supplements is calculated from pill counts performed at the Clinical Center.

In addition, beginning with Follow-Up Visit 5 and every 4 months thereafter, a 4-Month Compliance Summary will be prepared.

Compliance will be assessed from monthly values and from 4-month mean values.

Desired range for each assessment is given in Table 12.2. Values outside the desired range will trigger action items (Section 13.3). Action items triggered by analysis of monthly compliance assessment will be initiated at the time of the Follow-Up Visit or by telephone call after the Follow-Up Visit. Action Items triggered by analysis of 4-month compliance assessment will be initiated at the next Follow-Up Visit (i.e., F5 for F2-4; F9 for F5-8; F13 for F9-12, etc.).

TABLE 12.2

Desired Range for Estimated Protein Intake (g/kg/day)

Diet	Target	Estimated from a Single UNA or 3-Day Food Record, or from Average of 4 UNAs or 3-Day Food Records -20% to +50% for K, -30% to +30% for L, -25% to +25% for M
M	1.3	0.975 - 1.625
L	0.575	0.402 - 0.748
K	0.28	0.224 - 0.420

Desired Range for Dietary Phosphorus Intake (mg/kg/day)

Diet	Target	Intake Estimated from a Single 3-Day Food Record, or from Average of 4 3-Day Food Records (± 30%)
M	16 - 20	11.2 - 26.0
L	5 - 10	3.5 - 13.0
K	4 - 9	2.8 - 11.7

12.8.1 Analyzing 24-hour Urine Collection.

a. Dietary protein intake is estimated from urea nitrogen appearance (UNA) calculated from 24-hour urine urea nitrogen (UUN) excretion, standard body weight (SBW), and most recent 24-hour urine protein excretion (measured monthly until FU8 and then every 4 months thereafter). For patients on Diet K, dietary protein intake estimates will be adjusted for keto acid consumption. (See Manual of Operations, Volume I, Chapter 1.)

The desired range for estimated protein intake from one measurement is within -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M (see Table 12.2). A single value for EPI which deviates from the target by more than -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M is defined as a Monthly UNA Out-Of-Range action item. The monthly UNA out-of-range action item does not begin until the F5 visit. (See Section 13.3.)

At Follow-Up Visit 5 and every four months thereafter, the mean of EPI estimated from UNA from the previous 4 months (three months for F5) will be calculated. The desired range for EPI for the 4-month mean value is within -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M. (See Table 12.2.) A mean value that deviates from the target by more than -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M is defined as a Four Month UNA Out-Of-Range action item. (See Section 13.3)

b. Dietary phosphorus intake is judged to be excessive if the 24-hour urine phosphorus excretion exceeds the limits given in Table 12.2. There is no action item if phosphorus intake estimated from 24-hour urine phosphorus is out of range but the serum phosphorus is not out of range. (Note: There are action items for elevated or low serum phosphorus values.)

12.8.2 Analyzing Dietary Data

a. Three-Day Food Records

Desired range of dietary protein and phosphorus intake is within -20% to +50% for Diet K, -30% to +30% for Diet L, or -25% to +25% for Diet M for single three-day food record or from the mean of four records every four months. There is no action item if EPI estimated from three-day food records is out of range but the EPI estimated from UNA is not out of range.

b. One-Day Food Recalls

One-day food recalls are not utilized to calculate EPI unless the three-day food record is not submitted at the monthly visit. In this case, the one-day food recall will be obtained and will be substituted for the missing three-day food record.

12.8.3 Plasma Alloisoleucine

Plasma alloisoleucine will be measured as specified in Table 12.1. Acceptable value in Diet K patients is 18 uM. If alloisoleucine is under 18 uM, an Absent Alloisoleucine Action Item #14 is identified. (See Section 13.3.)

12.8.4 Analysis of Intake of Supplements

Percent adherence will be calculated for keto acids from pill counts (Form 73).

Acceptable percent compliance for each supplement is listed below:

Ketoacids (Diet K only)	90-110%
Calcium carbonate	80-120%
MDRD Multi-Vite	80-120%
Iron supplements	80-120%

12.9 TREATMENT OF HYPERLIPIDEMIA DURING FOLLOW-UP

Strict control of serum lipids is desirable during follow-up. However, it is recognized that dietary modification to regulate serum lipids is secondary to the primary goal of achieving target values for dietary protein and phosphorus intake. Desired range for serum lipids is as follows: total cholesterol, $\leq$240 mg/dl; LDL cholesterol $\leq$160 mg/dl; triglycerides $\leq$600 mg/dl. Values which exceed these targets result in action items (see Section 13.3.3).

12.10 MISSED VISIT OR MEASUREMENT

If a visit or measurement is not completed within the allowable range (window), the visit or measurement is "missed" and the patient is re-scheduled for the next regular visit. If the visit is missed, a monthly visit form is marked "missed" to document this occurrence.

12.11 TRANSFER

If study patients move to another city or section of the Continental United States, efforts will be made to maintain the treatment regimens specified in the Protocol, and to document the subsequent clinical course and renal function. If a patient moves into a geographic area served by a different clinical center, the patient (with informed consent) will be reassigned to the care of the new center, in the treatment group to which he was originally randomized. A Transfer Form 30 must be completed.

12.12 CLOSE OUT

12.12.1 Introduction

Close Out will take place over the last two months of the study, November and December 1992. Patients whose appointment schedules show GFR visits in September or November 1992 will have close out visits in November; patients whose appointment schedules show GFR visits in October or December 1992 will have close out visits in December. Post-Close Out visits to evaluate patient safety upon discontinuation of dietary intervention will be scheduled for two months after each patient's Close Out Visit.

Patients should be encouraged to maintain their assigned study diets until the time of the Close Out Visit. The Close Out Visit will take place in exactly the same fashion as an "Annual Visit," with all the procedures associated with an Annual Visit plus an EKG measurement. Patients will turn in all leftover study medications, and will be asked to complete an anonymous Patient Evaluation Form. All patients will receive a certificate of appreciation, and will be sent back to their referring physicians. Final close out documentation will also be completed for patients who were in Study F and for patients who have reached stop points.

12.12.2 Close Out Visits

Each patient continues monthly visits on his or her usual MDRD treatment regimen and is encouraged to keep complying until the day of the Close Out Visit. The Close Out Visits will be held between November 1, 1992 and January 15, 1993. Procedures to be done at Close Out Visits include all of the procedures done at an annual visit including the GFR.

12.12.3 Post Close Out #1 Visits

Two calendar months after the target date of each patient's Close Out Visit, the patient will have Post Close Out Visit #1. At the Post Close Out #1 Visit, the patient will receive his or her individual GFR data as well as summaries of MAP and EPI from over the course of the study. Procedures to be done at Post Close Out #1 are as planned before for Post Close Out, i.e., all of the things done at an annual visit except the GFR and the questionnaires. Anthropometry measures would be made. The Post Close Out #1 Visits will be held between January 1, 1993 and March 15, 1993.

12.12.4 Post Close Out #2 Visits

Three calendar months after the target date of each patient's Post Close Out Visit #1, the patient will have Post Close Out Visit #2. At the Post Close Out #2 Visit, the patient will receive information regarding the comparison of rates of progression of renal disease (GFR slopes) in the randomized groups. Procedures to be done at Post Close Out #2 Visits will be the same as those for the Post Close Out #1 Visit. The Post Close Out #2 Visits will be held between April 1, 1993 and June 15, 1993.

It should be noted that this final debriefing visit of Phase III could serve as an initial Baseline Visit for any of the new studies under consideration. A series of possible protocols are being considered for a MDRD Phase V, future follow-up of MDRD patients beyond MDRD Phase III.

12.12.5 Disseminating Results of GFR Slopes

By the time of the December 1992 meeting of the External Monitoring Committee (EMC), the Executive Committee will have a draft of the Phase III Major Results Paper, which used the most recently available data. This draft will be reviewed by the External Monitoring Committee at their December 1992 meeting.

The last Close Out Visit data will be collected on January 15, 1993, so a clean database (complete through close out) is anticipated by January 31, 1993. The DCC will have four weeks (February 1 through February 28) to use this database and prepare an update of the Phase III Major Results Paper. (The event data in this paper will not be complete, since we will learn more about patients reaching dialysis after close out when patients come to the Close Out #1 Visits.) A meeting of the Steering Committee will be convened in early March to approve the Major Results Paper. At the beginning of the meeting, Steering Committee members will be given a numbered draft of the paper and then given several hours to read the paper. The group will then reconvene and discuss the paper, as well as any revision required. After the meeting, the draft copies will be collected.

The Executive Committee will revise the paper and it will be submitted for publication to the journal selected. (This is assuming that only minor revisions are required, so no additional Steering Committee review is required.) The paper will be submitted as soon as possible in the hope that it would be published as soon as possible. A press conference would be held in conjunction with publication.

Between April 1, 1993 and June 15, 1993, the Post Close Out #2 visits will be occurring and the patients will be receiving the slope information which is part of the major results paper. Patients whose debriefing visits occur before the press conference will be asked not to talk to the press until after the press conference. For patients whose visits are scheduled after the press conference, it is recommended that the MDRD staff talk to the patient about the results before their visit, so they will know about the study before it is in the popular press.

12.12.6 Disseminating Results of Events (Such as Time to Dialysis)

The last Post Close Out #1 Visit data will be collected on March 15, 1993, so a clean database (complete through Post Close Out #1) is anticipated by March 31, 1993. The DCC will use these data to update the "events" analyses in the Phase III Major Results Paper; this will be done by April 15, 1993. It is hoped that this update will not impact the paper substantively, and that the paper will not need to be reviewed again by the Steering Committee. This update is important since it is anticipated that a number of patients will go on dialysis after the Close Out Visits; this was observed in the MDRD Pilot Study.

Although it is important to submit the Major Results Paper as soon as possible, if the Major Results Paper is submitted prior to April 15, complete event rate data for MDRD patients reaching dialysis will not be available for analysis.

SECTION 13

DEVIATIONS FROM ASSIGNED TREATMENT

13.1 INTRODUCTION

Deviations from assigned treatment during Follow-Up may be mandated as a result of an intercurrent illness, an action item, or a stop point. All three are discussed in this section.

13.2 INTERCURRENT ILLNESS

An intercurrent illness is defined as short-term or long-term illness which might affect renal function or nutritional status or which might be an important outcome measure for the study. Intercurrent illnesses do not constitute stop points. Intercurrent illnesses will be identified by the local principal investigator and the patient's physician.

13.2.1 Nutritional intake during and after intercurrent illness

Whenever possible and consistent with good medical care, the physician and dietitian will attempt to maintain compliance to the prescribed eating pattern by developing specific strategies with the patient.

13.2.2 Short-term illness

A short-term illness is defined as an intercurrent illness that persists for less than 6 weeks. Examples include dialysis for less than 6 weeks, respiratory or gastrointestinal infections, acute myocardial infarction, cholecystectomy, herniorrhaphy, etc., and any cause of hospitalization or disability for less than six weeks.

Anti-hypertensive regimen and diet prescription during intercurrent illness should reflect standard medical care. Patients should resume the study diet and anti-hypertensive regimen within 6 weeks. Patients who need insulin temporarily (six weeks or less) should be considered to have a short term illness. No follow-up visits should be held during a short-term illness. GFR and nutritional status may be affected by short-term illness and these parameters are not assessed for purposes of the study during a short-term illness. Because no visits are held, the data are not collected. Stop points should not be declared during a short-term illness. Measurements should be made after the illness if it is within the window for that measurement.

13.2.3 Long-term illness.

A long-term illness is defined as an intercurrent illness that persists for more than six weeks. Examples include development of a chronic infection, mild chronic congestive heart failure, inflammatory bowel disease, stroke with major residual neurologic difficulty, etc., and any cause of hospitalization or disability for more than six weeks. Therapy and diet prescription should reflect standard medical practice. Follow-up visits are held during a long-term illness. GFR and nutritional status are assessed according to Protocol and stop points are declared if they arise. If a long-term illness requires a permanent change in diet so that the assigned diet can no longer be prescribed, this will be considered a "serious medical condition" stop point.

13.3 ACTION ITEMS

An action item is defined as an event that occurs during follow-up which prompts a change in the diet, anti-hypertensive regimen, vitamin prescription, or in the frequency of measurements. This section contains a summary of action items, priorities for modification of diet prescription in response to action items, and detailed explanations of the action items. Clinical center identification and response to action items will be recorded on the Action Item Response Form (Form 23).

13.3.1 Action Item Summary

Item		Definition	Page
1.	GFR (Study A only)	B3 GFR 41-55: Decrease in GFR to ≤20 B3 GFR ≤40: Decrease in GFR to <50% of value at B3	13.4
	Physical Exam		
2.	Weight Loss	>5% SBW loss to 75-95% SBW	13.4
3.	Weight Gain	>5% gain	13.5
4.	Overweight Diabetics	>115% SBW	13.5
5.	High Blood Pressure (at two consecutive visits)	MAP above goal	13.5
6.	Persistent High Blood Pressure	MAP above goal 4 months after HBP action item	13.5
7.	Low Blood Pressure Symptoms	Symptoms of low BP at or above MAP goal	13.6
8.	Persistent Low Blood Pressure	Persistent symptoms	13.6
	Serum Measurements		
9.	Declining Serum Albumin	>0.5 g/dl decrease to 3.0-3.9 g/dl	13.6
10.	Low Serum Albumin	<3.0 g/dl	13.8
11.	Declining Serum Transferrin	>50 mg/dl decrease to <200 mg/dl	13.8
12.	High Serum Phosphorus	>4.9 mg/dl	13.8
13.	Very High Serum Phosphorus	>6.0 mg/dl (fasting)	13.8
14.	Absent Alloisoleucine (Diet K only)	Alloisoleucine out of range	13.10
15.	Monthly UNA Out Of Range	Outside desired range at F5 or beyond	13.10
16.	Four Month Mean UNA Out Of Range	Outside desired range	13.11
17.	Persistent Four Month Mean UNA Out Of Range	Persistently outside desired range	13.11
18.	Low Serum Phosphorus	<2.5 mg/dl	13.11
19.	Low Serum Calcium	<8.5 mg/dl (adjusted for albumin)	13.11
20.	High Serum Calcium	>10.5 mg/dl (adjusted for albumin)	13.11
21.	High Serum Potassium	>5.5 mEq/L	13.12
22.	Low Serum Bicarbonate	<18 mEq/L	13.12
23.	Low Serum Magnesium	<1.5 mg/dl	13.12
24.	Low Serum Iron	<40 mcg/dl	13.12
25.	High Serum Cholesterol	>240 mg/dl	13.13
26.	High Serum LDL Cholesterol	>160 mg/dl	13.13
27.	High Serum Triglycerides	>600 mg/dl	13.14

13.3.2 Priority for Modification of Diet Prescription in Response to Action Items

1. Low Serum Albumin
2. Declining Serum Albumin
3. Very High Serum Phosphorus
4. Declining Serum Transferrin
5. High Serum Phosphorous
6. Weight Loss
7. Absent Alloisoleucine
8. Four-Month Mean UNA Out-Of-Range
9. Monthly UNA Out-Of-Range

The remaining action items do not conflict with one another.

13.3.3 Description of Action Items

1. GFR (Study A only)

Definition: For patients with B3 GFR 41-55 ml/min/1.73m2, a decrease in GFR to $\leq$20 ml/min/1.73m2. For patients with B3 GFR 25-40 ml/min/1.73m2, a decline in GFR to less than 50% of the value at Baseline Visit 3. (Because Clinical Center staff members are blind to GFR results, Data Coordinating Center will notify the involved Clinical Center if a GFR Action Item occurs.)
Action: Repeat GFR within one month.
Follow-up: The Data Coordinating Center will notify the Clinical Center of the outcome of the second GFR measurement. If the repeat GFR is above the level indicated above, then the patient continues in Follow-up and the GFR is measured at next routinely indicated visit. If the repeat GFR is below the indicated level, the patient has reached a GFR stop point (see Section 13.4).

2. Weight Loss

Definition: a) Undesired loss of more than 2.5 kg from target weight (see below) or 5% of Standard Body Weight (SBW), which ever is less, at any time in a patient without edema, or b) loss of weight to less than 80% SBW.
(Note: Undesired weight loss is defined as a loss of weight that is not part of a planned weight reduction program.)
Action: Increase energy intake.
Follow-Up: Measure weight monthly (as usual).
Successful Resolution: Increase in weight to desired weight or greater than 80% SBW (whichever is higher).
Unsuccessful Resolution: No increase in weight. (Weight loss to a weight below 75% of SBW is a Weight Loss Stop Point, as indicated in Section 13.4.)
Target Weight: Target weight is defined to be the Baseline Visit 2 weight, except in the case where the patient has intentionally lost or gained weight whereupon a new target weight is defined, by indicating the new target weight on Form 5, at the visit at which the patient reaches his goal weight (not to be <90% of SBW).

3. Weight Gain
Definition: Undesired increase in weight greater than 5% of the target weight (see Action Item #2) in a patient without edema.
Action: Reduce energy intake.
Follow-Up: Measure weight monthly (as usual).
Successful Resolution: Decrease in weight by 5% of the target weight. Patients should be encouraged to maintain their usual body weight as long as it is 100-110% of SBW.
Unsuccessful Resolution: No decrease in weight. Action item persists. Usual medical care.

4. Overweight diabetic
Definition: Weight >115% in a diabetic patient without edema.
Action: Reduce energy intake.
Follow-Up: Measure weight monthly (as usual).
Successful Resolution: Decrease in weight to 90-110% SBW.
Unsuccessful Resolution: No decrease in weight. Action item persists. Usual medical care.

5. High blood pressure
Definition: MAP exceeds goal on two consecutive visits.
Action: See the 1988 Report of Joint National Commission on Detection, Evaluation, and Treatment of High Blood Pressure (Joint National Committee, 1988). The patient is counseled to intensify non-pharmacologic therapy (weight reduction if indicated; restriction of alcohol; restriction of sodium; avoidance of tobacco; biofeedback and relaxation). If the blood pressure remains elevated, dosage of antihypertensives are increased or additional drugs begun, as clinically appropriate. Blood pressures are charted and medication adjusted monthly or more often according to usual clinical practice.
Successful Resolution: Blood pressure declines to target levels within four months.
Unsuccessful Resolution: Blood pressure remains elevated after four months. Persistent High Blood Pressure Action Item.

6. Persistent high blood pressure
Definition: Persistent high blood pressure (as defined in #5) four consecutive months after High Blood Pressure Action Item.
Action: Review of patient record by Patient Compliance Committee. Communication between Clinical Center Principal Investigator and Patient Compliance Committee representative.

Successful Resolution: Blood pressure declines to target levels within two months.
Unsuccessful Resolution: Blood pressure remains elevated. Usual medical care. Action item persists (continued communication between Clinical Center Principal Investigator and Clinical Management Committee representative).

7. Symptoms of Low Blood Pressure (at MAP above assigned target)
Definition: Symptoms (persisting 2 or more days) related to low blood pressure, such as orthostatic light headedness, syncope, excessive fatigue, or impotence in patients whose mean arterial blood pressure is at or above goal.
Action: Raise blood pressure by 5 mmHg. Review and adjust anti-hypertensive regimen as appropriate.
Successful Resolution: Symptoms resolve.
Unsuccessful Resolution: Symptoms persist. Persistent Symptoms at Low Blood Pressure Action Item.

8. Persistent Symptoms of Low Blood Pressure (at MAP above assigned goal)
Description: Persistent symptoms of low blood pressure (as defined in #7) for 1 month after Symptoms of Low Blood Pressure Action Item.
Action: Review of patient record by Clinical Center Principal Investigator and Clinical Management Committee representative.

9. Declining Serum Albumin
Definition: Decrease in serum albumin by more than 0.5 g/dl from the Baseline Visit 3 value to a value between 3.0-3.9 mg/dl.
Action: Repeat the measurement in one month. If it persists, first alter the energy prescription and then alter the protein prescription as indicated in Table 13.1.
Follow-Up: Measure serum albumin monthly until resolution.
Successful Resolution: Maintenance of serum albumin $\geq$3.5 mg/dl for six months. (Thereafter, a further Action Item is defined by declining serum albumin by >0.5 g/dl from the highest value after first action item to 3.0 to 3.9 g/dl.)
Unsuccessful Resolution: Decline of serum albumin to below 3.0 mg/dl within six months (Low Serum Albumin Action Item).

TABLE 13.1
Alteration in Energy and Protein Prescription for Albumin and Transferrin Action Points

Alterations in Energy Prescription

Diet	Weight (% SBW)	Action
All	<120% (≤115% in diabetics)	increase energy intake (until patient objects)
All	>120% (>115% in diabetics)	decrease energy intake (until patient objects or loses weight)

Alterations in Protein Prescription

Diet	EPI estimated from UNA (g/kg/day) (most recent values)	Action
M	≥1.0	none
M	<1.0	increase protein intake to 1.0 g/kg/day (all of added protein prescription as HBV)
L	≥0.7	none
L	0.55-0.69	increase protein prescription to 0.7 g/kg/day (1/2 of added protein prescription as HBV)
L	<0.55	increase protein intake to 0.55 g/kg/day
K	≥0.40	none
K	0.28-0.39	increase protein prescription to 0.4g/kg/day
K	<0.28	increase protein intake to 0.28 g/kg/day

10. Low Serum Albumin
Definition: Serum albumin <3.0 g/dl.
Action: Repeat measurement in one month. If it persists, then alter energy and protein prescription as described in Table 13.1.
Follow-Up: Measure serum albumin monthly until resolution.
Successful Resolution: Serum albumin ≥3.0 g/dl for six months.
Unsuccessful Resolution: Serum albumin remains <3.0 g/dl. If low on four consecutive occasions after initiation of dietary alteration, this is a low serum albumin stop point.

11. Declining Serum Transferrin
Definition: Decrease in serum transferrin by more than 50 mg/dl from the Baseline Visit 3 value to a value of <200 mg/dl.
Action: Repeat the measurement in one month. If the low level persists, alter energy and protein prescription as indicated in Table 13.1.
Follow-Up: Measure serum transferrin monthly for 3 months.
Successful Resolution: Maintenance of serum transferrin at the Baseline Visit 3 value or >200 mg/dl, whichever is lower.
Unsuccessful Resolution: No increase in serum transferrin. Action item persists. Usual medical care.

12. High Serum Phosphorus
Definition: Serum phosphorus >4.9 mg/dl.
Action: Repeat the measurement of phosphorus in one month. If serum phosphorus is >4.9 mg/dl, first alter dietary phosphorus, then add phosphorus binders as described in Table 13.2.
Follow-Up: Measure serum phosphorus monthly until resolution.
Successful Resolution: Serum phosphorus ≤4.9 mg/dl on two successive occasions.
Unsuccessful Resolution: Serum phosphorus 4.9-6.0 mg/dl. Action item persists. Usual medical care.

13. Very High Serum Phosphorus
Definition: Serum phosphorus >6.0 mg/dl.
Action: Alter dietary phosphorus intake and add phosphorus binders as described in Table 13.2 and measure fasting serum phosphorus in one month. If fasting serum phosphorus >6.0 mg/dl, continue action.
Follow-Up: Measure fasting serum phosphorus monthly until successful resolution.

TABLE 13.2
TREATMENT OF HIGH SERUM PHOSPHORUS

Alterations in Phosphorus Prescription

Diet	Phosphorus Intake Estimated From Diet Records (mg/kg/day)	Action
M	>20 mg/kg/day	Reduce phosphorus intake to 16-20 mg/kg/day
M	16-20 mg/kg/day	Reduce phosphorus intake to <16 mg/kg/day but do not reduce protein intake to <1 g/kg/day
M	<16 mg/kg/day	Add phosphorus binders (see below)
L	>10 mg/kg/day	Reduce phosphorus intake to 5-10 mg/kg/day
L	≤10 mg/kg/day	Add phosphorus binders (see below)
K	>9 mg/kg/day	Reduce phosphorus intake to 4-9 mg/kg/day
K	≤9 mg/kg/day	Add phosphorus binders (see below)

Addition of Phosphorus Binders (Diets M, L, K)

1. First, add aluminum hydroxide with meals in dosage sufficient to lower serum phosphorus to ≤4.5 mg/dl.
2. Second, add calcium carbonate (1000 mg/day with meals).
3. Third, adjust doses of calcium carbonate and aluminum hydroxide in order to:
   a. Maintain serum phosphorus ≤4.5 mg/dl.
   b. Maintain serum calcium ≤10.5 mg/dl (adjusted for albumin).
   c. Minimize dose of aluminum hydroxide.
   d. Minimize gastrointestinal side effects.
4. If serum phosphorus returns to normal and a need for binders persists, aluminum hydroxide should be replaced by calcium carbonate. Calcium citrate should be avoided until aluminum hydroxide has been discontinued.

Successful Resolution: Fasting serum phosphorus 4.5-6.0 mg/dl. Return to monthly non-fasting measurements (as in High Serum Phosphorus Action Item).
Unsuccessful Resolution: Fasting serum phosphorus > 6.0 mg/dl for four consecutive months (Very High Serum Phosphorus Stop Point).

14a. Aminogram out of Range (Diet K only) (Do not include F2 Visit aminogram

Definition:

I. Fasting plasma alloisoleucine is <18uM

or

II. Fasting plasma alloisoleucine is ≥18uM but plasma ornithine is >121uM

Action: I. If fasting plasma alloisoleucine is <18uM, counsel patient regarding compliance to ketoacids. Attempt to define and remediate causes for non-compliance. Repeat fasting plasma amino acid measurement monthly for 2 months.
Successful Resolution: Aminogram in range for 2 consecutive months.
Unsuccessful Resolution: Plasma alloisoleucine is <18uM in two measurements during any 4-month compliance review period and unadjusted EPI from UNA is >0.4 gm/kg/day at any two visitis in a four month compliance period. This leads to a Four-Month Aminogram out-of-range action item (See 14b below).

Or

If plasma alloisoleucine remains <18uM in two measurements in any four month compliance review period and if unadjusted EPI (the mean of the four-month compliance period) is <0.40 gm/kg/day and the mean protein intake of six days of food records is <0.40 gm/kg/day, this leads to review by the Compliance Committee and to a Persistent Aminogram out-of-range action item (See 14b below).

II. If fasting plasma alloisoleucine is ≥18uM but plasma ornithine is >121, counsel the patient regarding the need to be fasting when plasma amino acids are measured. Repeat fasting plasma amino acid measurements monthly for 2 months.
Successful Resolution: Aminogram in range for 2 consecutive months.
Unsuccessful Resolution: Aminogram continues to be out-of-range in two measurements during any 4-month compliance review period.

14b. Four-Month Aminogram out of range (Diet K only)
Definition: Plasma alloisoleucine <18uM or Plasma alloisoleucine >18uM and plasma ornithine >121uM twice in any 4-month compliance review period.

Action: Principal Investigator presents patient to Compliance Committee for review. Continue plasma amino acid measurements for 2 months.
Successful Resolution: Aminogram in range for 2 consecutive months.
Unsuccessful Resolution: Aminogram remains out of range. Leads to a persistent action item. (Reported to Clinical Center, NCC, Compliance Committee, and Clinical Management Committee.)

15. Monthly UNA Out Of Range (F5 Visit and later)
Definition: Monthly Estimated Protein Intake from UNA that deviates from target value by -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M.
Action: Estimate protein intake from recent 3-day food record, records of self-monitoring, or other recent dietary data. Classify patient according to concordance of UNA and diet records. Strategy to improve compliance for each situation is discussed in Manual of Operations (Chapter 1). Patient is telephoned to identify factors which lead to deviation of UNA and implement appropriate strategy. Urine collection and diet records collected in one month, as usual.
Successful Resolution: UNA not out of range at next measurement.
Unsuccessful Resolution: UNA out of range at next measurement. Action item persists. (If UNA out of range but improving, Action item persists.)

16. Four-month UNA Out Of Range
Definition: Four-month mean Estimated Protein Intake from UNA deviates from target value by -20% to +50% for Diet K, -30% to +30% for Diet L, and -25% to +25% for Diet M.
Action: Review of 4-month mean EPI from three-day diet diaries by the NCC. Classify patient according to concordance of UNA and diet records. Consultation with NCC will be obtained to develop strategy to improve the patient's compliance.
Successful Resolution: Mean UNA for next four months not out of range.
Unsuccessful Resolution: Mean UNA for next four months remains out of range. Persistent four month mean UNA out of range action item.

17. Persistent Four Month Mean UNA Out Of Range
Definition: Four month mean UNA remains out of range after consultation with NCC.
Action: Referral to Compliance Committee for evaluation.
Successful Resolution: Mean UNA for next 4 months not out of range.

Unsuccessful Resolution: Mean UNA for next 4 months remains out of range. Action item persists (continued communication between Clinical Center Principal Investigator and dietitian and NCC representative).

18. Low Serum Phosphorus
Definition: Serum phosphorus <2.5 mg/dl.
Action: Measure serum phosphorus in one month. If it persists, reduce phosphorus binder dosage or increase dietary phosphorus intake as appropriate.
Follow-Up: Measure serum phosphorus monthly until successful resolution.
Successful Resolution: Serum phosphorus ≥2.5 mg/dl or two consecutive occasions.
Unsuccessful Resolution: Serum phosphorus <2.5 mg/dl. Action item persists. Usual medical care.

19. Low Serum Calcium
Definition: Adjusted serum calcium <8.5 mg/dl. If serum albumin is <3.5 g/dl, adjusted calcium is defined as measured calcium + (3.5-alb)x 0.8.
Action: Repeat the measurement of serum calcium and phosphorus in one month. If it persists, prescribe calcitriol in order to maintain adjusted serum calcium 8.5-10.5 mg/dl.
Follow-up: Measure serum calcium and phosphorus monthly until resolution.
Successful Resolution: Adjusted serum calcium >8.5 mg/dl for two consecutive months.
Unsuccessful Resolution: Adjusted serum calcium <8.5 mg/dl. Action item persists. Usual medical care.

20. High Serum Calcium
Definition: Adjusted serum calcium >10.5 mg/dl. If albumin is <3.5 g/dl, adjusted calcium is defined as measured calcium + (3.5-alb) x 0.8.
Action: Measure calcium and albumin in one month (or sooner if indicated). If it persists, reduce the dosage of calcitriol or calcium carbonate, as indicated.
Follow-up: Measure serum calcium and albumin monthly until successful resolution.
Successful Resolution: Adjusted serum calcium ≤10.5 mg/dl for two consecutive months.
Unsuccessful Resolution: Adjusted serum calcium >10.5 mg/dl. Action item persists. Usual medical care.

21. High Serum Potassium
Definition: Serum Potassium >5.5 mEq/L.

Action: Repeat measurement in one month (or sooner if indicated). If it persists, reduce dietary potassium, add sodium polystyrene sulfonate (kayexalate), or other measures, as indicated.
Follow-Up: Measure potassium monthly until successful resolution.
Successful Resolution: Serum potassium ≤5.5 mEq/L for two consecutive months.
Unsuccessful Resolution: Serum potassium >5.5 mEq/L. Action item persists. Usual medical care.

22. Low Serum Bicarbonate
Definition: Serum bicarbonate <18 mEq/L.
Action: Repeat measurement in one month (or sooner if indicated). If it persists, prescribe alkali.
Follow-up: Measure serum bicarbonate monthly until successful resolution.
Successful Resolution: Serum bicarbonate ≥18 mEq/L on two consecutive measurements.
Unsuccessful Resolution: Serum bicarbonate <18 mEq/L. Action item persists. Usual medical care.

23. Low Serum Magnesium
Definition: Serum magnesium <1.5 mg/dl.
Action: Repeat the measurement in one month or sooner if indicated. If it persists, prescribe a magnesium supplement.
Follow-up: Measure the serum magnesium monthly until successful resolution.
Successful Resolution: Serum magnesium ≥1.5 mg/dl for three consecutive measurements.
Unsuccessful Resolution: Serum magnesium <1.5 mg/dl. Action item persists. Usual medical care.

24. Low Serum Iron
Definition: Serum iron <40 mcg/dl.
Action: Repeat measurement in two months (or sooner if indicated). If it persists, test for gastrointestinal (or other) site of blood loss. If no site is found, prescribe additional iron.
Follow-up: Repeat measurement every two months.
Successful Resolution: Serum iron ≥40 mcg/dl for two consecutive measurements.
Unsuccessful Resolution: Serum iron <40 mcg/dl. Action item persists. Usual medical care.

25. High Serum Cholesterol
Definition: Total cholesterol >240 mg/dl.
Action: Obtain fasting measurements (12-hour fast) in two months. If the high cholesterol levels persist in

three consecutive measurements, treatment will proceed according to the Algorithms #1, #2, and #3 of the National Cholesterol Education Program (Expert Panel, 1988) (see Appendix). However, the content of the other prescribed ingredients in the diet, including the protein, phosphorus and total non-alcohol energy intake should not be modified.
Follow-up: Repeat fasting measurement every 2 months until successful resolution.
Successful Resolution: Total serum cholesterol <240 mg/dl.
Unsuccessful Resolution: Total cholesterol >240 mg/dl. Action Item persists. Proceed to Algorithm #4 of the National Cholesterol Education Program (Expert Panel, 1988), utilizing first or second choice drug therapy as prescribed by the Principal Investigator. (Note: If requirements of the lipid-lowering diet and study are incompatible, the study diet requirements take precedence, and the Principal Investigator should notify the Clinical Management Committee.)

26. High LDL Cholesterol
Definition: LDL cholesterol >160 mg/dl.
Action: Obtain fasting measurement (12-hour fast) in two months. If the high cholesterol level persists in three consecutive measurements, treatment will proceed according to Algorithm #4 of the National Cholesterol Education Program (Expert Panel, 1988). However, the content of the other prescribed ingredients in the diet, including the protein, phosphorus and total non-alcohol energy intake, should not be modified.
Follow-up: Repeat fasting measurement every two months until successful resolution.
Successful Resolution: LDL cholesterol ≤160 mg/dl for two consecutive measurements.
Unsuccessful Resolution: LDL cholesterol >160 mg/dl. Action item persists. Usual medical care. (Note: If requirements of lipid-lowering diet and study diet are incompatible, the Principal Investigator should notify the Clinical Management Committee.)

27. High Serum Triglycerides
Definition: Serum triglyceride concentration >600 mg/dl.
Action: Obtain fasting measurements (12-hour fast) in two months. If the high serum triglycerides persist in three consecutive measurements, treatment for hypertriglyceridemia will be prescribed as appropriate

for the contributing causes of hypertriglyceridemia: exercise and/or weight loss may be encouraged if appropriate; restriction or elimination of alcohol intake should be considered; and the carbohydrate and fat composition of the diet may be modified according to standard guidelines. However, the content of the other prescribed ingredients in the diet, including the protein, phosphorus and total non-alcohol energy intake, should not be modified.
Follow-up: Repeat fasting triglyceride measurements every two months until successful resolution.
Successful Resolution: Fasting serum triglyceride concentration $\leq$600 mg/dl.
Unsuccessful Resolution: Fasting serum triglyceride greater than 600 mg/dl. Action item persists. Usual medical care.

13.4 STOP POINTS

A stop point denotes the occurrence of a defined adverse clinical event after which the physician is no longer obligated to treat the patient with his or her study diet or MAP goal according to Protocol. The patient and physician are "free" to select any treatment, including the same diet the patient had been on, or an alternative study diet. However, the MDRD Study is not obligated to provide keto acids.

13.4.1 Procedure

A stop point is identified by the local Principal Investigator after reviewing the case with a representative of the Clinical Management Committee (who will remain "blind" to the patient's study diet). The local Principal Investigator and Study Coordinator will complete the Stop Point Form. The following stop points have been designated for the MDRD Study:

13.4.2 Definitions:

1. GFR (Study A only).
For patients with B3 GFR 41-55 ml/min/1.73m2, a decline in GFR on two occasions to ≤20 ml/min/1.73m2. For patients with B3 GFR 25-40 ml/min/1.73m2, a decline in GFR on two occasions to <50% of value at Baseline Visit 3.
(Study A Patients who reach a GFR Stop Point are eligible for Study C, as described in Section 14.)

2. Need for Initiation of Long-Term Dialysis or Transplantation (as determined by the Clinical Center Principal Investigator).
It is recognized that the date of initiation of dialysis or transplantation may occur later than the date indicated by the Principal Investigator. This will be recorded during follow-up after the stop point. (See Section 13.4.4 below.)

3. Low Serum Albumin.
Persistence of a low serum albumin (less than 3.0 g/dl) after four consecutive months following dietary intervention for the low serum albumin action item 13.3.8. (Low serum albumin is not a stop point if it occurs during an intercurrent illness.)

4. Weight Loss
Persistent low body weight (<75% SBW) for 3 months after dietary intervention for a Weight Loss Action Item.

5. Very High Serum Phosphorus
A fasting serum phosphorus value of greater than 6.0 mg/dl, observed on four consecutive monthly measurements, after intervention for Very High Serum Phosphorus Action Item.

6. Serious Medical Conditions
Serious medical conditions which require a permanent change in diet or blood pressure regimen so that the assigned diet or MAP goal can no longer be prescribed, or which might be affected adversely by the study diet or MAP goal to which the patient is assigned. Examples include:
pregnancy, severe CHF, liver disease, type I diabetes mellitus, any condition requiring insulin therapy for more than six weeks, or acute renal failure (rise in serum creatinine by 3 mg/dl or greater in one week).

7. Termination of the Study.
(For statistical analysis, this stop point will be considered as a censoring point, not an event.)

13.4.3 Measurements at the Time of a Stop Point

At the time that a stop point is declared, measurements of GFR (except for GFR stop point) and an additional battery of blood tests are obtained. The blood tests to be included are the tests included at the Follow-Up 4 Visit. Measurements should be obtained within two weeks.

13.4.4 Follow-Up After Stop Points

After reaching a stop point, patients are followed to determine the occurrence of important outcome measures, even though they may no longer be on a study diet according to Protocol. Follow-up after Stop Points is as follows:

1. Every four months (at the time that Follow-Up Visits 4, 8, 12, etc. had been scheduled) for all patients:
   a. Serum albumin
   b. Serum transferrin
   c. Intercurrent illnesses in the preceding interval
   d. Physical exam (including blood pressure measurement)
   e. Current medications recorded
2. On the first four-month visit after the stop point and on the annual visits thereafter (at the time that Follow-Up Visits 12, 24 and 36 had been scheduled) for all patients.
   a. Dietary intake as assessed by three-day food record
   b. Anthropometric measurements (weights; skin folds--triceps, biceps, subscapular; and upper arm circumference)
3. In addition, every four months for patients who are not on dialysis and have not had a transplant:
   a. Serum creatinine
   b. Dietary protein intake as estimated by 24-hour urinary urea nitrogen excretion
   c. GFR
4. Every 12 months (at the time that Follow-Up Visits 12, 24 and 36 had been scheduled) for all patients:
   Quality of Well-Being Questionnaire (Form 27), SC:-90-R (Form 28), Patient Symptom Form (Form 26), and Annual Follow-Up Information (Form 13)
5. Events to be documented as they occur:
   a. Death
   b. Initiation of dialysis or transplantation

13.4.5 Death

A MDRD Death Notification Form (Form 15) should be sent to the DCC immediately upon the patient's death. Death certificates and autopsy reports should be forwarded to the DCC as soon as these are available.

SECTION 14

STUDY C

14.1 GOALS

The goal of Study C is to compare the effects of a change from Diet M or Diet L to Diet K without a change in blood pressure regimen in the same patient with progressive change in GFR. The specific aim of the study is to compare the rate of change in GFR in the same patient during treatment with two different study diets.

14.2 PATIENT SELECTION

Patients eligible for Study C will include patients from Study A who subsequently reach a GFR stop point only. A separate consent form is provided to be signed at the time of enrollment (after the stop point in Study A), and a Form 31 is completed for all Study C patients.

14.3 PROTOCOL

The protocol for a patient in Study C is exactly as described in the Follow-up Period in Study B for a patient assigned to Diet K. The patient's original visit schedule and blood pressure regimen should be followed.

14.4 DATA ANALYSIS

The number of patients likely to be available should permit comparisons of the change in the rate of decline in GFR in individual patients switched from the different study diets to Diet K. Patients entering Study C after treatment with Diet M and Diet L will be analyzed separately.

SECTION 15

STUDY F

15.1 GOALS

The goal of Study F is to obtain follow-up data on patients who enter the Baseline Period but are excluded prior to randomization to study diets.

15.2 PATIENT SELECTION

All patients who are excluded during the Baseline Period are included in Study F. Informed consent for Study F is part of the informed consent for the Baseline Period.

15.3 PROTOCOL

As much of the following information as possible will be obtained at six-month intervals and at termination of the Study. This information should be obtained by phone from the patient or the patient's physician at the X6, X18, X30 and X42 visits. Study F visits should be held at the X12, X24, and X36 visits if this information is not available.

1. Vital status.
2. Date of initiation of long-term dialysis or transplantation.
3. Weight.
4. Serum creatinine. *
5. Serum albumin. *
6. Blood pressure (Sitting only)

Note: During the Recruitment Period, patients may be seen at more frequent intervals for screening to determine if they become eligible to re-enter the Baseline Period (See Section 9.18).

The patient is seen every year based on the date of the Baseline 0 Visit. The window is + or - 30 days.

* Biochemical tests to be run at the Central Biochemistry Laboratory.

SECTION 16

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SECTION 17

ANALYSIS PLAN

17.1 BASELINE ANALYSES

Since the sample for this study will not be a random sample from a general population, a description of the baseline variables of the patients selected for the study will help characterize these patients. A careful analysis will be made of all patients who attend a screening visit in the cooperating Clinical Centers. The reason for non-participation of some patients will be described. Comparisons will be made between those who participate and those who do not participate in the study.

For each treatment group, percentages of patients with specified baseline findings known or suspected to influence the study endpoints will be noted. Appropriate statistical tests will be performed comparing the distribution of these findings among the treatment groups. These analyses will be done comparing diet groups and comparing blood pressure regimens within each of the Studies A and B. In evaluating such analyses, consideration will be given to the number of such statistical tests performed.

17.2 OUTCOME VARIABLES

The primary outcome variable is:

1. Rate of change of Glomerular Filtration Rate (GFR) in ml/min/month.

Other important outcome measures are listed below.

2. Dialysis or transplantation.
3. Death.
4. Occurrence of serious medical conditions and intercurrent illnesses.
5. Nutritional status.
6. Achieved blood pressure and compliance with blood pressure regimens.
7. Complications related to high or low blood pressure.
8. Compliance and satisfaction with dietary regimens.
9. Symptoms.
10. Quality of well being.
11. Cost of care provided to patients, assessed from physician's time, dietitian's time, laboratory tests, and prescribed supplements.

In the proposed clinical study, it is quite possible that non-compliance with the dietary regimens may be fairly prevalent among study participants. This may be true even though attempts

will be made to obtain a high level of compliance. Similarly, it is anticipated that it will not be possible to control mean arterial pressure (MAP) below the prescribed level for all patients. Quantitative summaries of dietary compliance and of the numbers and distribution of patients failing to meet targeted blood pressure goals for various reasons will be prepared. However, the study is designed to compare groups based on prescribed, rather than achieved, diet and blood pressure groupings. In particular, for the primary analyses, actual protein intake will not be used as an independent variable when examining the effect of diet, and actual follow-up MAP will not be used as an independent variable when examining effects of blood pressure. While failure to achieve dietary goals may preclude the possibility of observing a true beneficial effect of diet, it may also demonstrate that compliance, even when diets are administered under the most optimum conditions, cannot be obtained. The primary question to be answered concerning blood pressure is whether those patients with the stricter (low) target goal have less disease progression than those with the higher (moderate) target goal, in the context of a well-defined program of stepped-care blood pressure control.

Compliance to other aspects of the protocol will also be monitored by close attention to the number of missed visits, and, especially, the amount of missing data. Attempts will be made to follow the non-compliers and the patients who drop out as closely as possible.

Finally, it is believed that the expenses involved in maximizing compliance will be significant. These expenses should be carefully tracked as part of the HCFA study of the cost-effectiveness of diet as a means of managing progressive renal failure.

17.3 ANALYSIS PLAN

The use of a 2x2 factorial design employed in Studies A and B makes it possible to examine the effects of both treatments (i.e., diet and blood pressure regimen) simultaneously. Primary analyses will examine the main effects of each of the treatments on the major outcome variables. The main effect of each treatment (e.g., diet) is the average effect of the treatment across the two levels of the other factor (e.g., blood pressure), and is interpretable as an average effect, regardless of whether or not an interaction exists between the treatments. For example, in Study A, the main effect of diet on GFR slope is defined as the average of the Diet M means for the two blood pressure groups minus the average of the Diet L means for the two blood pressure groups.

Although Studies A and B are not designed to have high power to detect interactive effects of diet and blood pressure control (see Section 3.1), sample sizes are sufficiently large in each study so that there is 80% power to detect a 30% difference in GFR slopes between diets within each blood pressure stratum. If a qualitative interaction of diet with blood pressure regimen is found, secondary analyses will examine the effects of diet within each blood pressure stratum and the effects of blood pressure regimen within each diet group.

The primary analysis will be directed towards comparing the mean slopes of GFR between two treatments where each patient has his or her own slope calculated based upon all of his or her GFR measurements starting at the Baseline 3 Visit. An exception will be made such that if a patient has a surgical loss of renal mass during follow-up, the patient's GFR slope will be calculated using only those GFR's measured prior to surgery. GFR measurements will be taken every 4 months (except for an additional measurement at 2 months after Baseline). It should be noted that the rate of mortality and drop-out is expected to be minimal for patients enrolled in this clinical trial for the planned follow-up period. However, approximately 10% of the Study A patients and 50% of the Study B patients are expected to reach "stop points" before the end of the follow-up period.

Mean GFR slopes in a treatment group can be obtained as an unweighted average of the slopes across individuals. However, the individual slopes are not estimated with equal precision since each person may have a different number of GFR measurements due to missed visits or as a result of censoring (reaching a stop point or the end of the study). Therefore, unless there is informative censoring, a weighted mean slope should be used in determining the group average and its variance. Appropriate weights are the inverse of the variance of the estimated individual slope. These weighted mean slopes in different groups can be compared using a weighted regression model which can also include covariate factors (such as Baseline GFR, Baseline MAP, or Clinical Center) that need to be adjusted for. An assumption of this model is that the true slope is the same for all persons in a group. A more general model which does not make this assumption is the random effects model of Laird and Ware (1982).

A model proposed by Ware (1985) has several advantages over the usual growth curve type of model: (1) individuals do not have to be measured at the same times or with the same number of observations; (2) time-varying covariates can be included in the model; and, (3) both cross-sectional (level) and longitudinal (rate of change) effects can be modeled along with covariates for each effect. This model, however, requires a great deal of computation. A further disadvantage shared by this model as well as other more recent approaches (Rosner et al, 1985; Zeger and Liang, 1986; Liang and Zeger, 1986; Wei and Lachin, 1984) is that missing observations are assumed to be missing completely at random (Rubin, 1976), i.e., not related to the process being

studied. In the present study, this may not be the case since individuals reaching stop points (with later measurements censored) are not missing at random. However, these missing values may be "ignorable" since they are related to the past history of the individual. Missing values are "non-ignorable", and need to be modeled, if they are related to unobserved values. The only presently available model to handle "non-ignorable" missing data is that of Wu and Bailey (1986). This is a random effects linear model where the missing process is modeled assuming a probit function which allows tractable estimation.

The outcome of this study will be judged primarily on the differences (if any) between the randomized groups' mean GFR slopes over the period of the study. However, we anticipate that there will be a significant degree of non-compliance despite the optimal efforts at remediation as described above. For this reason, the calculated dietary protein and phosphorus intakes will be used as covariates in a secondary analysis of GFR slopes, independent of the group to which the patient was assigned. Hence, regression analysis techniques will be used to relate changes in renal function or other outcome measurements to protein and phosphorus intake. Similarly, we will also use regression techniques to relate changes in renal function and other outcome measures to summary measures such as the mean or rate of change (slope) of mean arterial pressure (MAP) during Follow-Up. However, it is recognized that the analyses relating outcomes to measured dietary intake and/or follow-up MAP are based upon non-randomized comparisons, and they will be interpreted cautiously. For example, patients with the most disease progression might become discouraged, leading to a decrease in dietary compliance. Also, failure to achieve MAP goals during Follow-Up may often be a natural consequence of renal disease progression.

Survival analysis methods will be used to evaluate the time to specified outcome events such as mortality, renal function "stop points", malnutrition, and reduction in body weight below 80% of the patient's standard body weight (Cox, 1972).

In an attempt to provide a thorough analysis of data, analyses will not be limited to overall comparisons but will include subgroup comparisons as well. For example, it will be of interest to examine the consistency of treatment effects across centers (Fleiss, 1986). Moreover, subgroups of patients may be identified by diagnostic categories, demographic characteristics, and laboratory data. It is conceivable that treatment effectiveness may vary from subgroup to subgroup. Hence, questions relating to interaction must also be considered. Such subgroup analyses will be interpreted with caution, however, considering the problems of multiple comparisons and statistical power that are involved in such analyses.

Also of interest will be the levels of renal function before and after randomization and the rates of renal function deterioration (slopes) before and after randomization. Changes pre- and post-randomization can be compared across groups. Although not a comparison based upon a randomized design, comparisons pre- and post-randomization can also be performed within groups. Such a before-after analysis will be performed for patients in Study C (i.e. before and after reaching a renal function stop point for patients originally randomized to the moderate protein diet).

17.4 INTERIM ANALYSES

The usual approach to tests of significance have definite limitations for a study of this type. Difficulties in applying standard statistical procedures arise from at least one major design feature of the study: its plan to review outcome at frequent intervals throughout the study to detect any positive therapeutic effects as soon as possible, to maximize safety, and to minimize the impact of possible adverse effects. Statistical methods are available for monitoring accumulating data in a clinical study. These methods address whether the study should be terminated early or continued to a planned termination. Several general statistical approaches are available (DeMets and Lan, 1984). For this study, there will be a review of the accumulating data by the External Monitoring Committee five times during the course of the study. The five interim analyses will be performed using type I error spending function and definition of scaled time as was described in Lee and DeMets (1990) in order to control the rate at which the type I error is used at interim analyses.

The "exit probabilities" are defined as $p_1=a(t_1)$, $p_j=a(t_j)-a(t_{j-1})$, $j=2,\ldots,5$ where p_j is the probability under the null hypothesis of stopping the trial at the jth analysis and $a(t_j)$ is the cumulative probability of rejection on or before time t_j under the null hypothesis. With this choice of spending function, the cumulative probabilities of rejection and exit probabilities are as follows:

Analysis	t_j	$a(t)=.05t^{2.5}$	p_j
1	.2	.0009	.0009
2	.4	.0051	.0042
3	.6	.0139	.0088
4	.8	.0286	.0147
5	1.0	.0500	.0214

In either Study A or Study B, critical values $C_1, \ldots, C_5$ will be determined recursively at each analysis time. If the z-test statistic at the jth interim analysis exceeds c_j in absolute value, then the test will be declared statistically significant. The following table shows estimated values for the cutpoints C_j, $j=1,\ldots,5$ in Studies A and B respectively, based on the projected rates of information vs. time.

Estimated Cutpoints at Interim Analyses: Studies A and B

Analysis	Cutpoint Study A	Study B
1	3.32	3.32
2	2.84	2.83
3	2.53	2.50
4	2.28	2.21
5	2.03	1.99

In both Studies A and B, the cutpoint for the Z-statistic in the final analysis is not elevated very much abouve the unadjusted value of 1.96, indicating little loss in final power.

Clinic staff members will not be privy to interim results. As the study progresses, statistically significant "positive" or "negative" trends may develop in the outcome data. If these trends were known, staff members might feel ethically uneasy about continuing the study or might treat participants differently. To prevent this, strict confidentiality of results will be maintained.

17.5 COST-EFFECTIVENESS ANALYSIS

Congress has mandated that the Health Care Financing Administration (HCFA) study the cost-effectiveness of nutrition therapy for patients with degenerative kidney disease. Kidney failure that necessitates chronic maintenance dialysis makes a

Also of interest will be the levels of renal function before and after randomization and the rates of renal function deterioration (slopes) before and after randomization. Changes pre- and post-randomization can be compared across groups. Although not a comparison based upon a randomized design, comparisons pre- and post-randomization can also be performed within groups. Such a before-after analysis will be performed for patients in Study C (i.e. before and after reaching a renal function stop point for patients originally randomized to the moderate protein diet).

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Clinic staff members will not be privy to interim results. As the study progresses, statistically significant "positive" or "negative" trends may develop in the outcome data. If these trends were known, staff members might feel ethically uneasy about continuing the study or might treat participants differently. To prevent this, strict confidentiality of results will be maintained.

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Congress has mandated that the Health Care Financing Administration (HCFA) study the cost-effectiveness of nutrition therapy for patients with degenerative kidney disease. Kidney failure that necessitates chronic maintenance dialysis makes a

patient eligible for Medicare through the End-Stage Renal Disease (ESRD) program. Such patients cost Medicare about $30,000 per patient year. If nutrition therapy delays or obviates the need for maintenance dialysis, this may reduce Medicare's ESRD costs.

Total costs and savings of the therapy are to be assessed, even those not expected to be paid, covered, or accrued by a Federal program. Within these total costs, data is to be collected and analyzed in a manner that permits distinguishing actual/potential Federal costs from other third-party payors' actual/potential costs, and from consumers' out-of-pocket costs. It will be important to answer the question, "Cost-effective for whom?", that is, to determine cost-effectiveness in a manner that is meaningful to those who will be paying the costs of the therapy.

A goal of this project is to test the feasibility and develop alternative policies for making the nutrition therapy available under the Medicare program, if nutrition therapy is both efficacious and cost-effective, issues that are being simultaneously tested in this trial.

If the nutrition intervention regimen is efficacious and cost effective, the study should also answer questions as to how it can be made a covered benefit under health insurance plans. Most ESRD patients under age 65 are covered by employer group health plans (EGHPs) when they become eligible for the ESRD program. Under relatively recent Federal law, EGHPs have been made primary payor for the first year of ESRD costs, with Medicare functioning as secondary payor. Therefore, EGHPs, as well as Medicare, have an interest in knowing whether nutrition therapy is cost-effective, and whether they should make it a covered benefit. In Phase II, more than 90% of the patients participating had health insurance, the majority of this being EGHPs.

Nutrition therapy is intended to be a preventive measure and is initiated prior to kidney failure and before the patient becomes Medicare-eligible through the ESRD program. Therefore, if it is to become a covered benefit under Medicare, it is likely to mean that a mechanism must be found for making the patient Medicare-eligible at an earlier stage of the disease, or at least eligible for some specified set of services prior to eligibility for the ESRD program. Even if this were to be done, it is almost certain that Medicare would require EGHPs to be primary payor for these pre-ESRD services.

17.6 DATA FOR COST-EFFECTIVENESS ANALYSIS

17.6.1 Data for Pricing Nutrition Therapy as a Potential "Covered Benefit" Under Health Insurance

The data collection protocols for the trial are well developed. There are numerous data collection instruments on many aspects of patients' history, treatment, compliance, and attitudes. These data are collected locally at each participating center and then assembled by the Data Coordinating Center into one central database.

In addition, data for cost-effectiveness must be obtained from NIH and HCFA, the payors of nutrition therapy in the clinical trial. Both NIH and HCFA are paying for some services and items that are mandated by the protocol as part of the clinical trial, but would not be required if nutrition therapy were a covered benefit under health insurance. There must be distinguished in the analysis of cost-effectiveness, so that "research-only" costs are not priced in, making the therapy appear to be more costly than it actually would be as a covered benefit.

NIH pays for some items that are large components in the pricing of nutrition therapy: physician and dietitian services, vitamins, and foodstuffs. It will be necessary to assess these payments in a manner that permits converging them to prices recognizable to potential health insurance payors, such as a price per visit or per patient month.

HCFA pays for some items that are substantial components in the pricing of nutrition therapy. Some of these, such as ketoacids, are paid in bulk, and the pricing must be converted to a price per dose or price per patient month. Clinics also submit bills to HCFA for services performed at visits, and these costs per visit will also be a major item in the analysis of cost-effectiveness.

Additional decisions must be made as to items in the clinical trial that may or may not be considered important for cost-effectiveness analysis that prices nutrition therapy as a potential covered benefit under health insurance. Among these is the price of the GFR, an expensive component.

17.6.2 Data for Estimating Savings

Since the major hypothesis related to the study of cost-effectiveness is that nutrition therapy will save ESRD dialysis costs, it will be necessary to have an estimated date (month or at least calendar quarter) when the patient would have been expected to begin maintenance dialysis, in the absence of nutrition therapy. With this information, HCFA can use data from its ESRD program to estimate savings that offset the costs of nutrition therapy.

17.6.3 Other Data Items to be Used in the Analysis of Cost-Effectiveness

1. Patient Family Income
   Income data are always important in understanding patient response to incentives. Of particular interest to this study is the importance of determining patient response to different insurance schemes, and income is likely to be an important element in this regard.

2. Incremental Cost of Food
   While the trial is supplying patients with some food supplements, there is a high likelihood that patients are incurring other costs and trouble obtaining food for the nutrition alternative. How much these other costs are and other qualitative factors about the hassle are likely to be important in understanding the cost of the nutrition alternative. Current plans in the trial are not to measure these costs and difficulties. Such a study should be considered, perhaps at a few participating centers.

3. Quality Adjusted Life Years
   It is anticipated that in Phase III, the estimation of quality adjusted life years will be possible. If this project cannot address the question of changes in the quality of life, it will be most difficult to derive meaningful policy conclusions if nutrition is an efficacious therapy.

4. Patients' Value of Nutrition Therapy
   It is important to determine how patients value nutrition therapy. This will be helpful in understanding compliance with the protocol but will also be in designing policies Medicare should consider to make this therapy widely available. This topic will require some original work as how best to

address this question within the confines of the current study.

Since all patients in the current trial will basically face no prices, there will be no experimental data generated on which to base the estimates of patient response. This implies that if this issue is to be developed as part of this trial, then patient subjective responses or other type of "marketing tests" will be required to estimate how patients value the nutrition therapy. This is a separate analysis from whether nutrition therapy is cost-effective.

To address this issue, patients must be asked how much of their own money they would spend for this therapy. In general, finding out how much patients would pay for this service is not likely to be an exact science but is most important, and imperfect attempts are necessary.

SECTION 18

QUALITY CONTROL

18.1 INTRODUCTION

In addition to the quality control methods routinely used at Clinical Center Labs and Central Units, specific quality control mechanisms for the MDRD Study are being utilized.

18.2 QUALITY CONTROL OF THE CLINICAL CENTERS

Quality control of the clinical centers include training and certification of study personnel and monitoring study procedures.

18.2.1 TRAINING AND CERTIFICATION OF STUDY PERSONNEL

Clinical center personnel will be trained for the specific tasks they perform and will be certified. Certification requirements for each member of the study team are given below:

Investigators

No specific training and certification measures are required for Principal Investigators and Co-Investigators. All investigators are expected to be actively involved in study activities at their centers, in meetings of the Steering Committee, and in subcommittees (as assigned).

Dietitians

Meet requirements as defined by the Nutrition Coordinating Center and the "Forms Completion" certification by the DCC.

Study Coordinators

Attendance at Study Coordinator and Data Entry training session, and successful completion of 1) Forms Completion, 2) Data Entry, 3) Data Transmission, 4) Error Correction, and 5) Electronic Mail certification requirements. Recertification will be done at the second annual Study Coordinators' Meeting, at the end of year two of the four-year study.

MDRD Technicians

Attendance at a training session at the Central GFR Lab, as well as the "Forms Completion" certification by the DCC.

Blood Pressure Recorder
Two or more members of each clinical center team will be trained by Central GFR Lab personnel and certified in blood pressure and recording and in equipment and quality control logs regarding calibration and performance of blood pressure measurement devices. Recertification will be done at the annual meetings of the MDRD Technicians.

Recruitment Coordinators
Meet requirements as defined by NIH and the "Forms Completion" certification by the DCC

Data Entry Clerks
Attendance at a Data Entry training session, and successful completion of 1) Forms Completion, 2) Data Entry, 3) Data Transmission, 4) Error Correction, and 5) Electronic Mail certification requirements.

18.2.2 DATA ENTRY

The Data Coordinating Center staff will re-enter a random subset of the data forms entered at the Clinical Centers. Because all forms are re-key verified at the Clinical Centers, few key entry errors are anticipated. Discrepancies will be resolved and results will be reported.

18.2.3 BIOCHEMISTRY LABORATORY

For Quality Control of the local biochemistry labs, yearly CAP survey results will be reviewed.

18.2.4 GFR PROCEDURE

GFR procedure is described in Section 6. For quality control of the Clinical Center GFR procedure:

1. The CV of the GFR period results and the flow rates of the urine collection periods for each GFR will be reported to the Clinical Centers and these CVs as well as the CVs of the flow rates will be summarized and analyzed by the Data Coordinating Center.
2. A member of the staff of the Central GFR Laboratory will do site visits of Clinical Centers to observe the GFR technician conducting a GFR, answer questions, and offer suggestions whenever there is a problem with a center's GFR measurements.

18.2.5 BLOOD PRESSURE MEASUREMENTS

Blood pressure measurement procedure is defined in Section 6. For quality control, blood pressure devices will be calibrated regularly and the results will be recorded in a log kept at the clinical center.

18.2.6 ANTHROPOMETRY MEASUREMENTS

Measurement procedure is defined in Section 6. Quality control will be maintained through a process of training and on-going semi-annual recerfication of observers by a certified anthropometric trainer. The data will be renewed on a regular basis to monitor variability.

18.3 QUALITY CONTROL OF THE CENTRAL BIOCHEMISTRY LABORATORY

The means of internal quality control are applied to the Central Biochemistry Laboratory as follows:

With every run of patient samples, the technologists must run at least two known quality control samples. These quality control results must fall within specified ranges. Also, a split patient sample must be assayed with each run to check precision.

In addition, the CCF Biochemistry Laboratory participates in CAP and Wellcome External Surveillance Studies on an on-going basis. The Lipid Laboratory participates in the Centers for Disease Control Standardization Project.

Two means of external quality control are applied to the Central Biochemistry Laboratory:

1. The Central Biochemistry Lab is tested using the same CAP specimen that is analyzed by the CCF Lab staff. The CAP specimen is reconstituted by the CCF QC staff; split serum and urine are utilized. The Central Lab staff measures the following constituents: serum phosphorus, urea nitrogen, creatinine, transferrin, albumin, uric acid, bilirubin, LDH, SGOT, triglycerides, total cholesterol and HDL cholesterol; and urine urea nitrogen, phosphorus, creatinine, protein, sodium, and potassium. Results are compared with CAP peer group and reference results.

2. Twice a year, according to a schedule prepared by the Data Coordinating Center, the local Clinical Center Lab technicians split patient serum and urine samples and send the split samples to the Central Biochemistry Lab. At the beginning of each month when an external quality control sample is to be taken, the Data Coordinating Center will randomly select the patient to be used for quality control and will notify the Clinical Center. Several alternate patients will also be selected as back-ups. No patient will be selected for a quality control sample for both biochemistry and Amino Acids in the same month, since both samples require extra blood to be drawn. One serum and urine set is labelled with the patient's actual ID; the second is labelled with a quality control ID. The lab reports serum phosphorus, serum urea nitrogen, serum creatinine, serum albumin, serum transferrin, hemoglobin A1c, LDH, SGOT, triglycerides, HDL, bilirubin, uric acid, total cholesterol, and 24-hour urine protein, urea nitrogen, creatinine, phosphorus, sodium and potassium. The duplicate results are compared.

18.4 QUALITY CONTROL OF THE CENTRAL AMINO ACID LABORATORY

The means of internal quality control are applied to the Central Amino Acid Laboratory as follows:

The between sample variability of the amino acid analyses, as a result of day-to-day changes in the ninhydrin, are assessed by the inclusion of a standard sample of deproteinized plasma with each batch of patient samples analyzed. This standard sample is an aliquot of a large volume of deproteinized plasma obtained from one individual and stored at -70 degrees in small aliquots. Runs of samples in which the amino acid totals of this standard sample differ from the mean totals for this standard by more than +/-10% are reanalyzed until the standard sample values are within this range.

For external quality control, each Clinical Center Lab performs quality control of the Central Amino Acid Lab twice annually, according to a staggered schedule prepared by the Data Coordinating Center. At the beginning of each month where a quality control sample is to be sent, the Data Coordinating Center will randomly select a patient from among those scheduled to have blood samples drawn at that Clinical Center and will notify the Clinical Center. Several alternate patients will also be selected randomly in case a blood sample cannot be obtained from the first patient chosen. The Clinical Center lab technician draws additional blood from the selected patient, prepares it, splits it, and sends the two specimens to the Central Amino Acid Lab. Duplicate results are prepared and the results will be reported to the Quality Control Committee.

18.5 QUALITY CONTROL OF THE CENTRAL GFR LABORATORY

Quality control of the Central GFR Laboratory is carried out as follows:

1. The pipette used for GFR samples is routinely evaluated for volumetric accuracy and precision using the weighing of water on an electronic microbalance as a quality control technique.

2. The gamma counter is calibrated with ^{137}Cesium standards to assure accurate peak locations and window settings.

3. The counter efficiency is monitored daily using ^{137}Cesium standards. Counter background activity is monitored on a daily basis as well.

4. The patient counts are bracketted by matched 125I-sodium iothalamate standards to eliminate instrumental malfunctions during sample counting as an error source.

5. A precision study is run weekly by selecting a GFR study and rerunning it the following day.

External quality control of the Central GFR Laboratory will be carried out as follows:

Each Clinical Center will prepare and send one external quality control sample every three months, according to a schedule prepared by the Data Coordinating Center. On months when a quality control GFR sample is required, the Data Coordinating Center will randomly select one of the patients on whom a GFR measurement has been obtained at that Clinical Center, and will notify the Clinical Center. The clinical center technician will prepare and mail the backup specimens, using that center's quality control identification number and name code. Results from the first GFR and the second GFR will be compared for quality control.

Quality control precision limit for precision studies and split samples is that the two counts must be within +/- 10% or 2 ml/min/1.73 m^2, whichever is greater.

18.6 QUALITY CONTROL OF THE CENTRAL EKG LABORATORY

Two external quality control samples from each Clinical Center per year will be randomly selected by the Data Coordinating Center from the collection of EKG strips sent by that Clinical Center. The EKG strips will be prepared and sent to the Central EKG Laboratory using a quality control ID number, and the results will be compared to the original reading.

18.7 QUALITY CONTROL OF THE NUTRITION COORDINATING CENTER

Internal quality control for the entry of dietary data includes:

1. Routine editing at the point of entry to measure the entry quality of all items entered.
2. Routine editing after entry to measure entry quality of all records and recalls and each entry person.
3. The processing of quality control records to measure entry quality of a random subset of all records under test conditions and to compare the entry quality of different entry personnel.
4. The documentation and monitoring of entry judgement calls to ensure their consistency and accuracy.

Food records will be used for external quality control of dietary data. Yearly, two 3-day food records will be randomly chosen by the DCC from previously entered records from each clinical center. This data will be submitted by clinical centers to the NCC on a staggered schedule set by the DCC. A pool of

these quality control records will be accumulated and will constitute the pool of MDRD external quality control dietary data. This same pool of dietary data would be re-copied by clinical centers and re-submitted for future external quality control submissions to the NCC. Multiple analyses of the consistency of dietary data will be performed over the multiple years of the MDRD Study. The clinical center will transcribe the record, label it with a Quality Control ID as designated by the DCC, and send it to the NCC as if it were an original. The output of this record will be compared to the original output by the DCC, the data will be summarized and be provided as part of a quality control report. These revised procedures would start July 1, 1989.

18.8 QUALITY CONTROL OF THE DATA COORDINATING CENTER

All data entered into the MDRD Study Database are verified and must pass a series of interform and intraform edit checks defined in the schema. A random subset of data forms entered at the clinical centers will be re-key verified by DCC staff to check for keypunch errors (see Section 18.2.2). Frequencies of data items and changes over time will be examined to look for unusual data distributions or unlikely values.

The communications programs which send the data files to the Data Coordinating Center include an automatic backup procedure where the data being transmitted are written to a floppy disk at the clinical center. A separate floppy disk will be used for each month's data at each clinical center. This procedure is described in Section 5.6 of Volume I of the MDRD Manual of Operations. The Information Services Division at The Cleveland Clinic Foundation performs an entire system back-up weekly and incremental back-up (for files that change) on a daily basis. Additionally, the entire MDRD database is written to magnetic tape each month and is stored in a secure off-site location.

Procedures will be monitored by the Clinical Center and Central Lab Evaluation Committee and by site visits of the DCC.

SECTION 19

ADMINISTRATIVE STRUCTURE

19.1 INTRODUCTION

This chapter describes the organizational structure of the Modification of Diet in Renal Disease (MDRD) Study including the specific responsibilities and lines of communication among each of the study components. The organizational structure is developed to ensure the uniform adherence of the Protocol and Manual of Operations and the smooth coordination of activities among all study components. Figure 19.1 is the primary reference for this section.

19.2 ADMINISTRATIVE STRUCTURE: NATIONAL INSTITUTE OF DIABETES, DIGESTIVE AND KIDNEY DISEASES

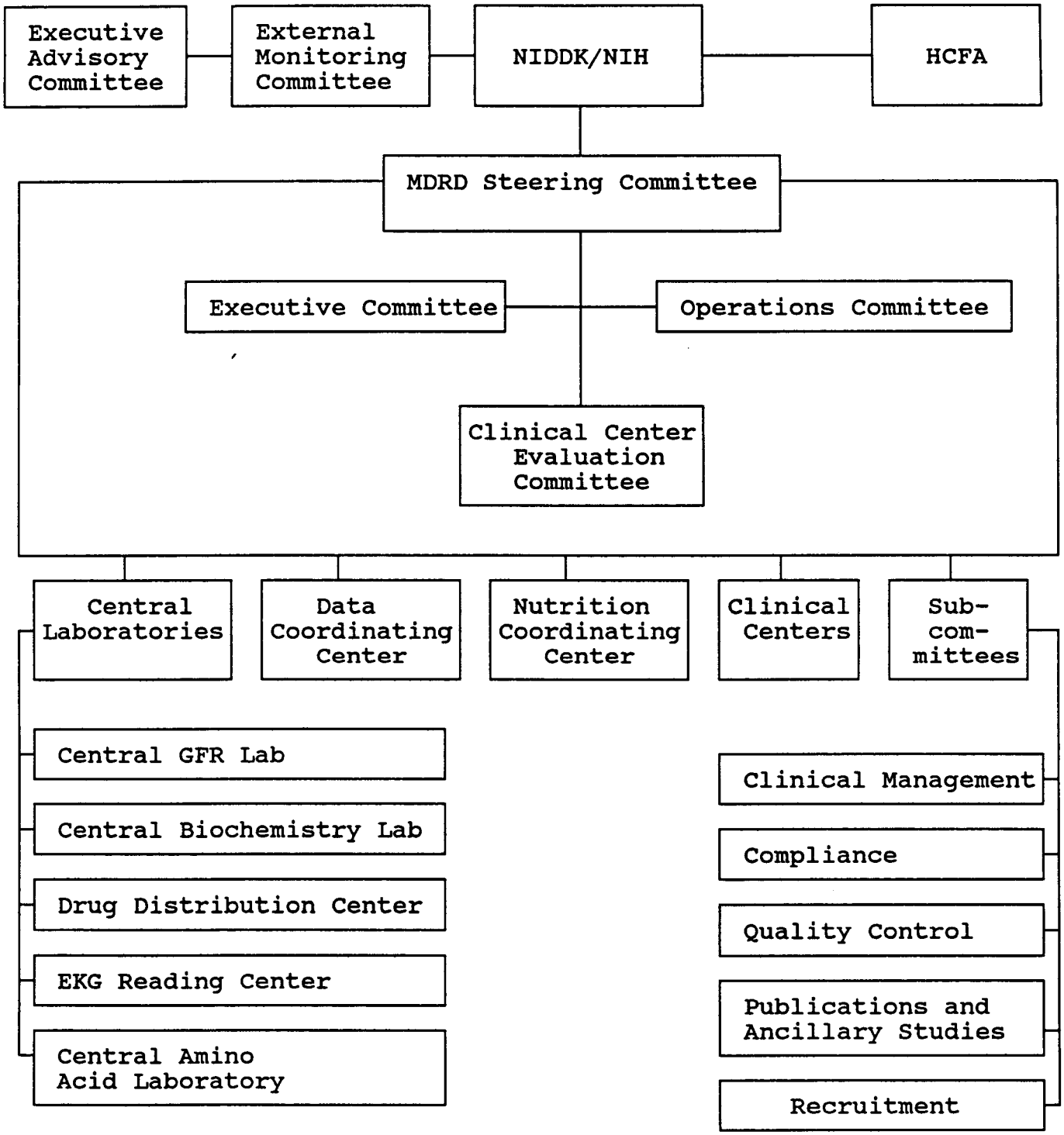
19.2.1 The Director of the National Institute of Diabetes and Kidney Diseases (NIDDK) has the ultimate responsibility for major program decisions of the Institute, including the management and allocation of funds and other resources.

19.2.2 The Director of the Division of Kidney, Urologic and Hematologic Diseases (DKUHD) is the representative of the Institute Director and is responsible for ensuring that the scientific and technical goals of the study are consistent with the mission and responsibilities of the NIDDK and NIH. The Division Director is responsible for appointing the Chairman and the Vice-Chairman of the MDRD Steering Committee as well as the chairmen and members of the External Monitoring Committee and the Executive Advisory Committee.

19.2.3 The Clinical Trial Program Director, based in DKUHD, serves as the liaison between the MDRD Study Group and the NIDDK. This individual has overall responsibility for the coordination of all components of trial activity and assumes primary responsibility for the administrative management of the study. The Program Director, in collaboration with other DKUHD staff, represents the Institute in matters which concern the scientific and technical direction of the trial. The Program Director is a member of the Steering Comittee, the Executive Committee and, along with other DKUHD staff, retains full or ex-officio membership on each of the working committees. The Program Director, in collaboration with the Director of the Drug Distribution

FIGURE 19.1

MDRD ADMINISTRATIVE STRUCTURE



Center, is responsible for all communication with the commercial sector for the acquisition of the ketoacid mixture "EE" and other nutritional supplements. All contact with federal agencies, such as the Health Care Financing Administration (HCFA) and the Food and Drug Administration (FDA) is coordinated by the MDRD Program Office.

19.2.4 The Health Care Financing Administration (HCFA) is collaborating with the NIDDK/NIH in supporting the MDRD Study through the payment of medical services related to the study and in the conduct of a cost-effectiveness study. An Interagency Agreement between the two Agencies delineates the responsibilities of each organization in the implementation of the study. Specifically, the NIDDK has lead responsibility for the management and scientific direction of the trial. HCFA has lead responsibility for conducting a cost-effectiveness study of the intervention strategy. Within HCFA, a representative in the Office of Demonstrations and Evaluations serve as the liaison to the NIH and the MDRD Study Group and are members of the MDRD Steering Committee, the Executive Committee and other working committees. In addition, the Division of Research and Demonstrations Systems Support of the Office of Research and Demonstrations serves as fiscal intermediary to the clinical centers for covered services required by the Study Protocol and provides billing and reimbursement data to the HCFA evaluator and the Data Coordinating Center.

19.3 ADMINISTRATIVE COMMITTEES

19.3.1 The Executive Advisory Committee (EAC) is comprised of experts in the fields of nephrology, nutrition, blood pressure, biochemistry and ethics, who are independent of the trial and the NIH. The members of this group are appointed by the Director of DKUHD and will meet approximately annually or more frequently if it is deemed to be necessary. The Chairman of the External Monitoring Committee and the Steering Committee will hold ex-officio membership. A member of the DKUHD staff will serve as the Executive Secretary. The responsibilities of the EAC in the full-scale trial will include the following:

1. Review reports on the progress of the study and make recommendations to the Director of DKUHD on major changes in the protocol or proposals of early termination of the study.

2. Review ethical aspects of the MDRD Protocol and communicate any concerns relative to the protection of MDRD subjects from research risks.

3. Review interim and final results and provide advice to the Director of DKUHD regarding their interpretation and implications for the treatment of chronic renal disease.

19.3.2 The External Monitoring Committee (EMC) is comprised of individuals with expertise in nephrology, nutrition, blood pressure, clinical trials, biostatistics, laboratory science and renal function measures who are independent of the study and NIH. The members of the EMC are appointed by the Director of DKUHD and will meet twice annually or as deemed necessary by the Chairman of the EMC or the Director of DKUHD. The Chairman of the Steering Committee and Directors of the Data and Nutrition Coordinating Centers are ex-officio members of the committee. The MDRD Program Director serves as the Executive Secretary. The responsibilities of the EMC are as follows:

1. Review all activities which affect the broad operational and methodological aspects of the trial, including the quality control procedures and performance of clinical centers and central facilities.

2. To ensure patient safety, the EMC will routinely monitor study data to which the investigators of the study are blinded. Specific patient safety problems may also be referred to the EMC by the Chairman of the Steering Committee for immediate consideration.

3. The EMC will monitor study data to ensure the quality of the data and procedures for analysis. They may advise the Data and Nutrition Coordinating Centers on the content of study reports and manner of data display and may request specific data analysis for clarification of adverse or beneficial treatent effects.

4. The Committee will review all proposed major modifications to the protocol and advise NIDDK as to whether the proposed changes are appropriate and necessary. All ancillary studies approved by the Steering Committee will be reviewed by the EMC for scientific merit and impact on the objectives and performance of the major study.

5. The EMC will prepare an annual report on the progress of the study which will be submitted to the Executive Advisory Committee (EAC) by NIDDK. In the event that special problems are identified during the course of the study, the Chairman of the EMC will inform NIDDK in a special written communication describing the issues or problems and make recommendations of appropriate actions.

19.3.3 The Steering Committee is the official representative of all trial participants. It is composed of a Chairman, a Vice-Chairman and representatives from each of the participating clinical centers, the Data Coordinating Center, the Nutrition Coordinating Center, HCFA and NIDDK. The Chairman is appointed by the DKUHD Director.

The Chairman of the Steering Committee is the official representative of the MDRD Study and provides general scientific direction to the trial. He is also the Chairman of the Executive Committee and appoints the chairpersons and members of the working committees as well as writing teams charged with the preparation of official study papers.

The Vice-Chairman is selected from one of the Principal Invesigators of the participating clinical centers and appointed by the Director of DKUHD. The selection is made in consultation with the Chairman of the Steering Committee.

The Steering Committee will provide overall direction of the study. The committee will meet approximately three times annually to address study-wide issues and consider recommendations submitted by the individual working committees. One representative from each of the clinical centers, Data Coordinating Center, Nutrition Coordinating Center, HCFA and NIDDK shall be entitled to a vote. A representative from each institution must be present at each meeting. An additional person from each clinical center may attend at the discretion of the Principal Investigator. A Principal Investigator unable to attend may designate an alternate to act on his behalf. The Data Coordinating Center will be responsible for maintaining a log of attendance and items requiring follow-up actions and will prepare and distribute the meeting minutes. All recommended changes to the protocol must receive an affirmative vote by as least two-thirds of the members present.

19.3.4 The Executive Committee monitors study activities and makes day-to-day management decisions that arise between meetings of the MDRD Steering Committee. The comittee consists of the Study Chairman, the Vice-Chairman, the Directors of the Data and Nutrition Coordinating Centers, the the MDRD Program Director and the HCFA Project Coordinator. Actions taken by the committee will be reported to members of the Steering Committee at the next scheduled meeting. No major actions are taken by this committee without prior discussion with members of the Steering Committee. Communications is generally via conference call. The Executive Committee will review and approve the Steering Committee Agendas.

19.3.5 The Operations Committee assures that all study issues are appropriately dealt with in a timely manner. The committee monitors assignments to individual working committees and reviews the recommendations of the committees prior to presentation to the Steering Committee. The Working Committees in the MDRD Study are identified as the Clinical Management Committee, the Quality Control Committee, the Compliance Committee, the Publications and Ancillary Studies Committee, the Clinical Center Evaluation Committee, and the Recruitment Committee. The membership of this committee includes the Chairman, who is also the Vice-Chairman of the Study, the Chairpersons of each of the Working Committees, a representative from the Data Coordinating Center and the Nutrition Coordinating Center, the HCFA Project Coordinator and the MDRD Program Director. The Chairman of the Steering Comittee is an ex-officio member. This committee will meet approximately one month prior to each Steering Comittee meeting. Meetings may be held via conference call.

19.4 WORKING COMMITTEES.

As previously noted, the Working Committees in the MDRD Study are the Clinical Center Evaluation Committee, the Clinical Management Committee, the Quality Control Committee, the Compliance Committee, the Publications and Ancillary Studies Committee, and the Recruitment Committee. Initial appointments to these committees will be for one year for half the committee and for two years for the other half of the committee. All secondary appointments will be for two year terms. This will allow for rotation of membership, but provide the required continuity. The names of the persons who serve on each committee will be listed in the most current MDRD Address Directory.

19.4.1 The Clinical Center Evaluation Committee will serve as the representative of the Steering Committee and will assist the Data Coordinating Center in monitoring the adherence of clinical centers to procedures described in the Protocol and Manual of Operations. The members of this committee will consist of three from the Clinical Center investigators, a representative from the Data Coordinating Center and the Nutrition Coordinating Center, the HCFA Project Coordinator and the NIH Program Director. One of the principal investigators will serve as chairman. Monitoring activities will include review of clinic performance data (as opposed to masked study data), including progress in meeting recruitment goals. The Data and Nutrition Coordinating Centers will provide the committee with sufficient data to allow evaluation of clinical center adherence to study procedures. The committee will meet as necessary and will conduct clinical center site visits of sufficient frequency to assure continued adherence to the protocol. Minutes will be maintained of committee meetings and site visits. Actions and recommendations will be documented and forwarded to the Data Coordinating Center for distribution to the MDRD Program Director and appropriate committees and clinical center.

19.4.2 The Clinical Management Committee will review and monitor the safety of all clinical procedures and dietary prescriptions described in the Protocol and Manual of Operations and will assist the clinical centers in interpreting and implementing them in a uniform manner. This is to ensure consistency in treatment regimens across all participating clinical centers. The committee will review and monitor all intercurrent events, including patients who have died, reached Action and Stop Points or are lost to follow-up. To assure maintenance of patient safety, the committee will review nutritional and biochemical markers and may recommend modifications in clinical management procedures and/or refer cases to the External Monitoring Committee, through the Chairman of the Steering Committee, for further evaluation. All drugs and devices used by the clinical centers to implement the Protocol must have the approval of this committee. The committee will meet once between Steering Comittee meetings or as deemed necessary by the Chairman.

19.4.3 The Quality Control Committee will assist the Data Coordinating Center in developing the internal and external quality control procedures used by the central laboratories to assure the collection of high quality

data. The committee will monitor the performance of the central laboratories as well as the performance of the local laboratories to assure that procedures are conducted in a technically correct and acceptable manner. The committee will identify procedural and technical difficulties and formulate recommendations to resolve problems and improve quality control procedures. Membership includes representatives from the clinical centers, Data Coordinating Center, Nutrition Coordinating Center, central laboratories and the Clinical Trial Program Office. The committee will consider all suggestions of improvements to quality control procedures and will make appropriate recommendations to the Steering Committee through the Operations Committee. The committee will meet once between Steering Committee meetings or as deemed necessary by the Chairman.

19.4.4 The Patient Compliance Committee will collaborate with the Data and Nutrition Coordinating Centers in monitoring and promoting patient compliance to study procedures as described in the Protocol and Manual of Operations, including adherence to visit schedules and laboratory tests, urine and dietary data collection schedules, dietary prescriptions, blood pressure targets, and medications. The committee will review the accuracy of measures used to assess dietary compliance and adherence to blood pressure medication and will make recommendations to the Steering Committee, through the Operations Committee, if changes in the criteria used to make these assessments appear to be warranted. The committee will assist the Data and Nutrition Coordinating Centers in identifying patient compliance problems and will provide guidance in the interpretation and analysis of compliance data as well as interpreting and analyzing the results. The committee will meet once between Steering Committee meetings or as deemed necessary by the Chairman.

19.4.5 The Publications and Ancillary Studies Committee will monitor and provide editorial review of all releases of information about study activities according to the standards described in the Manual of Operations. This includes the preparation of manuscripts, abstracts, presentations, and formal interviews.

The committee may make recommendations to the Executive Committee for preparation and final approval of journal articles, and monitor writing assignments. The committee will maintain an updated bibliography of MDRD

publications and abstracts, as well as manuscripts under preparation, which will be submitted to the Data Coordinating Center and the DKUHD Clinical Trial Program Office on a timely basis.

The committee will review all proposals of ancillary studies and make recommendations to the Steering Committee, through the Operations Committee, as to the scientific merit of the study as well as the burden of the proposed study on the MDRD Protocol, as defined in Section 21 of the Protocol and the Administrative Manual of Operations. The committee will maintain an updated log of ancillary studies submitted for consideration, including the status of on-going studies and will monitor the progress of on-going studies and the burden of these studies on the MDRD trial on an annual basis. The membership of this committee includes representatives from Clinical Centers, Data and Nutrition Coordinating Centers, HCFA and the MDRD Program Office. The committee will meet once between Steering Comittee meetings or as deemed necessary by the Chairman.

19.4.6 The Recruitment Committee (Temporary) will develop an overall recruitment strategy for the MDRD Study, including short and long-term recruitment goals for the clinical centers. The committee will assist the MDRD Program Director in monitoring the achievement of these goals at the clinical centers and review the effectiveness of various recruitment strategies used in the study. The committee will coordinate and monitor the effectiveness of national publicity campaigns and provide guidance in the development of recruitment brochures and other publicity material to enhance interest in the MDRD Study among eligible patients, physicians and other professionals.

The committee will be responsible for developing and amending prototype Informed Consent documents which will be submitted by clinical centers to their Institutional Review Boards (IRBs). The model Informed Consent documents will be submitted to the MDRD Program Office for approval to assure that they comply with NIH established regulations on the "General Requirements for Informed Consent."

The membership of this committee will consist of three investigators, one of whom will serve as chairman, a representative from the Nutrition Coordinating Center, the Data Coordinating Center, recruitment coordinators

from two institutions and the MDRD Program Office. Consultant expertise will be available to the committee on an "as needed" basis. The committee will meet at least once between Steering Committee meetings or as deemed necessary by the Chairman.

Following is a general description of the responsibilities of the clinical center research team and central units supporting the MDRD Study.

19.5 THE CLINICAL CENTERS AND CENTRAL UNITS

The clinical centers are each directed by a Principal Investigator. The responsibility of this individual is to provide the appropriate supervision of the clinical center research team to assure the adherence to the Protocol and procedures described in the Manual of Operations. The clinical center research team consists of a Principal Coordinator, Co-Investigator(s), Study Coordinator, Recruitment Coordinator, Dietitians, GFR Nurse, Data Monitor and Secretary/Administrative Assistant. The responsibility of the Principal Investigator is also to collaborate with the Steering Committee, the central units supporting the study as well as the NIDDK and HCFA staff to implement the MDRD Protocol and Manual of Operations. The clinical centers are required to meet recruitment goals and will work with the central units in the implementation of the Protocol and the Manual of Operations for collection and transmission of high quality data. The Principal Investigator will assure that an appropriate clinic and administrative environment exists and that there is adequate institutional commitment to support the conduct of the study.

19.6 THE DATA COORDINATING CENTER (DCC)

The Data Coordinating Center (DCC) is responsible for providing guidance and direction to the Steering Committee in the design, development and implementation of the Protocol and Manual of Operations and will work collaboratively with all study components, including NIDDK and HCFA staff. The DCC will provide logistical and administrative support to the Clinical Trial Program Office in planning meetings, workshops, setting agendas, preparing minutes of all Steering Committee and Executive Committee meetings, and arranging for consultant services as necessary to implement the study. They will serve as the central repository for all study related material and will maintain appropriate confidentiality and security of data files. They will assume responsibility for establishing quality control procedures for the collection, transmittal and entry of data and will develop appropriate methods of analysis, interpretation and presentation of data collected during the course of the study. The Data

Coordinating Center will prepare reports and other documents as requested by the Steering Committee or the Program Office. In collaboration with the Nutrition Coordinating Center (NCC), the DCC will provide training and certification of clinical center staff on an as needed basis and will review and document clinic performance to assure standardization of procedures and data quality. The DCC will arrange for appropriate consultation, if requested by the Steering Committee or the Program Office and will collaborate with the NCC in the preparation of reports and other documents. The Data Coordinating Center will administer the Quality of Well Being (QWB) Questionnaire to MDRD patients via telephone. The DCC will be responsible for reviewing and maintaining the quality standards of the following five central laboratories serving the MDRD study.

19.6.1 The Central GFR Laboratory will serve as the central ordering point of the marker (^{I}125-Iothalamate or the selected alternative marker) used in the study to measure the glomerular filtration rate (GFR). They will receive serum and urine samples from clinical centers for central counting and GFR calculation as described in the Central GFR Lab Manual of Operations.

They will be responsible for training, certification and recertification of personnel performing GFRs and blood pressure measurements in the clinical centers and will maintain and transmit study data as specified in the procedures manual. The Central GFR Laboratory will follow internal quality control procedures, as specified in the Manual of Operations, and will prepare quarterly reports for submission to the Quality Control Committee.

19.6.2 The Central Biochemistry Laboratory (CBL) will analyze baseline and repeated measurements of serum and urine specimens as described in the Central Biochemistry Laboratory Manual of Operations as well as the Internal CBL Manual and will maintain appropriate internal and external quality control procedures. The CBL staff will train MDRD technicians to collect and process the serum and urine specimens. The CBL will prepare quarterly reports pertaining to the quality standards of its own laboratory as well as the adherence to standards in laboratories at the clinical centers. These reports will be submitted to the Quality Control Committee.

19.6.3 The Drug Distribution Center (DDC) will work with the MDRD Program Office in the acquisition of drugs and vitamins required for patients in the MDRD Study; will serve as the official liaison with the pharmaceutical supplier of the vitamins and mixture of essential amino

acid and ketoacid analogues (Mixture EE); and arrange for independent verification of the vitamin formula. The DDC will distribute, or arrange the distribution of these supplies to each of the clinical centers on a timely basis and will assist the clinical center pharmacies in establishing and following procedures required by the Food and Drug Administration for the control of investigational new drugs as described in the Drug Distribution Center Manual of Operations. Quarterly reports will be submitted to the Quality Control Committee.

19.6.4 The EKG Reading Center will receive and read, code and report EKG recordings using standardized procedures described in the EKG Reading Center Manual of Operations. Quality control procedures described in the Manual of Operations will be employed. Quarterly reports will be submitted to the Quality Control Committee.

19.6.5 The Central Amino Acid Laboratory will receive, analyze and report the amino acid and alloisoleucine concentration of plasma samples according to the procedures described in the Central Amino Acid Laboratory Manual of Operations. Appropriate quality control procedures will be maintained and reported to the Quality Control Committee on a quarterly basis.

19.7 THE NUTRITION COORDINATING CENTER

The Nutrition Coordinating Center (NCC) is responsible for providing guidance and direction to the Steering Committee in the development, implementation, maintenance and review of the nutrition intervention as specified in the Protocol and Manual of Operations. The NCC will work collaboratively with all MDRD study components, including NIDDK and HCFA staff, will participate in clinical center performance evaluations and will provide training and performance monitoring of clinical center dietitians, including dietary interviews and anthropometry measures. The NCC will support clinical center dietitians in the implementation of nutrition intervention. The NCC will develop systems and strategies to monitor, maintain and improve patient adherence such as behavior modification strategies, and the development and evaluation of educational material for dietitians and patients. The NCC will develop strategies for evaluation of the intervention and for assuring that appropriate quality control mechanisms are in place for nutrient database management, dietary data collection, processing and recipe calculation procedures, as well as documentation, handling and reporting of study forms and results. The NCC will arrange for expert consultations, if

requested by the Steering Committee or the Program Office, and will collaborate with the DCC in the preparation of reports and other documents. The NCC will be responsible for ordering and distributing the low protein food supplements to the clinical centers as well as equipment and instruments used by the MDRD dietitians for patient teaching and nutrition monitoring and assessment. The NCC will serve as the liaison with The CBORD Group in the acquisition and maintenance of the Diet Analyzer computer program and will provide appropriate teaching and data base support to facilitate the implementation of this software system by the clinical center dietitians.

SECTION 20

PROTOCOL CHANGES

20.1 GENERAL PRINCIPLES

During the conduct of Phase III, Protocol changes are not desirable and should not be made unless patient safety is compromised or if new information arises, strongly suggesting changes that would strengthen the scientific validity of the study. In the event that alterations are necessary, the following procedures will be followed:

20.2 PROCEDURES

Recommendations for Protocol changes may originate from the External Monitoring Committee, the NIDDK, the Data Coordinating Center, the Nutrition Coordinating Center or one of the Working Committees. All proposed changes will be submitted to the Executive Committee for consideration. The Executive Committee will make a recommendation to the Steering Committee as to whether the proposed modification merits consideration and the method of incorporating the proposed change in the Protocol. Approval by the Steering Committee must have support from two-thirds of the voting members. The recommendations of the Steering Committee will then be presented to the External Monitoring Committee who will advise the NIDDK as to whether the Protocol change is advisable. The NIDDK may seek further advice from the Executive Advisory Committee or other experts outside of the MDRD Study, before making the final decision as to whether or not to approve the Protocol change.

SECTION 21

ANCILLARY STUDIES

21.1 GENERAL PRINCIPLES

The Publications and Ancillary Studies Committee will evaluate all ancillary study proposals. Each proposal will be carefully considered on the basis of scientific merit and impact on the objectives and performance of the MDRD Study. Ancillary studies which are compatible with the overall goals and objectives of the MDRD Study and which do not disrupt study procedures or compromise patient compliance will be encouraged by the study group. All approved ancillary studies will be reviewed annually to monitor their progress and impact on the trial.

21.1 DEFINITION

An ancillary study is defined as a specific area of research which is not included in the MDRD Protocol. It may involve the collection of new data or the use of existing data obtained by various means, such as questionnaires, interviews, special procedures, observations or any other technique involving MDRD volunteers.

21.3 APPROVAL PROCEDURES

Proposals for ancillary studies may be made by any individual or group within or outside of the MDRD Study, and submitted to the Publications and Ancillary Studies Committee for review. This committee will make a recommendations to the Steering Committee who will make a decision on a case by case basis.

The Publications and Ancillary Studies Committee will review each ancillary study to assure that its inclusion will not create an undue burden on available resources at the local clinical centers and central units as to jeopardize the conduct of the primary purpose of the study, diminish patient compliance and adherence to the Protocol, or in any way compromise the scientific integrity of the MDRD Study.

Final approval will be given for the conduct of an ancillary study following the receipt of a written statement from the investigators of that study indicating that they will abide by the policies and procedures set forth for the conduct of these studies, including the procedure to obtain MDRD approval prior to the publication and presentation of ancillary study results.

21.4 FUNDING OF ANCILLARY STUDIES

No funds are available in the MDRD Study for the conduct of ancillary studies. This includes funding for extra activities which may be required by the central units, particularly the Data Coordinating Center or the Nutrition Coordinating Center. An ancillary study proposal submitted for review must not only identify the amount of money needed to conduct the study but also the sources where funds may be obtained. For example, an investigator may wish to submit a new research grant application, request support from foundations or drug companies, or seek other sources of support.

21.5 PUBLICATION OF ANCILLARY STUDY RESULTS

All reports, manuscripts or presentations using data derived from the ancillary study must be approved by the Publications and Ancillary Studies Committee prior to publication or presentation according to the procedures set forth in the Manual of Operations.

SECTION 22

MAINTENANCE AND DISPOSITION OF STUDY DOCUMENTS, DATA, AND MATERIALS

22.1 INTRODUCTION

This Section describes the procedure which will be employed for maintenance and disposition of study documents, data forms, tapes, results of analysis, and materials during and at the conclusion of the MDRE Study.

22.2 INTERNAL DISTRIBUTION OF STUDY DOCUMENTS

The Data Coordinating Center is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to the MDRD Study. During the conduct of the MDRD Study, the Data Coordinating Center will be responsible for the distribution of the Protocol, Manual of Operations, and study reports to MDRD participants, and if requested by the MDRD Program Office, to the EMC and the EAC. At the end of the study, these documents will be archived by the DCC and forwarded to the National Technical Information Service (NTIS).

Minutes of all appropriate committee meetings, including minutes of Advisory Committee meetings, will be maintained in the files of the Data Coordinating Center. The Nutrition Coordinating Center will maintain minutes of meetings with MDRD dietitians and other meetings pertaining to the dietary intervention procotol. At the conclusion of the study, these minutes will be microfiched and forwarded to the NIDDK. The Data Coordinating Center will maintain a copy of all signed Informed Consent documents.

22.3 EXTERNAL DISTRIBUTION OF STUDY DOCUMENTS

The NIDDK will be responsible for distribution of study documents and manuscripts requested by individuals not associated with the MDRD Study.

22.4 DATA FORMS

The Data Coordinating Center will maintain a complete set of all study forms used in the collection of data, including information collected to ascertain quality standards of the central laboratories. At the end of the study, these forms, without personal identifiers, will be microfiched and forwarded to the NIDDK. Clinical centers will maintain a file on each patient which will become a part of the individual's medical record at the conclusion of the MDRD Study.

22.5 DATA TAPES AND ANALYSIS OF RESULTS

The Data Coordinating Center will prepare a computer tape of study data, results, and analysis at the conclusion of the study. This tape will be accompanied by appropriate documentation. One copy will be forwarded to NIDDK and one to the National Technical Information Service (NTIS), U.S. Department of Commerce, Springfield, Virginia so that the information may be generally available, at a small charge, to the scientific community.

The Data and Nutrition Coordinating Centers will prepare a data tape of analysis pertaining to each major study paper. At the end of the Data and Analysis Phase (Phase IV), all of these tapes with appropriate accompanying documentation will also be submitted to NIDDK and NTIS.

The Data and Nutrition Coordinating Centers will provide documentation of all formulas and statistical analyses used in the study or referred to in the study documents. This information will also be made available to NIDDK and NTIS.

22.6 LABORATORY SPECIMENS AND MATERIALS

All after thought specimens collected by the central laboratories will be kept for long-term storage until the end of the MDRD Study. At that time, the Steering Committee will decide as to the disposition of these specimens. EKGs and other materials will be stored at the Data Coordinating Center until the end of the study at which time they will be offered to each clinical center for incorporation in the medical records of individual patients. All specimens and materials not claimed or undesignated by the Steering Committee will be destroyed.

SECTION 23

SCHEDULE OF PATIENT EVENTS - PHASE III

23.1 SCREENING

Prior to Screening Visit

Eligibility and exclusion criteria checked.
ID assignment (Form 1). Form 2 if patient does not attend the Screening Visit.

Screening Visit (Form 3):

Review of eligibility and exclusion criteria.
Serum creatinine and albumin measurements, if necessary.
Height, weight and elbow breadth.
Education regarding MDRD Study.
Instructions on how to collect a 24-hour urine, how to prepare for a GFR.
Informed consent.

23.2 BASELINE

Up to 3 Days prior to Visit 0:

Special clinic visit for a pregnancy test for menstruating females. (Result recorded on Form 16.)

Day prior to Visit 0:

Collect a 24-hour urine sample.
Begin fasting for GFR and fasting blood test.

Baseline Visit 0: The Demographic and Baseline Exam.

GFR measurement (Form 16).
Full exam and medical history (Form 4, 26).
Height, elbow breadth.
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
1-day food recall (Form 62).
Distribute nutrition history questionnaire (Form 78) if the patient did not complete it prior to the B0 Visit.
Instruct patient in procedure for completing 3-day food record (Form 64).
Distribute Dietary Satisfaction Questionnaire (Form 74).

Between Visit 0 and Visit 0-A: (2 Weeks)

Assessment of B0 GFR.
Complete a 3-day food record from days 5-7 (Form 64).

Baseline Visit 0-A:

Review of the 3-day food record (Form 64).
Assess usual dietary protein intake.
Review Dietary Satisfaction Questionnaire (Form 74).
Anthropometry (Form 65).

Between Visit 0-A and Visit 1: (3 Weeks)

Day prior to Visit 1: Collect a 24-hour urine sample.
Calculate Baseline Diet Prescription (Form 70).

Baseline Visit 1:

Exam (no labs) (Form 5, 26).
Physical Activity Questionnaire (Form 48).
Assign Baseline Diet Prescription (Form 70).
Bring 24-hour urine collection (Form 17).
Renal Diagnosis Form (Form 7).

Day Prior to Visit 2:

Collect a 24-hour urine to bring to Visit 2.

Baseline Visit 2:

Exam (Form 5, 26).
Anthropometry.
Bring 24-hour urine collection (Form 17).
EKG (Form 18).
Distribute 3-day food record (Form 64).

Between Visit 2 and Visit 3: (4 Weeks)

Complete a 3-day food record (Form 64).

Up to 3 Days prior to Visit 3:

Special clinic visit for a pregnancy test for menstruating females. (Result recorded on Form 16.)

Day prior to Visit 3:

Collect a 24-hour urine to bring to Visit 3.
Begin fasting for GFR and fasting blood test.

SECTION 23

SCHEDULE OF PATIENT EVENTS - PHASE III

23.1 SCREENING

Prior to Screening Visit
Eligibility and exclusion criteria checked.
ID assignment (Form 1). Form 2 if patient does not attend the Screening Visit.

Screening Visit (Form 3):
Review of eligibility and exclusion criteria.
Serum creatinine and albumin measurements, if necessary.
Height, weight and elbow breadth.
Education regarding MDRD Study.
Instructions on how to collect a 24-hour urine, how to prepare for a GFR.
Informed consent.
Economic Information Form 29.
Recruitment Information Form 50.

23.2 BASELINE

Up to 3 Days prior to Visit 0 or at B0
Special clinic visit for a pregnancy test for menstruating females. (Result recorded on Form 16.)

Day prior to Visit 0:
Collect a 24-hour urine sample.
Begin fasting for GFR and fasting blood test.

Baseline Visit 0: The Demographic and Baseline Exam.
GFR measurement (Form 16).
Full exam and medical history (Form 4, 26).
Height, elbow breadth.
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
1-day food recall (Form 62).
Distribute nutrition history questionnaire (Form 78) if the patient did not complete it prior to the B0 Visit.
Instruct patient in procedure for completing 3-day food record (Form 64).
Distribute Dietary Satisfaction Questionnaire (Form 74).

Between Visit 0 and Visit 0-A: (2 Weeks)
Assessment of B0 GFR.
Complete a 3-day food record from days 5-7 (Form 64).

Baseline Visit 0-A:
Review of the 3-day food record (Form 64).
Assess usual dietary protein intake.
Review Dietary Satisfaction Questionnaire (Form 74).
Anthropometry (Form 65).

Between Visit 0-A and Visit 1: (3 Weeks)
Day prior to Visit 1: Collect a 24-hour urine sample.
Get Baseline Diet Prescription Report.

Baseline Visit 1:
Exam (no labs) (Form 5, 26).
Physical Activity Questionnaire (Form 48).
Assign Baseline Diet Prescription
Bring 24-hour urine collection (Form 17).
Renal Diagnosis Form (Form 7).

Day Prior to Visit 2:
Collect a 24-hour urine to bring to Visit 2.

Baseline Visit 2:
Exam (Form 5, 26).
Anthropometry.
Bring 24-hour urine collection (Form 17).
EKG (Form 18).
Distribute 3-day food record (Form 64).

Between Visit 2 and Visit 3: (4 Weeks)
Complete a 3-day food record (Form 64).

Up to 3 Days prior to Visit 3 or at B3:
Special clinic visit for a pregnancy test for menstruating females. (Result recorded on Form 16.)

Day prior to Visit 3:
Collect a 24-hour urine to bring to Visit 3.
Begin fasting for GFR and fasting blood test.

Baseline Visit 3:
GFR measurement (Form 16).
Exam (Form 5, 26).
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Quality of Well Being (Form 27).
Symptom Check List (Form 28).

Between Baseline Visit 3 and Randomization (2 week target, 6 week maximum):
Assessment of Blood Pressure at B3.
Assessment of GFR at B3.
Assessment of Urinary Protein Excretion at B3.
Assessment of Mean Baseline Estimated Protein Intake.
Assessment of Compliance to Study Protocol.
Additional assessments at B3.
Sign Follow-Up Consent Form before Randomization.

23.3 RANDOMIZATION (Form 9)

Between Randomization and Follow-up Visit 1 (2 week target):
Calculate Study Diet Prescription (Forms 71 & 72).
Complete 7-day menu plan.

23.4 FOLLOW-UP

Day prior to Visit 1:
Collect a 24-hour urine to bring to Visit 1.

Follow-Up Visit 1:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Assign Study Diet Prescription (Forms 71 & 72).
Begin intervention for new eating pattern.
Receive supplements as appropriate.
Patient Symptom Form (Form 26).
Complete Dietary Information Summary Form (Form 75).

Follow-Up Visit 1A:
Distribute 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).

Between Visit 1A and Visit 2:
Complete a 3-day food record (Form 64).

Up to 3 days prior to visit 2 or at F2:
Special clinic visit for a pregnancy test for menstruating females. (Record results on Form 16.)

Day prior to Visit 2:
Collect a 24-hour urine to bring to Visit 2.
Begin fasting for GFR and fasting blood test.

Follow-Up Visit 2:
GFR measurement (Form 16).
Exam (Form 5, 26).
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73) (Diet K only).
Patient Symptom Form (Form 26).

Follow-up Visit 2A:
Complete Monthly Dietary Counseling Summary Form (Form 76).

Between Visit 2-A and Visit 3:

Day prior to Visit 3:
Collect a 24-hour urine to bring to Visit 3.

Follow-Up Visit 3:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73)
Patient Symptom Form.
Distribute 3-day food record (Form 64).

Between Visit 3 and Visit 4:
Complete a 3-day food record (Form 64).

Up to 3 Days prior to Visit 4 or at F4
Special clinic visit for a pregnancy test if you are a menstruating females. (Record results on Form 16.)

Day prior to Visit 4:
Collect a 24-hour urine to bring to Visit 4.
Begin fasting for GFR and fasting blood test.

Follow-Up Visit 4:
GFR measurement (Form 16).
Exam (Form 5, 26).
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Patient Symptom Form (Form 26).
Symptom Check List.

Day prior to Visit 5:
Collect a 24-hour urine to bring to Visit 5.

Follow-Up Visit 5:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Pill count; receive new supplements (Form 73).
Patient Symptom Form (Form 26).
Distribute 3-day food record (Form 64).

Between Visit 5 and Visit 6:
Complete a 3-day food record (Form 64).

Day prior to Visit 6:
Collect a 24-hour urine to bring to Visit 6.

Follow-Up Visit 6:
Exam (Form 5, 26).
Anthropometry (Form 65).
Blood measurements (not fasting) (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Quality of Well Being (Form 27).
Patient Symptom Form (Form 26).
Dietary Satisfaction Questionnaire (Form 74).

Day prior to Visit 7:
Collect a 24-hour urine to bring to Visit 7.

Follow-Up Visit 7:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Patient Symptom Form (Form 26).
Distribute 3-day food record (Form 64).

Between Visit 7 and Visit 8:
Complete a 3-day food record (Form 64).

Up to 3 Days prior to Visit 8 or at F8
Special clinic visit for a pregnancy test for menstruating females. (Record results on Form 16).

Day prior to Visit 8:
Collect a 24-hour urine to bring to Visit 8.
Begin fasting for GFR and fasting blood test.

Follow-Up Visit 8:
GFR measurement (Form 16).
Exam (Form 5, 26).
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Symptom Check List.
Patient Symptom Form (Form 26).

Day prior to Visit 9:
Collect a 24-hour urine to bring to Visit 9.

Follow-Up Visit 9:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Patient Symptom Form (Form 26).
Distribute 3-day food record (Form 64).

Between Visit 9 and Visit 10:
Complete a 3-day food record (Form 64).

Day prior to Visit 10:
Collect a 24-hour urine to bring to Visit 10.

Follow-Up Visit 10:
Exam (Form 5, 26).
Anthropometry (Form 65).
Physical Activity Questionnaire (Form 48).
Blood measurements (not fasting) (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Patient Symptom Form (Form 26).

Day prior to Visit 11:
Collect a 24-hour urine to bring to Visit 11.

Follow-Up Visit 11:
Exam (Form 5, 26).
Bring 24-hour urine collection (Form 17).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
EKG (Form 18).
Patient Symptom Form (Form 26).
Distribute 3-day food record (Form 64).

Between Visit 11 and Visit 12:
Complete a 3-day food record (Form 64).

Up to 3 Days prior to Visit 12 or at F12
Special clinic visit for a pregnancy test for menstruating females. (Record results on Form 16.)

Day prior to Visit 12:
Collect a 24-hour urine to bring to Visit 12.
Begin fasting for GFR and fasting blood test.

Follow-Up Visit 12:
GFR measurement (Form 16).
Exam (Form 5, 26).
Fasting blood measurements (Form 6, 17).
Bring 24-hour urine collection (Form 17).
Review and document 3-day food record (Form 64).
Complete Monthly Dietary Counseling Summary Form (Form 76).
Pill count; receive new supplements (Form 73).
Dietary Satisfaction Questionnaire (Form 74).
Quality of Well Being (Form 27).
Symptom Check List (Form 28).
Patient Symptom Form (Form 26).
NOTE: From this point on, the yearly cycle should repeat itself. Visit 13 will be the same as Follow-up Visit 1, etc. (There is no GFR at Visit 14, and there are no special visits between Visits 12 and 13 or between Visits 13 and 14.)

POST STOP POINT SCHEDULE OF PATIENT EVENTS

At the Time of the Stop Point (P1.0):

GFR (Form 16) (Except for a GFR Stop Point)
Blood Tests as done for F-4.0 (Forms 6, 17)

Abbreviated Follow-Up Visits:

NOTE: Abbreviated follow-up visits are scheduled every 4 months starting with what would have been the next "four-month" visit if the patient was still in follow-up (i.e., 4.0, 8.0, etc. visit type = A).

Four Month Abbreviated Visits:

24-Hour Urine (Form 17)	(Except for Dialysis/Transplant)
3 Day Food Record (Form 64)	(First four-month visit only)
Serum Creatinine (Form 17)	(Except for Dialysis/Transplant)
Serum Albumin (Form 17)	
Serum Transferrin (Form 17)	
Anthropometric Measurements (Form 65)	(First four-month visit only)
GFR (Form 16)	(Except for Dialysis/Transplant)
Physical Exam (Forms 12, 46)	

Annual Abbreviated Visits:

24-Hour Urine (Form 17)	(Except for Dialysis/Transplant)
3 Day Food Record (Form 64)	
Serum Creatinine (Form 17)	(Except for Dialysis/Transplant)
Serum Albumin (Form 17)	
Serum Transferrin (Form 17)	
Anthropometric Measurements (Form 65)	
GFR (Form 16)	(Except for Dialysis/Transplant)
Physical Exam (Forms 12, 46)	
Give QWB Symptom List and Inform DCC	
SCL-90 (Form 28)	
Patient Symptom Form (Form 26)	
Annual Follow-Up Information (Form 13)	

Events to be documented:

Death (Form 15)
Initiation of Dialysis or Transplantation (on Next Form 12)
Intercurrent Events Requiring Hospitalization (Form 10)

23.5 STUDY F SCHEDULE OF PATIENT EVENTS

Patients who enroll in Baseline but drop out during the course of Baseline or are excluded at the end of Baseline are not randomized and followed in Study F.

Note: It may not be necessary to have study visits to collect data for Study F. "Visits" below refer to time of data collection.

Study F "Visit":

(Schedule every six months from the date of the B-0 Visit. Window is +/- 30 days. Label X6, X12, etc. Six months visits should be phone calls. Twelve month visits should be actual visits.)

Exam.
Blood pressure.
Blood tests (serum creatinine and albumin) (FORM 17, 47).
Study F "Visits" continue every 6 months until Study termination.

SECTION 24

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SECTION 25

GLOSSARY OF ABBREVIATIONS

B#	B0 refers to Baseline Visit 0, B1 refers to Baseline Visit 1, etc.
Br	Bromide
CAP	College of American Pathologists
CBL	Central Biochemistry Laboratory
CCF	Cleveland Clinic Foundation
CDDT	Computerized Diet Design Tool
CV	Coefficient of Variation
D_2O	Deuterium Oxide
DCC	Data Coordinating Center
DDC	Drug Distribution Center
Diet K	.28 g protein/kg standard body weight/day
Diet L	.575 g protein/kg standard body weight/day
Diet M	1.0 to 1.4 g protein/kg standard body weight/day
DPI	Dietary Protein Intake
EE	Keto Acid Mixture EE
Expert Panel	Expert Panel on Detection, Evaluation and Treatment of High Blood Pressure in Adults
F#	F1 refers to Follow-Up Visit 1, F2 refers to Follow-Up Visit 2, etc.
GFR	Glomerular Filtration Rate
HBV	High Biological Value Protein
HCFA	Health Care Financing (Finance) Administration

JNC Report	Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
MAP	Mean Arterial Pressure
MDRD Study	Modification of Diet in Renal Disease Study
NCC	Nutrition Coordinating Center
SBW	Standard Body Weight
Study A	A comparison of Diets L and M in patients with GFRs of 25 to 80 ml/min/1.73m^2
Study B	A comparison of Diets K and L in patients with GFRs of 8 to 24 ml/min/1.73m^2
Study C	A within-patient comparison of Study A patients who reach GFR stop points and are put on Diet K
UNA	Urea Nitrogen Appearance
UUN	24-hour Urine Urea Nitrogen

SECTION 26

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The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure

1988 Joint National Committee

• **The National High Blood Pressure Education Program has released three Joint National Committee reports and a task force report on the detection, evaluation, and treatment of high blood pressure. Like its predecessors, the 1988 Joint National Committee report was developed using the consensus process; it is based on the latest scientific research and reflects the state of the art regarding hypertension management. This report updates findings of previous reports in several respects: it broadens the step-care approach to provide more flexibility for clinicians; encourages greater patient involvement in the treatment program; emphasizes a consideration of the quality of life in the management of patients; and addresses the cost of care. It also provides more emphasis on control of other risk factors for cardiovascular disease; includes a discussion of the new cholesterol guidelines; recommends a reduction in alcohol consumption; and discusses the use of calcium and fish oil supplementation. This document expands earlier reports on special populations, including blacks and other racial and ethnic minority groups, young and elderly patients, pregnant patients, surgical candidates, and hypertensive patients with cerebrovascular disease, coronary artery disease, left ventricular hypertrophy, congestive heart failure, peripheral vascular disease, renal disease, chronic obstructive pulmonary disease or bronchial asthma, gout, diabetes mellitus, and hyperlipidemia. The report also updates previous drug tables to include new drugs, revised recommended doses of some drugs, and drug interactions. Consideration of step-down therapy after blood pressure has been controlled is suggested. This report is intended as a guide for practicing physicians and other health professionals in their care of hypertensive patients and as a reference for those participating in the many community high blood pressure control programs throughout the country.**

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Since publication of the first report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, remarkable changes have occurred in the control of hypertension. The public is more knowledgeable about high blood pressure, more likely to visit a physician for hypertension, and more likely to follow medical advice. These practices have led to impressive gains in hypertension control and have contributed to the 50% decline in the national age-adjusted stroke mortality rate since 1972. During this period, there has also been a 35% decline in coronary artery disease mortality.

If this progress is to continue, a number of events must occur. The hypertension control process must be extended to the entire population, and aggressive treatment must also take into consideration the life-styles and concomitant conditions of individual patients. The availability of an increased variety of therapeutic approaches provides the

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From the National High Blood Pressure Education Program, Bethesda, Md.

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Table 1.—Classification of BP in Adults Aged 18 Years or Older*

BP Range, mm Hg	Category†
DBP	
<85	Normal BP
85-89	High-normal BP
90-104	Mild hypertension
105-114	Moderate hypertension
≥115	Severe hypertension
SBP, when DBP	
<90 mm Hg	
<140	Normal BP
140-159	Borderline isolated systolic hypertension
≥160	Isolated systolic hypertension

*Classification based on the average of two or more readings on two or more occasions. BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

†A classification of borderline isolated systolic hypertension (SBP, 140 to 159 mm Hg) or isolated systolic hypertension (SBP, ≥160 mm Hg) takes precedence over high-normal BP (DBP, 85 to 89 mm Hg) when both occur in the same person. High-normal BP (DBP, 85 to 89 mm Hg) takes precedence over a classification of normal BP (SBP, <140 mm Hg) when both occur in the same person.

Table 2.—Follow-up Criteria for Initial BP Measurement for Adults Aged 18 Years or Older*

BP Range, mm Hg	Recommended Follow-up
DBP	
<85	Recheck within 2 y
85-89	Recheck within 1 y
90-104	Confirm within 2 mo
105-114	Evaluate or refer promptly to source of care within 2 wk
≥115	Evaluate or refer immediately to source of care
SBP, when DBP	
<90 mm Hg	
<140	Recheck within 2 y
140-199	Confirm with 2 mo
≥200	Evaluate or refer promptly to source of care within 2 wk

*BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure. If recommendations for follow-up of DBP and SBP are different, the shorter recommended time for recheck and referral should take precedence.

opportunity to improve hypertension control while minimizing adverse effects that may influence cardiovascular complications and adherence to therapy.

PURPOSE OF THE REPORT

This report serves two purposes: (1) to guide practicing physicians and other health professionals in their care of hypertensive patients; and (2) to guide health professionals participating in the many community high blood pressure programs.

The National High Blood Pressure Education Program Coordinating Committee anticipates the release of additional publications that will expand on the guidelines presented herein.

DEFINITION AND PREVALENCE OF HIGH BLOOD PRESSURE

As many as 58 million people in the United States have elevated blood pressure (systolic blood pressure [SBP] of 140 mm Hg or greater and/or diastolic blood pressure [DBP] of 90 mm Hg or greater) or are taking antihypertensive medication. The prevalence rate of hypertension increases with age and is higher in blacks than in whites.[1] Regional variations in blood pressure have also been observed. For example, blacks in the southeastern United States have a greater prevalence rate and severity of hypertension as well as a greater stroke death rate than do blacks in other areas of the country.

Risk of cardiovascular complications related to hypertension increases continuously with increasing levels of both SBP and DBP. Table 1 provides a categorical scheme based on risk level for classification of SBP and DBP for persons aged 18 years and older. High-normal blood pressure is included as a category for monitoring purposes. In this classification scheme, the term *mild* is relative to the other categories and should not be interpreted to patients as unimportant. Data from clinical trials have indicated that mild hypertension requires medical attention.

DETECTION, CONFIRMATION, AND REFERRAL

Hypertension control begins with detection and requires continued surveillance. Health care professionals are strongly encouraged to measure blood pressure at each patient visit. Most adults already know their blood pressure value or have had it measured. Although active detection efforts should continue, mass screening programs for this purpose are not seldom indicated. Rather, resources should be concentrated primarily on the following: controlling blood pressure in those persons already identified as having hypertension; detecting those groups at high risk of developing hypertension; and contacting those with limited access to the health care system. Wherever blood pressure measurements are obtained, the following guidelines are recommended for identifying persons at risk and bringing them under continuing medical care.

Measurement

Hypertension should not be diagnosed on the basis of a single measurement. Initial elevated readings should be confirmed on at least two subsequent visits, with average DBP levels of 90 mm Hg or greater or SBP levels of 140 mm Hg or greater required for diagnosis.

Since blood pressure is variable and can be affected by multiple extraneous factors, it should be measured in such a manner that the values obtained are representative of patients' usual level.[2] The following techniques are strongly recommended:

1. Patients should be seated with their arm bared, supported, and positioned at heart level. They should not have smoked or ingested caffeine within 30 minutes prior to measurement.
2. Measurement should begin after five minutes of quiet rest.
3. The appropriate cuff size must be used to ensure an accurate measurement. The rubber bladder should encircle at least two thirds of the arm. Several sizes of cuffs (eg, child, adult, and large adult) should be available.
4. Measurements should be taken with a mercury sphygmomanometer, a recently calibrated aneroid manometer, or a validated electronic device.
5. Both the SBP and DBP should be recorded. The disappearance of sound (phase V) should be used for the diastolic reading.
6. Two or more readings should be averaged. If the first two readings differ by more than 5 mm Hg, additional readings should be obtained.

Patients should be informed of their blood pressure reading and advised of the need for periodic remeasurement. Table 2 provides follow-up advice based on the initial blood pressure measurement.

Confirmation and Follow-up

Repeated blood pressure measurements will determine whether initial elevations persist and require close observation or prompt attention, or whether they have returned to normal and need only periodic remeasurement. Initial blood pressure readings that are markedly elevated (ie, DBP of 115 mm Hg or greater) or associated with evidence of target organ damage may require immediate drug therapy. The timing of subsequent readings should be based on the initial blood pressure level (Table 2). In patients with mild hypertension, observation over a three- to six-month interval may be elected before initiating drug therapy since pressures may return to normal during that time. Individuals with such temporary elevations of pressure are at increased risk of later developing persistent hypertension and should be informed accordingly and observed at approximately six-month intervals.

As an adjunct to repeated office readings, blood pressure may be measured at the work site or at home by patients (or a friend or family member), provided they are instructed in proper measurement techniques. A standard cuff with sphygmomanometer is generally the most practical instrument. Automatic and semiautomatic devices using acoustic or oscillometric methods and digital display of readings are acceptable for home use, provided that the manufacturer has documented the validity and reliability of the unit and that it is periodically calibrated and maintained.[3]

Twenty-four-hour ambulatory blood pressure devices are currently available, but such ambulatory monitoring is not recommended for diagnosis and follow-up of the majority of hypertensive patients.[3] In a few patients (eg, those in whom therapeutic decisions may be difficult because of marked lability in blood pressure), 24-hour monitoring may be of value. However, the technique is not usually cost-effective.

EVALUATION AND DIAGNOSIS

Clinical evaluation of patients with confirmed hypertension should help answer the following questions: (1) Does the patient have primary or secondary (possibly reversible) hypertension? (2) Is target organ involvement present? (3) Are cardiovascular risk factors other than high blood pressure present?

Medical History

A medical history should include the following: (1) family history of high blood pressure and cardiovascular disease; (2) patient history of cardiovascular, cerebrovascular, and renal disease, as well as diabetes mellitus; (3) known duration and levels of elevated blood pressure; (4) results and side effects of previous antihypertensive therapy; (5) history of weight gain, exercise activities, sodium intake, fat intake, and alcohol use; (6) symptoms suggesting secondary hypertension; (7) psychosocial and environmental factors (eg, emotional stress, cultural food practices, and socioeconomic status) that may influence blood pressure control; and (8) other cardiovascular risk factors (including obesity, smoking, hyperlipidemia, and carbohydrate intolerance).

Health practitioners should obtain a history of all prescribed and over-the-counter medications from all patients. Several medications may either raise blood pressure or interfere with the effectiveness of antihypertensive drugs. These drugs include, but are not limited to, oral contraceptives, steroids, nonsteroidal anti-inflammatory agents, nasal decongestants and other cold remedies, appetite suppressants, cyclosporin, tricyclic antidepressants, and monoamine oxidase inhibitors.

Physical Examination

The initial physical examination should include the following: (1) two or more blood pressure measurements with the patient either supine or seated and standing; (2) verification in the contralateral arm (if values are discrepant, the higher value should be used); (3) measurement of height and weight; (4) funduscopic examination for arteriolar narrowing, arteriovenous compression, hemorrhages, exudates, and papilledema; (5) examination of the neck for carotid bruits, distended veins, and an enlarged thyroid gland; (6) examination of the heart for increased rate, increased size, precordial heave, clicks, murmurs, arrhythmias, and S_3 and S_4 heart sounds; (7) examination of the abdomen for bruits, enlarged kidneys, masses, and dilation of the aorta; (8) examination of the extremities for diminished or absent peripheral arterial pulsations, bruits, and edema; and (9) neurologic assessment.

Secondary hypertension is rare; nevertheless, examination should seek to eliminate this possibility. Physical findings that are suggestive of secondary hypertension include abdominal or flank masses (polycystic kidneys); abdominal bruits, particularly those that lateralize or have a diastolic component (renovascular disease);[4] delayed or absent femoral arterial pulses or decreased blood pressure in legs (aortic coarctation); truncal obesity with pigmented striae (Cushing's syndrome); and tachycardia, orthostatic hypotension, sweating, and pallor (pheochromocytoma). Additional diagnostic procedures may be indicated to discover causes of secondary hypertension, particularly in patients (1) in whom age, history, physical examination, severity of hypertension, or initial laboratory finding suggests secondary hypertension; (2) whose blood pressures are responding poorly to drug therapy; (3) with well-controlled hypertension whose blood pressures begin to increase; and (4) with accelerated or malignant hypertension.

Laboratory Tests

A few simple laboratory tests should be performed before initiating therapy. These include determination of hemoglobin and hematocrit values; complete urinalysis; measurement of serum potassium, calcium, and creatinine levels; electrocardiography; and measurement of plasma cholesterol (total and high-density lipoprotein) (if abnormal, plasma triglycerides and calculated low-density lipoprotein levels), plasma glucose (fasting, if possible), and serum uric acid concentrations.

Some of these tests are needed for determining severity of cardiovascular disease and possible causes of hypertension. The remainder relate to other cardiovascular risk factors or provide baseline values for judging biochemical effects of therapy.

Opinions differ regarding risks and specificity of some diagnostic procedures. An automated battery of blood chemistry tests is often used to minimize costs. Physicians may select additional tests based on their clinical judgment. Type and frequency of repeated laboratory tests should be based on the severity of target organ damage and the effects of the selected treatment program.

TREATMENT

The goal of treating patients with hypertension is to prevent morbidity and mortality associated with high blood pressure. The objective is to achieve and maintain arterial blood pressure below 140/90 mm Hg, if possible.

Although numerous multicenter clinical trials have demonstrated the benefits of therapy, the decision to initiate

treatment in individual patients requires physicians to consider at least two factors: the severity of blood pressure elevation and the presence of other complications. The effectiveness of antihypertensive drugs in reducing elevated arterial pressure is well established. In this regard, recent evidence suggests that nonpharmacologic approaches, particularly weight reduction, salt restriction, and moderation of alcohol consumption, may lower elevated pressure and improve the efficacy of pharmacologic agents. Therefore, nonpharmacologic approaches are used both as definitive intervention and as an adjunct to pharmacologic therapy and should be considered for all antihypertensive therapy.[6] Clinicians may wish to refer to other health providers for specific counseling related to life-style changes.

Nonpharmacologic Therapy

Some of the following nonpharmacologic therapies are recommended for hypertension control. The remainder are included to reduce other cardiovascular risk factors.

Weight Reduction.—As shown by worldwide epidemiologic studies, obesity and blood pressure are closely associated. Moreover, a strong correlation exists between body weight and blood pressure and between increases in body weight and subsequent development of hypertension.[6] Weight reduction may reduce arterial pressure in overweight hypertensive patients; this fall in pressure may occur with caloric restriction alone, even without reduction in sodium intake and before ideal body weight is achieved.

Because of the clear relationship between obesity and blood pressure, all obese hypertensive adults should participate in weight reduction programs, with goal body weight being within 15% of desirable weight. Concomitantly, health professionals should vigorously promote weight control, particularly for those at increased risk of becoming hypertensive because of a family history of this condition. These recommendations are made with the clear recognition that weight reduction is difficult to achieve and that the rate of recidivism is high.

Restriction of Alcohol.—Excess alcohol intake may lead to elevated blood pressure, poor adherence to antihypertensive therapy, and, occasionally, refractory hypertension.[7] Therefore, for controlling hypertension, those who drink should do so in moderation (ie, no more than 30 mL [1 oz] of ethanol daily). Thirty milliliters (1 oz) of ethanol is contained in 60 mL [2 oz] of 100-proof whiskey, approximately 240 mL [8 oz] of wine, or 720 mL [24 oz] of beer.

Restriction of Sodium.—A high sodium intake plays a critical role in maintaining the elevated blood pressure of some hypertensive patients and in limiting the effectiveness of certain antihypertensive drugs. Moreover, some patients with mild or moderate blood pressure elevation may achieve control through moderate sodium restriction to 70 to 100 mEq/d (approximately 1.5 to 2.5 g of sodium or 4 to 6 g of salt). There is no easy way to identify those patients who will benefit from sodium restriction.[8] Although the effect of sodium restriction on individual patients cannot be predicted, this degree of limitation produces no serious adverse consequences. Since much of daily sodium intake comes from prepared foods,[9] merely refraining from adding salt at the table is usually inadequate to control hypertension. Thus, proper counseling is necessary to achieve moderate sodium restriction. This counseling should include reference to sodium labeling of canned, frozen, and other processed foods, both to reduce sodium intake and to maintain adequate overall nutrition.

Role of Other Cations.—Data have suggested that reduced potassium intake may be associated with high blood pressure[10] and that high potassium intake (>80 mEq or 3 to 4 g/d) has a modest blood-pressure-lowering effect.[11] The evidence in this regard is still developing, and if increased potassium intake is recommended, it should be restricted to those patients who have normal renal function and who are not taking drugs known to raise serum potassium levels, such as potassium-sparing diuretics and angiotensin-converting enzyme (ACE) inhibitors.

Increased intake of calcium has been reported to lower blood pressure in some individuals.[12] However, some studies have suggested that a direct relationship exists between serum calcium concentration and blood pressure.[13] It is still not known which patients will benefit from dietary calcium supplementation. Moreover, the risk for developing renal calculi may become greater with increased dietary calcium. The data concerning calcium appear inadequate at this time to warrant specific recommendations. Similarly, the evidence regarding magnesium, zinc, and lead is too meager to justify any recommendations.

Tobacco Avoidance.—Although nicotine may increase arterial blood pressure acutely, prolonged use is not associated with an increased prevalence of hypertension. However, individuals who smoke definitely increase their risk for cancer and pulmonary diseases and, overall, more than double their cardiovascular risk for coronary artery disease and sudden death.[14,15] Smokers appear to have a higher frequency of malignant hypertension[16] and subarachnoid hemorrhage.[17] In addition, studies have shown an interaction between propranolol hydrochloride and smoking in which smokers require larger doses of this drug to achieve reductions in blood pressure similar to those attained by nonsmokers. Furthermore, risk reduction induced by antihypertensive therapy may not be as great in smokers as in nonsmokers.[18]

The benefits of tobacco avoidance have been proven conclusively, and smoking cessation is strongly recommended. A key component of every therapeutic regimen for hypertension should include counseling to help patients stop smoking.[19]

Biofeedback and Relaxation.—Recent data concerning behavioral approaches to hypertension management have demonstrated that various relaxation and biofeedback therapies produce modest long-term reductions in blood pressure in selected groups.[20,21] These studies have suggested that combining biofeedback and relaxation procedures may produce better therapeutic results than either approach alone.[22] Such regimens are most useful for the treatment of mild hypertension and may also be used in combination with pharmacologic therapy. These promising methods have yet to be subjected to rigorous clinical trial evaluation and should not be considered as definitive treatment for patients with high blood pressure.

Exercise.—A regular aerobic exercise program (eg, walking, bicycling, jogging, or swimming) facilitates weight control and may be helpful in reducing blood pressure. Health practitioners should advise hypertensive patients who are initiating an exercise program to do so gradually and after appropriate clinical evaluation.

Modification of Dietary Fats.—Some studies have suggested that low intake of saturated fat and high intake of polyunsaturated fat are associated with arterial blood pressure[23]; others have not demonstrated this effect.[24] The evidence is still inadequate to recommend such dietary changes for hypertension control, but these modifications could be important for lowering blood cholesterol and reducing risk of developing coronary artery disease.

Public attention has focused recently on the value of fish and fish oils in the diet as a result of observations that populations eating large amounts of fish have lower rates of coronary artery disease. Eating fish that are rich in the polyunsaturated ω-3 fatty acids may lower blood levels of triglycerides. However, fish oil supplementation can interfere with the ability of blood to clot and, in some individuals, may cause excessive bleeding. Therefore, while fish consumption is recommended, the health benefits of fish oil capsules have not been proven.

Pharmacologic Therapy

Efficacy.—Reduction of blood pressure with drugs clearly decreases cardiovascular mortality and morbidity in patients with DBP greater than 104 mm Hg.[25] In patients with mild hypertension (DBP, 90 to 104 mm Hg), trials of antihypertensive therapy have shown protection against stroke, congestive heart failure, progression to more severe levels of hypertension, and all-cause mortality.[25-28] a 30% to 50% reduction in both fatal and nonfatal strokes with therapy has been demonstrated. These clinical trials usually involved diuretics as initial therapy, although the Medical Research Council trial did include a propranolol-treated group.[28] Clinical trials have not yet produced long-term data on the effects of α-blockers, ACE inhibitors, or calcium antagonists on cardiovascular complications and mortality in hypertensive patients.

Protection against the complications of coronary artery disease as a result of antihypertensive therapy has not been convincingly demonstrated. A summary analysis of nine clinical trials shows a trend of reduced mortality from coronary artery disease in the intervention groups, but the difference does not reach statistical significance.[29] Many explanations have been proposed for the lack of demonstrated benefit for coronary artery disease, including: (1) multifactorial causes of coronary artery disease and the failure to reduce other risk factors; (2) reduction of perfusion to below a critical level in the coronary circulation by lowering blood pressure in those individuals with preexisting coronary artery disease[30]; (3) insufficient sample size, inadequate duration of clinical trials to detect favorable changes, and inappropriate type of population studied; (4) undesired effects of the antihypertensive drugs causing increased coronary risk; and (5) initiation of studies too late in the natural course of hypertension. However, it is unknown whether these explanations account for the inability of studies to demonstrate significant effects of therapy on the incidence of coronary artery disease.

Mild Hypertension.—*Selection of Patients for Drug Treatment.*—The benefits of drug therapy appear to outweigh any known risks to individuals with a persistently elevated DBP greater than 94 mm Hg and to those with lesser elevations who are otherwise at high risk (eg, men, smokers, or patients with target organ damage, diabetes mellitus, hyperlipidemia, or other major risk factors for cardiovascular disease). Data from the 1976 through 1980 National Health and Nutrition Examination Survey indicate that approximately 58% of the individuals (age range, 20 to 74 years) with DBPs 90 to 94 mm Hg also have one or more of the following conditions: smoking, self-reported diabetes, or serum cholesterol levels equal to or greater than 6.21 mmol/L (≥240 mg/dL) (C. Haines, MPH [NHBLI], unpublished data, December 1987).

Patients whose DBPs fall between 90 and 94 mm Hg and who are otherwise at relatively low risk of developing cardiovascular disease should be treated with nonpharmacologic approaches. Some experts believe that drug therapy should be initiated in these patients if the DBP remains above 90 mm Hg despite vigorous attempts with nonpharmacologic approaches. Physicians who elect not to use drug therapy for patients in the 90- to 94-mm-Hg range should monitor their patients closely, since some will progress to higher levels of blood pressure that clearly warrant antihypertensive drug therapy.

Selection of Drug Treatment for Uncomplicated Hypertension.—Table 3 lists several classes of currently available antihypertensive drugs that have demonstrated antihypertensive efficacy, although individual patients may respond better to one drug than to another. In about half of the patient group with mild hypertension, a moderate dose of any one of several antihypertensive drugs will achieve a DBP reduction of 10 mm Hg or more or lower the DBP to the desired goal (<90 mm Hg).

Initial Drug Therapy.—*The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*[31] recommended that either thiazide-type diuretics or β-blockers be used as initial therapy, unless contraindications exist. Clinical experience obtained since then indicates that ACE inhibitors and calcium antagonists are also useful drugs for this purpose. The Figure illustrates a scheme for individualized stepped care therapy. Some drugs, such as the direct-acting vasodilators (eg, hydralazine and minoxidil) are not well suited for initial monotherapy since they often induce reflexed sympathetic stimulation and fluid retention. However, the large numbers of effective antihypertensive drugs provide many excellent therapeutic options for lowering blood pressure effectively and minimizing side effects.

Subsequent Therapy.—If, after a one- to three-month interval, the response to the initial choice of therapy is inadequate, the patient is not experiencing significant side effects, and adherence to therapy is adequate, three options for subsequent therapy should be considered (Figure): increase the dose of the first drug if it is below the recommended maximum; add an agent from another class; or discontinue the initial choice and then substitute a drug from another class.

Combining antihypertensive drugs with different modes of action using the step-care approach will often allow small doses of drugs to be used to achieve control, thereby minimizing the potential for dose-dependent side effects. If a diuretic is not chosen as the first drug, it will often be required as the second one since fluid retention (pseudotolerance) may be responsible in part for the suboptimal response to nondiuretic agents and since the addition of a diuretic will usually enhance the effects of other drugs. When additional drugs are added and the combination succeeds, a later attempt should be made to reduce the dose and, if possible, to eliminate the initial drug.

Before proceeding to each successive treatment step, physicians should address possible reasons for lack of responsiveness, including those listed in Table 4.

After blood pressure is reduced to goal level and maintenance doses of antihypertensive drugs are stabilized, substituting comparable combination tablets may simplify patients' regimens, reduce medication costs, and promote adherence to a comprehensive antihypertensive treatment program.

Step-Down Therapy and Drug Withdrawal.—For patients with mild hypertension who have satisfactorily controlled their blood pressure through treatment for at least one year, antihypertensive drugs may be reduced in a stepwise fashion. Reduction may be particularly effective in patients who are also following nonpharmacologic therapeutic recommendations. In a study in which medications were discontinued and patients received no nutritional

Table 3.—Antihypertensive Drugs

Type of Drug	Dosage Range, mg/d* Usual Minimum	Usual Maximum
Diuretics		
Thiazides and related sulfonamide diuretics		
Bendroflumethiazide	2.5	5
Benzthiazide	12.5-25	50
Chlorothiazide	125-250	500
Chlorthalidone	12.5-25	50
Cyclothiazide	1	2
Hydrochlorothiazide	12.5-25	50
Hydroflumethiazide	12.5-25	50
Indapamide	2.5	5
Methyclothiazide	2.5	5
Metolazone	1.25	10
Polythiazide	2	4
Quinethazone	25	100
Trichlormethiazide	1-2	4
Loop diuretics†		
Bumetanide‡	0.5	5
Ethacrynic acid‡	25	100
Furosemide‡	20-40	320
Potassium-sparing agents		
Amiloride	5	10
Spironolactone	25	100
Triamterene	50	150
Adrenergic inhibitors		
β-Adrenergic blockers§		
Acebutolol	200	1200
Atenolol	25	150
Metoprolol	50	200
Nadolol	40	320
Penbutolol sulfate	20	80
Pindolol‡	10	60
Propranolol hydrochloride‡	40	320
Propranolol, long-acting	60	320
Timolol‡	20	80
Centrally acting α-blockers		
Clonidine‡	0.1	1.2

Table 3.—Antihypertensive Drugs (cont)

Type of Drug	Dosage Range, mg/d* Usual Minimum	Usual Maximum
Clonidine TTS (Patch)‖	0.1	0.3
Guanabenz‡	4	64
Guanfacine hydrochloride	1	3
Methyldopa‡	250	2000
Peripheral-acting adrenergic antagonists		
Guanadrel sulfate‡	10	100
Guanethidine monosulfate	10	150
Rauwolfia alkaloids		
Rauwolfia (whole root)	50	100
Reserpine	0.1	0.25
α_1-Adrenergic blockers		
Prazosin hydrochloride‡	1-2	20
Terazosin hydrochloride	1-2	20
Combined α-β-adrenergic blocker:		
labetalol‡	200	1800
Vasodilators		
Hydralazine‡	50	300
Minoxidil‡	2.5	80
Angiotensin-converting enzyme inhibitors		
Captopril‡	25-50	300
Enalapril maleate	2.5-5	40
Lisinopril	5	40
Calcium antagonists		
Diltiazem hydrochloride¶	60	360
Nifedipine¶	30	180
Nitrendipine	5	40
Verapamil¶	120	480
Verapamil SR (long-acting)	120	480

*The dosage range may differ slightly from the recommended dosage in the *Physicians' Desk Reference* or package insert.

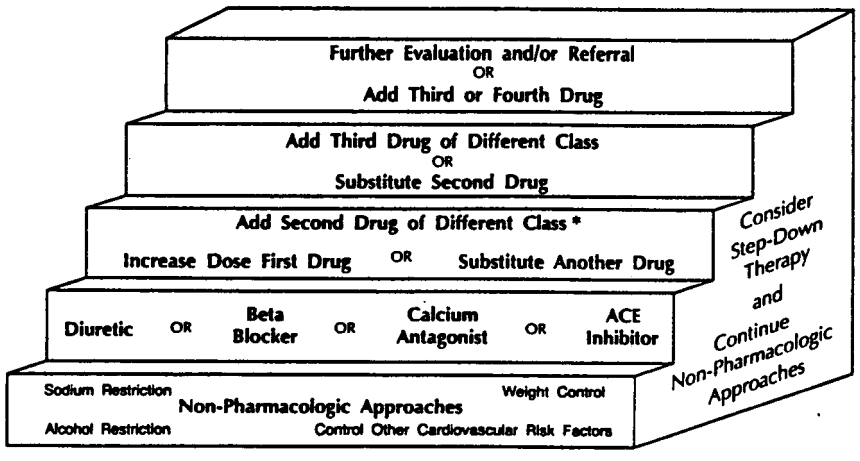
†Larger doses of loop diuretics may be required in patients with renal failure.

‡This drug is usually given in divided doses twice daily.

§Atenolol, metoprolol, and acebutolol are cardioselective; pindolol and acebutolol have partial agonist activity.

‖This drug is administered as a skin patch once weekly.

¶This drug is usually given in divided doses three or four times daily.



Individualized step-care therapy for hypertension. For some patients, nonpharmacologic therapy should be tried first. If blood pressure goal is not achieved, add pharmacologic therapy. Other patients may require pharmacologic therapy initially. In these instances, nonpharmacologic therapy may be helpful adjunct. ACE indicates angiotensin-converting enzyme; asterisk, drugs such as diuretics, β-blockers, calcium antagonists, ACE inhibitors, α-blockers, centrally acting α_2-agonists, rauwolfia serpentina, and vasodilators.

Table 4.—Causes of Refractory Hypertension

- Nonadherence to therapy
- Drug related
  - Doses too low
  - Inappropriate combinations (eg, two centrally acting adrenergic inhibitors)
  - Rapid inactivation (eg, hydralazine)
  - Effects of other drugs
    - Sympathomimetics
    - Antidepressants
    - Adrenal steroids
    - Nonsteroidal anti-inflammatory drugs
    - Nasal decongestants
    - Oral contraceptives
- Associated conditions
  - Increasing obesity
  - Excess alcohol intake: >30 mL/d (1 oz/d)
  - Renal insufficiency
  - Renovascular hypertension
  - Malignant or accelerated hypertension
  - Other causes of hypertension
- Volume overload
  - Inadequate diuretic therapy
  - Excess sodium intake
  - Fluid retention from reduction of blood pressure
  - Progressive renal damage

Table 5.—Drug Interactions in Antihypertensive Therapy

Diuretics
- Diuretics can raise lithium blood levels by enhancing proximal tubular reabsorption of lithium.
- Nonsteroidal anti-inflammatory agents, including aspirin, may antagonize antihypertensive and natriuretic effectiveness of diuretics
- Angiotensin-converting enzyme (ACE) inhibitors magnify potassium-sparing effects of triamterene, amiloride, or spironolactone.
- ACE inhibitors blunt hypokalemia induced by thiazide diuretics.

Sympatholytic agents
- Guanethidine monosulfate and guanadrel sulfate: Ephedrine and amphetamine displace guanethidine and guanadrel from storage vesicles. Tricyclic antidepressants inhibit uptake of guanethidine and guanadrel into these vesicles. Cocaine may inhibit neuronal pump that actively transports guanethidine and guanadrel into nerve endings. These actions may reduce antihypertensive effects of guanethidine and guanadrel.
- Hypertension can occur with concomitant therapy with phenothiazines or sympathomimetic amines.
- Monoamine oxidase inhibitors may prevent degradation and metabolism of released norepinephrine produced by tyramine-containing foods and may thereby cause hypertension.
- Tricyclic antidepressant drugs may reduce effects of clonidine and guanabenz.

β-Blockers
- Cimetidine may reduce bioavailability of β-blockers metabolized primarily by liver by inducing hepatic oxidative enzymes. Hydralazine, by reducing hepatic blood flow, may increase plasma concentration of β-blockers.
- Cholesterol-binding resins, ie, cholestyramine and colestipol, may reduce plasma levels of propranolol hydrochloride.
- β-Blockers may reduce plasma clearance of drugs metabolized by the liver (eg, lidocaine, chlorpromazine, coumarin).
- Combinations of calcium channel blockers and β-blockers may promote negative inotropic effects on the failing myocardium.
- Combinations of β-blockers and reserpine may cause marked bradycardia and syncope.

ACE inhibitors: Nonsteroidal anti-inflammatory drugs, including aspirin, may magnify potassium-retaining effects of ACE inhibitors.

Calcium antagonists
- Combinations of calcium antagonists with quinidine may induce hypotension, particularly in patients with idiopathic hypertrophic subaortic stenosis.
- Calcium antagonists may induce increases in plasma digoxin levels.
- Cimetidine may increase blood levels of nifedipine.

counseling, most cases eventually required reinitiation of drug therapy.[32] Since the goal of therapy is to control blood pressure with the fewest drugs at their lowest dose, sound patient management should include attempts to decrease the dosage or number of antihypertensive drugs while maintaining nonpharmacologic modalities. Regular follow-up must be maintained because blood pressure can rise again to hypertensive levels, even after years without therapy.

Special Considerations.—Other factors should be considered in the selection of initial therapy, particularly in those patients with mild or uncomplicated hypertension who are likely to require only one drug.

1. *Demographics.* Blacks and older patients tend to respond better to diuretics or calcium antagonists than to β-blockers or ACE inhibitors. Gender has not been found to be a significant determinant of the response to drugs.

2. *Concomitant diseases and therapies.* Antihypertensive drugs may worsen some diseases while improving other conditions. They also may interact with medications used to treat these problems, as shown in Table 5. For example, β-blockers may worsen asthma and peripheral arterial disease, but they may improve angina pectoris, certain cardiac dysrhythmias, and migraine headaches. Awareness of the more common side effects of the various agents, listed in Table 6, is necessary to select drugs that may improve concomitant diseases or symptoms and to avoid those that may worsen them.

3. *Life-style.* Antihypertensive drugs may cause undesirable symptoms. For example, many of these agents may impair sexual function; centrally acting drugs may impair mental acuity; and β-blockers may reduce exercise tolerance.

4. *Physiologic and biochemical measurements.* Some health practitioners have found certain physiologic and biochemical measurements (eg, body weight, heart rate, plasma renin activity, resting electrocardiograph tracing, and hemodynamic functions) to be helpful in choosing specific therapy.

5. *Economic considerations.* The cost of therapy may be a barrier to controlling hypertension. Treatment costs include not only the price of drugs, but also the expense of laboratory tests, supplemental therapies, office visits, and time lost from work for visits to physicians' offices.[33]

Tranquilizers and sedatives are not effective in lowering blood pressure and should not be considered for use as antihypertensive therapy.

Isolated Systolic Hypertension.—Isolated systolic hypertension frequently occurs in the elderly population and is discussed in more detail later in the "Special Populations and Management Problems" section. When isolated systolic hypertension occurs in adolescents and young adults, it often indicates a hyperdynamic circulation and may predict DBP elevation. Initially, nonpharmacologic therapy is the preferred treatment approach for most patients with isolated systolic hypertension. However, when the SBP is consistently 160 mm Hg or greater and the DBP is less than 90 mm Hg despite nonpharmacologic therapy, antihypertensive drug treatment should be considered.[34]

Moderate and Severe Hypertension.—Although similar general approaches are advocated for all patients with hypertension, modification may be appropriate for those with DBPs greater than 104 mm Hg. Although some patients may respond adequately to only one drug, a second agent may be prescribed after a short interval if control is

Table 6.—Adverse Drug Effects*

Drugs	Selected Side Effects†	Precautions and Special Considerations
Diuretics‡		
Thiazides and related sulfonamide diuretics	Hypokalemia, hyperuricemia, glucose intolerance, hypercholesteremia, hypertriglyceridemia, sexual dysfunction, weakness	May be ineffective in renal failure; hypokalemia increases digitalis toxicity; may precipitate acute gout; may cause an increase in blood levels of lithium
Loop diuretics	Same as for thiazides	Effective in chronic renal failure; hypokalemia and hyperuricemia as above
Potassium-sparing agents	Hyperkalemia	Danger of hyperkalemia or renal failure in patients treated with ACE inhibitor or nonsteroidal anti-inflammatory drug; may increase blood levels of lithium
Spironolactone	Gynecomastia, mastodynia	Interferes with digoxin immunoassay
Triamterene	...	Danger of renal calculi
Amiloride	...	...
Adrenergic inhibitors		
β-Adrenergic blockers§ Acebutolol Atenolol Metoprolol Nadolol Penbutolol sulfate Pindolol Propranolol hydrochloride Timolol	Bronchospasm, peripheral arterial insufficiency, fatigue, insomnia, sexual dysfunction, exacerbation of congestive heart failure, masking of symptoms of hypoglycemia, hypertriglyceridemia, decreased HDL cholesterol (except for pindolol and acebutolol)	Should not be used in patients with asthma, COPD, congestive heart failure, heart block (>first-degree), and sick sinus syndrome; use with caution in insulin-treated diabetic patients and patients with peripheral vascular disease; should not be discontinued abruptly in patients with ischemic heart disease
Centrally acting adrenergic inhibitors		
Clonidine	Drowsiness, sedation, dry mouth, fatigue, sexual dysfunction	Rebound hypertention may occur with abrupt discontinuance, particularly with prior administration of high doses or with continuation of concomitant β-blocker therapy
Guanabenz	As above	As above
Guanfacine hydrochloride	As above	As above
Methyldopa	As above	May cause liver damage and Coombs-positive hemolytic anemia; use cautiously in elderly patients because of orthostatic hypotension; interferes with measurements of urinary catecholamines levels.
Clonidine TTS (Patch)	As above; localized skin reaction to the patch	...
Peripheral-acting adrenergic inhibitors		
Guanadrel sulfate	Diarrhea, sexual dysfunction, orthostatic hypotension	Use cautiously because of orthostatic hypotension
Guanethidine monosulfate	Same as for guanadrel	Same as for guanadrel
Rauwolfia alkaloids	Lethargy, nasal congestion, depression	Contraindicated in patients with history of mental depression; use with caution in patients with history of peptic ulcer
Reserpine	Same as for rauwolfia alkaloids	Same as for rauwolfia alkaloids
α_1-Adrenergic blockers		
Prazosin hydrochloride	"First-dose" syncope, orthostatic hypotension, weakness, palpitations	Use cautiously in elderly patients because of orthostatic hypotension
Terazosin hydrochloride	As above	As above
Combined α-β-adrenergic blocker: Labetalol§	Bronchospasm, peripheral vascular insufficiency, orthostatic hypotension	Should not be used in patients with asthma, COPD, congestive heart failure, heart block (>first-degree), and sick sinus syndrome; use with caution in insulin-treated diabetic patients and patients with peripheral vascular disease
Vasodilators	Headache, tachycardia, fluid retention	May precipitate angina pectoris in patients with coronary artery disease
Hydralazine	Positive antinuclear antibody test	Lupus syndrome may occur (rare at recommended doses)
Minoxidil	Hypertrichosis	May cause or aggravate pleural and pericardial effusions; may precipitate angina pectoris in patients with coronary artery disease

Table 6.—Adverse Drug Effects* (cont)

Drugs	Selected Side Effects†	Precautions and Special Considerations
ACE Inhibitors Inhibitors	Rash, cough, angioneurotic edema, hyperkalemia, dysgeusia	Can cause reversible, acute, renal failure in patients with bilateral renal arterial stenosis or unilateral stenosis in a solitary kidney; proteinuria may occur (rare at recommended doses); hyperkalemia can develop, particularly in patients with renal insufficiency; rarely can induce neutropenia; hypotension has been observed with initiation of ACE inhibitors, especially in patients with high plasma renin activity or in those receiving diuretic therapy
Calcium antagonists	Edema, headache	Use with caution in patients with congestive heart failure; contraindicated in patients with second- or third-degree heart block
Verapamil	Constipation	May cause liver dysfunction
Diltiazem hydrochloride	Constipation	May cause liver dysfunction
Nifedipine	Tachycardia	. . .
Nitrendipine	Tachycardia	. . .

*Sexual dysfunction, particularly impotence in men, has been reported with the use of all antihypertensive agents. ACE indicators angiotensin-converting enzyme; HDL, high-density lipoprotein; and COPD, chronic obstructive pulmonary disease.
†The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing.
‡See Table 3 for a list of these drugs.
§Sudden withdrawal of these drugs may be hazardous in patients with heart disease. See Table 3 for a list of these drugs.

not achieved. The intervals between changes in the regimen should be decreased, and the maximum dose of some drugs may be increased. Patients with average DBPs of 130 mm Hg or greater require more immediate therapy and, at times, hospitalization. Physicians who are uncomfortable with treating such patients should seek consultation.

Refractory Hypertension.—The treatment program outlined earlier in this article will control high blood pressure in almost all patients. However, unacceptably high DBPs can persist in a few patients, despite combination therapy at full dose. Some of the causes of refractory hypertension are listed in Table 4. If these causes have been excluded, more potent drugs such as minoxidil may be needed. Failure to include diuretics in the antihypertensive regimen is a frequent cause of poor blood pressure control. If goal blood pressure cannot be achieved without intolerable side effects, partial reduction of DBP (90 to 100 mm Hg) may have to be accepted. Additional steps that may be taken include the following: (1) Increase doses of drugs beyond the levels recommended in Table 3 with the realization that the likelihood of developing side effects may be increased. (2) Persuade patients that they may have to tolerate some adverse effects to achieve goal blood pressure and to reduce the risk of morbidity and mortality. (3) Measure plasma renin activity, which may at times be useful for diagnostic purposes and for selecting additional antihypertensive drugs in the patient with refractory hypertension. (4) Consider referring patients for further evaluation, including assessment of secondary forms of hypertension.

Hypertensive Emergencies and Urgencies.—Although not common today, hypertensive emergencies warrant prompt recognition and management because they represent serious threats to organ function and life. Prompt inhibition of therapy may reduce or prevent these threats. The association between elevated blood pressure and evidence of new or progressive end-organ damage—and not necessarily the absolute blood pressure itself—determines the seriousness of the clinical situation and the possible need for immediate treatment in a monitored hospital setting. Consultation, referral, or both should be considered when indicated.

Hypertensive emergencies are those situations in which blood pressure must be lowered within one hour. Examples include hypertensive encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, eclampsia or severe hypertension associated with pregnancy, head trauma, extensive burns, unstable angina pectoris, or acute myocardial infarction.

Hypertensive urgencies are situations in which blood pressure should be reduced within a few hours, eg, accelerated or malignant hypertension without immediate complications and severe perioperative hypertension.

A clear distinction between emergencies and urgencies is not always possible. In these circumstances, specialized management may be appropriate from the outset. Tables 7 and 8 present those parenteral agents that have proven effective in treating hypertensive emergencies in addition to orally administered antihypertensive drugs that have been used to treat both emergencies and urgencies, including ACE inhibitors, minoxidil, clonidine, and nifedipine. Despite the benefits of timely and appropriate treatment, in these circumstances, the possible risks of overly aggressive intervention must always be considered. Elevated blood pressure alone rarely requires urgent therapy.

Long-term Maintenance of Therapy

Goal.—The goal of antihypertensive therapy is achievement and long-term maintenance of goal blood pressure (<140/90 mm Hg) with minimal, if any, adverse effects. Achieving hypertension control without side effects may at times require several changes in the regimen. The ultimate objective is to reduce cardiovascular morbidity and mortality.

Follow-up visits.—Follow-up visits for reexamination and laboratory tests are indicated at intervals that may

Table 7.—Parenteral Drugs for Treatment of Hypertensive Emergencies

	Dose*	Reaction Time, min	Adverse Reactions
Vasodilators			
Sodium nitroprusside	0.5-10 μg/kg/min as IV infusion	Instantaneous	Nausea, vomiting, muscle twitching, thiocyanate intoxication, methemoglobinemia
Nitroglycerin	5-100 μg/min as IV infusion	2-5	Headache, tachycardia, vomiting, methemoglobinemia
Diazoxide	50-150 mg/IV bolus, repeated, or 15-30 mg/min by IV infusion	1-2	Hypotension, tachycardia, aggravation of angina pectoris
Hydralazine	10-20 mg IV, 10-50 mg IM	10 20-30	Tachycardia, headache, vomiting, aggravation of angina pectoris
Adrenergic Inhibitors			
Phentolamine hydrochloride	5-15 mg IV	1-2	Tachycardia, orthostatic hypotension
Trimethaphan camsylate	1-4 mg/min as IV infusion	1-5	Paresis of bowel and bladder, orthostatic hypotension, blurred vision, dry mouth
Labetalol	20-80 mg IV bolus every 10 min, 2 mg/min IV infusion	5-10	Bronchoconstriction, heart block, orthostatic hypotension
Methyldopa	250-500 mg IV infusion	30-60	Drowsiness

*IV indicates intravenous; IM, intramuscular.

Table 8.—Oral Drugs for Treatment of Hypertensive Emergencies and Urgencies

Drug	Recommended Dose, mg	Frequency
Captopril	25	Repeat as required
Clonidine	0.1-0.2	Every hour as required
Minoxidil	2.5-5	Repeat after 2-3 h
Nifedipine	10	Repeat after 30 min

vary from a few weeks to several months depending on clinical judgment, patient adherence, adequacy of blood pressure control, and associated medical and abnormal test results. Patient monitoring should include blood pressure measurements in both the standing and the supine or sitting positions.

Clinician-Patient Interaction: Communication and Promoting Adherence to Treatment.—Poor adherence to long-term treatment, both nonpharmacologic and pharmacologic, has been identified as the major reason for inadequate control of high blood pressure. Recent studies suggest that an appropriately planned program of strategies for health education intervention can significantly improve adherence to treatment, increase adequate blood pressure control, and decrease hypertension-related morbidity and mortality.[36-37] Combinations of strategies are likely to achieve the greatest improvement in long-term adherence and are usually aimed at improving understanding of the specific treatment and treatment goals, correcting misconceptions, adjusting the interventions to patients' life-styles, and enhancing family or other social support.[37-39] The following suggestions should improve long-term adherence to antihypertensive therapy: (1) Inform patients of their blood pressure level. (2) Agree on a goal blood pressure. (3) Be sure patients understand that high blood pressure can be controlled but not cured; that they cannot tell their blood pressure level by the way they feel; and that they should not stop their treatment without discussing it with their physician. (4) Incorporate treatment requirements into patients' daily life-styles, to the extent possible. (5) Involve patients' families in the treatment process. (6) Encourage patients to self-monitor their blood pressure in selected cases. (7) In selected cases, provide positive reinforcement and encouragement for achieving specific adherence goals. (8) Simplify the regimen; most antihypertensive drugs can be taken twice daily, and many only once daily. (9) Provide simple oral and written instructions and adequate patient information material on drug dosages, anticipated or common side effects, and therapeutic goals. (10) Ask patients to state their understanding of their diagnosis and encourage them to discuss their antihypertensive medications, to report side effects, and to express problems and concerns. (11) Consider using clinician-patient contracts. (12) Demonstrate a willingness to modify dosages or to change drugs to avoid side effects. (13) Minimize the cost of therapy. (14) Increase the attention given to nonadherent patients by scheduling more frequent counseling visits. (15) Contact patients if they fail to keep follow-up appointments. (16) Collaborate with other health care providers such as nurses, pharmacists, nutritionists, optometrists, dentists, podiatrists, and physician assistants.

CONSIDERATIONS IN INDIVIDUAL THERAPY

Quality of Life

Although treatment of hypertension is a medical necessity, the impact of antihypertensive therapy on quality of life is a legitimate concern. Patients treated with various drugs sometimes experience subtle changes in emotional status, behavior, and both physical and cognitive function. Although some antihypertensive agents produce undesirable side effects more often than do other drugs, practitioners must address the impact of treatment on the quality of life for each patient. Hypertension management should be dictated by the needs and experiences of each individual.

The Cost of Care

For some patients, lifelong antihypertensive care produces a burdensome financial obligation.[40] Health care providers should be aware of the total cost of care to hypertensive patients (including indirect costs such as time lost from work and transportation costs) and should try to minimize these expenses. Determinants of cost include the following:

1. *Initial work-up.* Initial costs are usually for medical history, physical examination, and minimal laboratory work-up. Patients with moderate or severe hypertension may require a much more extensive and expensive assessment.

Table 9.—Classification of Hypertension in the Young*

Age Group	≥95th Percentile	≥99th Percentile
Newborns, d		
7 (SBP)	≥96	≥106
8-30 (SBP)	≥104	≥110
Infants (≤2 y)		
SBP	≥112	≥118
DBP	≥74	≥82
Children, y		
3-5		
SBP	≥116	≥124
DBP	≥76	≥84
6-9		
SBP	≥122	≥130
DBP	≥78	≥86
10-12		
SBP	≥126	≥134
DBP	≥82	≥90
13-15		
SBP	≥136	≥144
DBP	≥86	≥92
Adolescents (16-18 y)		
SBP	≥142	≥150
DBP	≥92	≥98

*SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Classification based on report of Second Task Force on Blood Pressure Control in Children—1987.[47] All values expressed as millimeters of mercury.

2. *Follow-up visits.* The costs of follow-up vary considerably. Frequent visits generate greater charges but may enhance adherence to therapy and blood pressure control, thereby reducing cardiovascular sequelae. Tactics that may contain costs include monitoring blood pressure at home or relying on other community resources and nonphysician staff for such monitoring.

3. *Drugs.* The selection of antihypertensive drugs influences the total cost of care. Realistic assessment of the economic impact of each drug must consider its intrinsic cost, the burden of the side effects, the impact on adherence, and additional laboratory tests that may be required to monitor biochemical changes.[23] Physicians should recognize that some drugs may be priced too high for certain patients, thus diminishing their benefit by reducing adherence. In addition, some drugs that reduce the quality of life, irrespective of cost, may reduce the overall benefit of treatment by reducing adherence.

Community Programs and Health Care Systems

In the United States, most people have had their blood pressure measured within the last year[41]; therefore, mass screenings to detect unaware hypertensive individuals need not be encouraged. Instead, community-based hypertension programs should increase their efforts to provide follow-up services, ie, patient tracking efforts that complement medical management.[42] For community hypertension programs to remain effective, the direct participation of practicing physicians is essential. Community or regional high blood pressure councils can coordinate activities to ensure that disadvantaged groups are included. There should be an ongoing commitment to remove economic barriers to adequate hypertension management in all settings in which economically disadvantaged patients are served. Cooperative arrangements among voluntary and professional agencies, local health departments, and industry are encouraged. These relationships have worked well in the past, resulting in increased numbers of controlled hypertensive patients. Community hypertension programs should also develop plans and methods to evaluate their effectiveness.[43]

Hypertension treatment sites should be designed with easy access for all patients, convenient hours unique to local needs, realistic appointment scheduling to avoid prolonged waiting periods, and a staff trained in effective communication. Sites serving economically disadvantaged populations should include staff members knowledgeable in local culture and language. An ongoing effort to assess the effectiveness of hypertension control programs should be included in the program design.

Primary Prevention

Studies to determine ways to prevent hypertension are in progress. Until the results of these investigations are available, definitive recommendations cannot be made. However, data from population studies suggest that low sodium intake, weight reduction, and moderation of alcohol consumption may prevent blood pressure levels from rising. Therefore, nonpharmacologic modalities that are of value for hypertension management may be considered for primary prevention, particularly in groups at high risk for developing high blood pressure (eg, offspring of hypertensive patients, blacks, obese individuals, and those with high-normal blood pressure).

SPECIAL POPULATIONS AND MANAGEMENT PROBLEMS

Black Patients

The prevalence rate of hypertension in the US black population is considerably higher than in the white population.[1] Blacks may develop hypertension at an earlier age, and the severity of hypertension in blacks is likely to be higher than that of hypertensive whites. The higher prevalence rate and greater severity of hypertension are related to the more common occurrence of strokes, end-stage renal disease, congestive heart failure, and left ventricular hypertrophy in blacks. In addition, hypertension-related death rates are disproportionately higher among blacks, particularly in younger age groups.

The potential for reduction of morbidity and mortality related to hypertension is greater in blacks, and concern about high blood pressure as a health issue has prompted an increase in control efforts throughout the country. Hypertension-related death rates are declining in blacks, and stroke mortality rates in some communities have experienced greater declines in blacks than in whites. Despite these encouraging trends, hypertension continues to be the most serious health problem for US blacks.

There are no recognized differences in the responses to nonpharmacologic therapy between whites and blacks. Therefore, such approaches should be prescribed for all patients accordingly. Weight reduction is strongly indicated in obese black hypertensive patients. Such programs not only benefit elevated blood pressure levels, but also lessen the risk of diabetes mellitus, a frequent complication of obesity.

With respect to drug therapy, black hypertensive patients usually do not respond as well to β-blockers or ACE inhibitors as do whites, and diuretics are generally more effective as monotherapy than either β-blockers or ACE inhibitors. However, combinations of β-blockers or ACE inhibitors with diuretics are equally effective in black and white hypertensive patients. Calcium antagonists, centrally acting α-adrenergic agonists, peripheral α-blockers,

and labetalol (a combined α-β-blocker) are equally effective in both groups.

Other Racial and Ethnic Minority Groups: American Indians, Asians and Pacific Islanders, and Hispanics

Little information is available to determine whether American Indians, Asians and Pacific Islanders, and Hispanics respond differently than whites to antihypertensive medications or nonpharmacologic therapy. Further studies are needed to better understand the factors influencing the control of hypertension in these groups.

Life-style factors are often culturally determined and may be important contributors to hypertension and its control. Therefore, clinicians who treat and counsel minority patients should pay special attention to factors such as cultural diets and beliefs, costs of therapy, education and literacy level, language preference or barriers, and environmental conditions.

Elderly Patients

By 1990, an estimated 29 million people in the United States will be 65 years of age or older. Forty-five percent of this population will have an SBP of 160 mm Hg or greater or a DBP of 95 mm Hg or greater. Approximately two thirds of those over age 65 years will have an SBP of 140 mm Hg or greater or a DBP of 90 mm Hg or greater. Elevations of SBP and DBP increase the relative risk of cardiovascular morbidity and mortality at least as much for elderly patients as for younger ones.

When the onset of diastolic hypertension appears after age 55 years or when hypertension in elderly patients no longer responds to a previously effective regimen, an underlying cause, usually renovascular disease, should be suspected. Efforts to identify the latter problem are particularly appropriate in view of the increased usefulness of angioplasty in the treatment of renovascular hypertension.

Data from the Veterans Administration Study,[25] the Hypertension Detection and Follow-Up Program,[26] the Australian Trial,[27] and the European Working Party on High Blood Pressure in the Elderly[44] indicate that elderly patients who have a DBP of 90 mm Hg or greater will benefit from antihypertensive therapy. In the Hypertension Detection and Follow-Up Program trial, the adherence of elderly patients to drug regimens was just as good as, if not better than, that of younger patients.[45]

No definitive data are available regarding the efficacy of antihypertensive treatment in reducing the increased risk of cardiovascular disease associated with isolated systolic hypertension. The Systolic Hypertension in the Elderly Program, a double-blind, placebo-controlled trial sponsored by the National Heart, Lung, and Blood Institute and the National Institute on Aging, Bethesda, Md, is in progress. Until the results of this trial are available, physicians will be guided by their clinical judgment. For most elderly patients with isolated systolic hypertension, nonpharmacologic therapy seems warranted. If the decision is made to treat the patient with drugs, the SBP should be lowered cautiously to the goal of 140 to 160 mm Hg.

Older patients may be more sensitive to volume depletion and sympathetic inhibition than are younger individuals because the elderly may have impaired cardiovascular reflexes that make them more susceptible to hypotention. For this reason, antihypertensive treatment should be initiated with smaller doses than usual. Increases in dosage also should be smaller and spaced at longer intervals than might be appropriate for younger patients. Drugs that have a propensity to cause orthostatic hypotension (eg, guanethidine monosulfate or sulfate, guanadrel sulfate, α_1-blockers, labetalol) should be used with caution.

All antihypertensive drugs have shown efficacy in elderly patients. In the feasibility phase of the Systolic Hypertension in the Elderly Program trial, diuretic therapy usually controlled isolated systolic hypertension in most patients without producing notable symptomatic side effects.[46] Calcium antagonists are effective in elderly patients as monotherapy for either diastolic or isolated systolic hypertension. β-Blockers and ACE inhibitors also are useful as monotherapy in elderly patients. Centrally and peripherally acting adrenergic inhibitors, as well as all drugs recommended for monotherapy, are useful as step 2 drugs.

Young Patients

Less than 3% of US children have arterial hypertension. Nonetheless, it is an important problem warranting guidelines. *The Report of the Second Task Force on Blood Pressure Control in Children—1987*[47] offers a comprehensive approach to the detection, evaluation, and treatment of high blood pressure in children. This study provides data on blood pressure distributions from more than 70 000 white, black, and Mexican-American children. Table 9 depicts the recommended classification of blood pressure levels in children, with *significant hypertension* defined as blood pressure persistently equal to or greater than the 95th percentile for age and *severe hypertension* defined as blood pressure persistently equal to or greater than the 99th percentile for age.

Hypertension should not be diagnosed on the basis of a single measurement. As in adults, children require repeated measurements to determine the stability or lability of blood pressure elevation. Attention should be given to using proper equipment and technique. The widest cuff that will comfortably encircle the arm without covering the antecubital fossa should be used. For infants in whom the accuracy of measurements by auscultation is uncertain, an electronic device using a Doppler technique can be used. Whenever possible, measurements should be obtained while patients are seated in quiet, nonstressful surroundings.

The higher the blood pressure and the younger the child, the greater the possibility of secondary hypertension. A careful medical history and physical examination are essential. The laboratory tests warranted for young patients are generally similar to those recommended for adults.

The underlying cause, severity, or complications of hypertension in children will determine the degree and types of intervention required. Therapy should reduce blood pressure without causing adverse effects that limit adherence or impair normal growth and development. Nonpharmacologic interventions can be introduced as initial treatment and tailored to meet the needs of individual patients. Antihypertensive drug therapy generally should be reserved for use in patients with levels of blood pressure above the 99th percentile or with significantly elevated levels that respond inadequately to nondrug approaches.

Pharmacologic agents generally used for adults are also effective in young persons. Uncomplicated elevated blood pressure, by itself, generally should not be a reason to restrict asymptomatic children from participating in sports and other physical activities.

Pregnant Patients

Hypertension during pregnancy may represent the syndrome of preeclampsia (pregnancy-induced hypertension)

or chronic (essential) hypertension. In either situation, treatment of hypertension is beneficial in reducing both maternal and fetal mortality. Therapy instituted before pregnancy may be continued in hypertensive women who become pregnant. In women with preeclampsia, modified bed rest and proper diet may reduce the blood pressure satisfactorily. If not, antihypertensive drug therapy should be used. Methyldopa and hydralazine have been used extensively in pregnant women, but recent clinical studies indicate that β-adrenergic blocking drugs are also effective in controlling blood pressure and improving fetal survival. Angiotensin-converting enzyme inhibitors have been demonstrated to increase fetal mortality in pregnant animals and should probably be avoided during pregnancy. The calcium channel blockers have proven effective in controlling severe hypertension in late pregnancy, but they could cause a decrease in uterine contractions during labor.

Surgical Candidates

Surgical patients who are adequately controlling their blood pressure with medication should be maintained on their regimen until the time of surgery, and therapy should be reinstated as soon as possible after surgery. If oral intake must be interrupted, parenteral therapy with diuretics, adrenergic inhibitors, vasodilators, sublingual nifedipine, or transdermal clonidine may be used to prevent the rebound hypertension that may follow sudden discontinuation of some of the adrenergic-inhibiting agents.

Adequate potassium supplementation should be provided to correct hypokalemia well in advance of surgery. A brief course of intravenous potassium just prior to surgery may not be sufficient to correct long-standing hypokalemia. In all cases, anesthesiologists should be informed of patients' medical status. Hypertensive patients whose blood pressure has been controlled on medication usually tolerate anesthesia better than do those whose pressures are poorly controlled.

Patients With Cerebrovascular Disease

Hypertension is the major risk factor for both thrombotic and hemorrhagic strokes. The risk of stroke is related to the level of elevated blood pressure, with SBP more closely correlated than DBP. The risk is escalated further when hypertension is present in association with smoking, excess alcohol intake, coronary artery disease, congestive heart failure, or diabetes mellitus.

Age-adjusted mortality rates from cerebrovascular disease have decreased approximately 50% between 1972 and 1986. Large-scale clinical trials have demonstrated that reduction of elevated blood pressure is associated with a 30% to 50% decrease in incidence of both fatal and nonfatal strokes.[48] The presence of cerebrovascular disease does not contraindicate treatment of hypertension except perhaps in the early period following an acute ischemic cerebral infarction or with transient ischemic attacks. In these cases, antihypertensive therapy may be withheld temporarily to avoid critical reduction in cerebral perfusion unless the DBP is very high (>105 mm Hg). Thereafter, the goal of therapy is to normalize blood pressure gradually and to avoid orthostatic hypotension.

An increase in blood pressure may occur in patients who have had acute stroke. Marked elevation of blood pressure associated with hemorrhagic stroke should be approached as a hypertensive emergency (see "Hypertensive emergencies and Urgencies" section).

Patients With Coronary Artery Disease

The effect of drug treatment on the development of complications of coronary artery disease remains a critical issue in antihypertensive drug therapy. Taken as a whole, findings from clinical trials suggest that benefits of antihypertensive treatment on the incidence of either fatal or nonfatal myocardial infarction or on mortality related to coronary artery disease are modest at best. Several possible explanations have been proposed to explain these results, but this issue remains unresolved. Nevertheless, certain recommendations regarding treatment would seem appropriate.

Careful attention should be placed on the control of other cardiovascular risk factors, especially smoking, hyperlipidemia, and diabetes mellitus. For patients with mild hypertension, smoking cessation may offer as much or greater benefit as the control of high blood pressure for reducing cardiovascular risk. In addition, some studies on mild hypertension have suggested that smoking might negate any benefit from β-blocker therapy in reducing the incidence of complications of coronary artery disease.[28]

Aggressive measures to control hyperlipidemia, including diet (and drugs if needed), should also be used.[49] In view of the findings that some antihypertensive drugs may have an adverse effect on serum levels of lipids and lipoproteins, health practitioners should monitor concentrations of serum lipids periodically. If adverse changes are observed, treatment should be altered or appropriate measures should be taken to counteract these effects.

Because of the potential adverse effects of hypokalemia and hypomagnesemia on the development of cardiac dysrhythmias, particularly in patients with coronary artery disease, therapy should include potassium supplementation or modification of antihypertensive drug treatment to prevent or to correct diuretic-induced hypokalemia. With coexisting magnesium depletion, correction of potassium deficit can be difficult unless the magnesium deficiency is also managed.

Coronary artery disease is not a contraindication to the treatment of hypertension. As with patients having cerebrovascular disease, the elevated blood pressure should be reduced gradually to avoid hypotensive episodes. β-Blockers or calcium-entry blockers may be specifically indicated because they decrease angina pectoris. In addition, for those who have had a myocardial infarction and who are at greater risk of having another event, β-blockers may prevent or delay a subsequent myocardial infarction and reduce the risk of sudden death. Patients with ischemic heart disease do not have an increased frequency of angina pectoris or myocardial infarction when elevated blood pressures are carefully reduced. Indeed, many patients with angina pectoris note a decrease in symptoms with lowering of blood pressure and reduction of myocardial oxygen demand.

Patients With Congestive Heart Failure

Control of hypertension can improve myocardial function, prevent congestive heart failure, and lessen mortality. Angiotensin-converting enzyme inhibitors, when used in combination with digitalis and diuretics in patients with congestive failure (New York Heart Association class IV), have proven effective in reducing mortality due to progressive congestive heart failure. A clinical trial has also indicated that hydralazine combined with isosorbide dinitrate significantly decreases mortality in patients with less severe (classes II and III) heart failure.[50]

Patients With Left Ventricular Hypertrophy (LVH)

Left ventricular hypertrophy permits cardiac adaptation to the increased pressure and afterload imposed by elevated blood pressure. However, LVH represents a major independent risk factor for cardiac dysrhythmias and sudden death,[51] and control of elevated blood pressure should be directed toward preventing the development of LVH.

The echocardiogram provides the most sensitive and specific diagnostic evidence of cardiac involvement and enlargement, but its use is somewhat limited by cost. The electrocardiogram remains of value not only for detecting LVH but also for identifying patients who may be more predisposed to the development of cardiac dysrhythmias.

A recent area of investigative interest relates to regression of LVH. Several antihypertensive therapies appear to be effective in reducing left ventricular mass and wall thickness; these include weight loss,[52] methyldopa, β-adrenergic blocking agents, ACE inhibitors, and calcium antagonists.[51] Diuretics also may cause reversal of hypertrophy, but not to the extent observed with these other agents. The direct-acting vasodilators minoxodil and hydralazine, which are rarely used as monotherapy, may actually increase mass.

At this time, it is not known whether reversal of hypertension-induced cardiac hypertrophy improves the independent risk of cardiovascular morbidity and mortality associated with its presence. However, evidenced of LVH is an indication for intensive therapy of patients with mild hypertension.

Patients With Peripheral Vascular Disease

Hypertension is a major risk factor for the development of arteriosclerosis obliterans. As with other atherosclerosis-related complications, however, it remains uncertain whether antihypertensive therapy will favorably influence the clinical course of the disease. In some individuals with peripheral vascular insufficiency and intermittent claudication, the lowering of blood pressure can increase symptoms.

β-Adrenergic antagonists, particularly of the nonselective type, may be contraindicated in some patients with arteriosclerosis obliterans or with Raynaud's disease since they may induce peripheral vasoconstriction. In patients with severe Raynaud's disease associated with collagen vascular diseases such as scleroderma, treatment with ACE inhibitors, with or without a calcium antagonist, may have a beneficial effect on Raynaud's disease as well as on blood pressure.

Patients With Diabetes Mellitus

Patients with hypertension and diabetes mellitus are very vulnerable to cardiovascular complications.[53] Hypertension control, as well as reduction of hyperlipoproteinemia and cessation of cigarette smoking, is particularly important in this group. Most antihypertensive therapies are effective and can be useful in diabetic patients. Many of the drugs have side effects peculiar to patients with diabetes, but none are specifically contraindicated for use in the diabetic population.

Certain drugs may impair the control of diabetes. Decreased insulin release with diuretic-induced hypokalemia is well recognized. Maintenance of the serum potassium level in the normal range generally prevents much of this adverse effect. Glucose control also may deteriorate with β-adrenergic blocking drugs.

Table 10.—Cholesterol Classification and Treatment Recommendations*

Risk Levels	Cholesterol, mmol/L (mg/dL) Total	LDL	Action
Desirable	<5.17 (<200)	<3.36 (<130)	Remeasure within 5 y
Borderline	5.17-6.18 (200-239)	3.36-3.59 (130-159)	Without CHD or two other risk factors: provide dietary information and recheck annually With CHD or two or more other risk factors: aggressive approach is indicated; dietary changes should be initiated and drug therapy may be warranted
High	≥6.21 (≥240)	≥4.14 (≥160)	Aggressive approach is indicated; dietary changes should be initiated and drug therapy may be warranted

*LDL indicates low-density lipoprotein; CHD, coronary heart disease. Classification based on Report of National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[49]

Another problem with β-blockers is their interference with catecholamine-induced counterregulatory responses to insulin-induced hypoglycemia. Thus, symptoms of hypoglycemia, such as palpitations, tremor, and feelings of anxiety, may be blunted, and the duration of hypoglycemia may be prolonged. Severe hypertension also can occur during hypoglycemia in diabetic patients treated with β-blockers. Blockade of the β_2 (vasodilatory) receptors leaves α (vasoconstrictive) receptors unopposed so that both SBP and DBP may increase.

Neuropathic complications of diabetes are common and may influence antihypertensive drug therapy. Autonomic neuropathy with orthostatic hypotension may occur in diabetic patients and may aggravate or precipitate orthostatic hypotension.

Sexual dysfunction is also relatively common in diabetic patients and will often deteriorate further with antihypertensive drugs. Changes in therapy may be required in such patients to help maintain adherence to drug regimens.

Hyporeninemic hypoaldosteronism with resultant hyperkalemia may be seen in patients with diabetic nephropathy. Potassium-sparing diuretics, ACE inhibitors, and β-blockers can aggravate this hyperkalemia and must be used cautiously with frequent monitoring of the serum potassium level. On the other hand, ACE inhibitors may be otherwise desirable in diabetic hypertensive patients with renal disease (see "Patients With Renal Disease" section).

Patients With Chronic Obstructive Pulmonary Disease or Bronchial Asthma

β-Blockers may cause major, often unpredictable, bronchospasm in some patients with asthma or chronic obstructive pulmonary disease (COPD). Therefore, β-blockers should be avoided if possible in these patients. If no suitable alternatives are available, β_1-selective agents and the

combined α-β-blocker, labetalol, may be used with caution in some patients with mild COPD and asthma.

Sympathomimetic agents are relatively contraindicated in hypertensive patients and must be used with caution. Phenylpropanolamine hydrochloride, which is used extensively in over-the-counter preparations (eg, nose drops and decongestants), and ephedrine inhibit the hypotensive effects of guanethidine monosulfate and reserpine. Patients receiving long-term systemic corticosteroid therapy need to have their blood pressure monitored frequently to detect increases. Some drugs used for the treatment of COPD and bronchial asthma (eg, methylxanthines, local steroid preparations, and anticholinergic nebulizers) do not significantly affect blood pressure.

Patients With Hyperlipidemia

New definitions and guidelines for the management of hypercholesterolemia and hyperlipidemia in adults are available in a recent report of an expert panel established by the National Heart, Lung, and Blood Institute.[49] Table 10 summarizes the recommended classification and treatment decisions based on total and low-density-lipoprotein cholesterol (LDL-C). The report recommends treating patients earlier and taking a more aggressive approach to the control of hyperlipoproteinemia than that currently used by most physicians. In view of their importance as a risk factor, serum levels of lipids should be monitored regularly in hypertensive patients.

Thiazide and loop diuretics can induce short-term increases in levels of total plasma cholesterol, triglyceride, and LDL-C in some patients.[53] Some studies have suggested that this hyperlipidemic effect decreases or disappears with long-term therapy, but several clinical trials have shown persistence of the adverse effect. Dietary modifications may reduce or eliminate these possible effects.

β-Blockers may increase levels of plasma triglycerides and reduce those of high-density lipoprotein cholesterol. Despite this effect, β-blockers are the only agents that have been shown to decrease the rate of both fatal and nonfatal recurrent myocardial infarction. β-Blockers with intrinsic sympathomimetic activity or labetalol have no adverse effect on lipids, but these agents have not demonstrated a cardioprotective effect after a myocardial infarction.

The α_1-blockers and the central adrenergic agonists may decrease serum cholesterol concentration to a slight degree, especially in the low-density lipoprotein subfraction. Therefore, these agents may offer an advantage in managing hypertensive patients with hyperlipidemia. Angiotensin-converting enzyme inhibitors and calcium antagonists have no adverse effects on levels of serum lipids and lipoproteins.

Patients With Gout

Thiazide diuretics may precipitate gout in susceptible patients. This is not likely to occur if gout is controlled with an agent to lower serum uric acid (eg, allopurinol) levels or with a uricosuric drug (eg, probenecid). For patients with poorly controlled gout, thiazide diuretics should be avoided. In the absence of gout or urate stones, diuretic-induced hyperuricemia usually does not require treatment.

Patients With Renal Disease

Antihypertensive treatment preserves renal function in severe or malignant hypertension and may decrease the degree of proteinuria or progression of renal failure in patients with primary renal disease or diabetic nephropathy. Hypertension secondary to renal parenchymal disease usually does not develop unless the serum creatinine level has risen above 130 μmol/L (1.5 mg/dL). This level corresponds to a more than 50% reduction in glomerular filtration rate and renal blood flow.

When renal function is impaired, sodium excretion may be compromised, leading to sodium retention and potential elevation of blood pressure. Consequently, sodium restriction and the use of diuretics are important in treatment. With marked impairment of renal function, large doses of loop diuretics (eg, furosemide, ethacrynic acid, and bumetanide) or metolazone, instead of conventional thiazide diuretics, may be necessary to control hypertension. All of the commonly used classes of antihypertensive drugs are usually effective in lowering blood pressure in patients with renal disease and thereby may favorably influence the degree of proteinuria and the progression of renal failure. With severe hypertension, minoxidil may be needed, but increased doses of a diuretic and an antiadrenergic drug are often required to control the sodium retention and tachycardia induced by minoxidil.

Recent studies, particularly in diabetic nephropathy, suggest that the use of ACE inhibitors may possess specific advantages in decreasing proteinuria and slowing progression of renal failure. These drugs may be administered in conjunction with a diuretic or other antihypertensive drug, as necessary, to control the systemic blood pressure. When an ACE inhibitor is given to patients with an elevated serum creatinine level (>220 μmol/L [>2.5 mg/dL]), the serum potassium level should be monitored frequently because of the increased risk for hyperkalemia. In patients with bilateral renal artery stenosis or stenosis in the artery supplying a solitary kidney, ACE inhibitors may lead to a further acute reduction in kidney function, which is usually reversible on discontinuation of the drug.

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The organizations listed below are current members of the National High Blood Pressure Education Program Coordinating Committee. This report has been endorsed by the committee. Ad Hoc Committee on Cardiovascular/Pulmonary Disease Risk Factors in Minority Populations, American Academy of Family Physicians, American Academy of Ophthalmology, American Academy of Physician Assistants, American Association of Occupational Health Nurses, American College of Cardiology, American College of Chest Physicians, American College of Physicians, American College of Preventive Medicine, American Dental Association, American Diabetes Association Inc, American Dietetic Association, American Heart Association, American Hospital Association, American Medical Association, American Nurses' Association Inc, American Occupational Medical Association, American Optometric Association; American Osteopathic Association; American Pharmaceutical Association; American Podiatric Medical Association; American Public Health Association; American Red Cross; American Society of Hospital Pharmacists; Association of Black Cardiologists; Association of Life Insurance Medical Directors of America; National Black Nurses Association Inc; National Heart, Lung, and Blood Institute; National Kidney Foundation; National Medical Association; National Optometric Association; and Society for Nutrition Education.

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Highlights *of the*
Report of the Expert Panel on

DETECTION,

EVALUATION,

and

TREATMENT

of

High Blood Cholesterol in Adults

NATIONAL CHOLESTEROL EDUCATION PROGRAM

Sponsored by the
NATIONAL HEART, LUNG AND BLOOD INSTITUTE
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Introduction

These highlights from the 1987 report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel) offer practical detection, evaluation, and treatment recommendations for physicians. The panel, which was composed of national experts in blood cholesterol control, was convened by the National Heart, Lung, and Blood Institute. Its purpose was to update and add more specific recommendations to basic policies set forth by previous expert committees, such as the 1984 NIH Consensus Panel on Lowering Blood Cholesterol to Prevent Heart Disease.

The report deals with three principal topics: classification of blood cholesterol and patient evaluation; dietary treatment, and drug treatment. The panel addressed only patients age 20 and above; another panel will focus on children and adolescents. The treatment approach is uniform for adults of both sexes and all ages. There is room, however, for modification based on the judgment of the physician and the preference of the patient, particularly when treating young adults (20-29), the elderly (over age 60), and women.

While this booklet is intended primarily for physicians, it is important to note that these interventions also require the active involvement of dietitians, nurses, pharmacists, other health professionals, and patients themselves. Working together, the professional-patient team can successfully reduce the risk of coronary heart disease (CHD).

Initial Classification Based on Total Cholesterol

<200 mg/dl	**Desirable Blood Cholesterol**
200-239 mg/dl	**Borderline-High Blood Cholesterol**
≥240 mg/dl	**High Blood Cholesterol**

Classification Based on LDL-Cholesterol

<130 mg/dl	**Desirable LDL-Cholesterol**
130-159 mg/dl	**Borderline-High-Risk LDL-Cholesterol**
≥160 mg/dl	**High-Risk LDL-Cholesterol**

To obtain a copy of the Adult Treatment Panel's full report, write to:

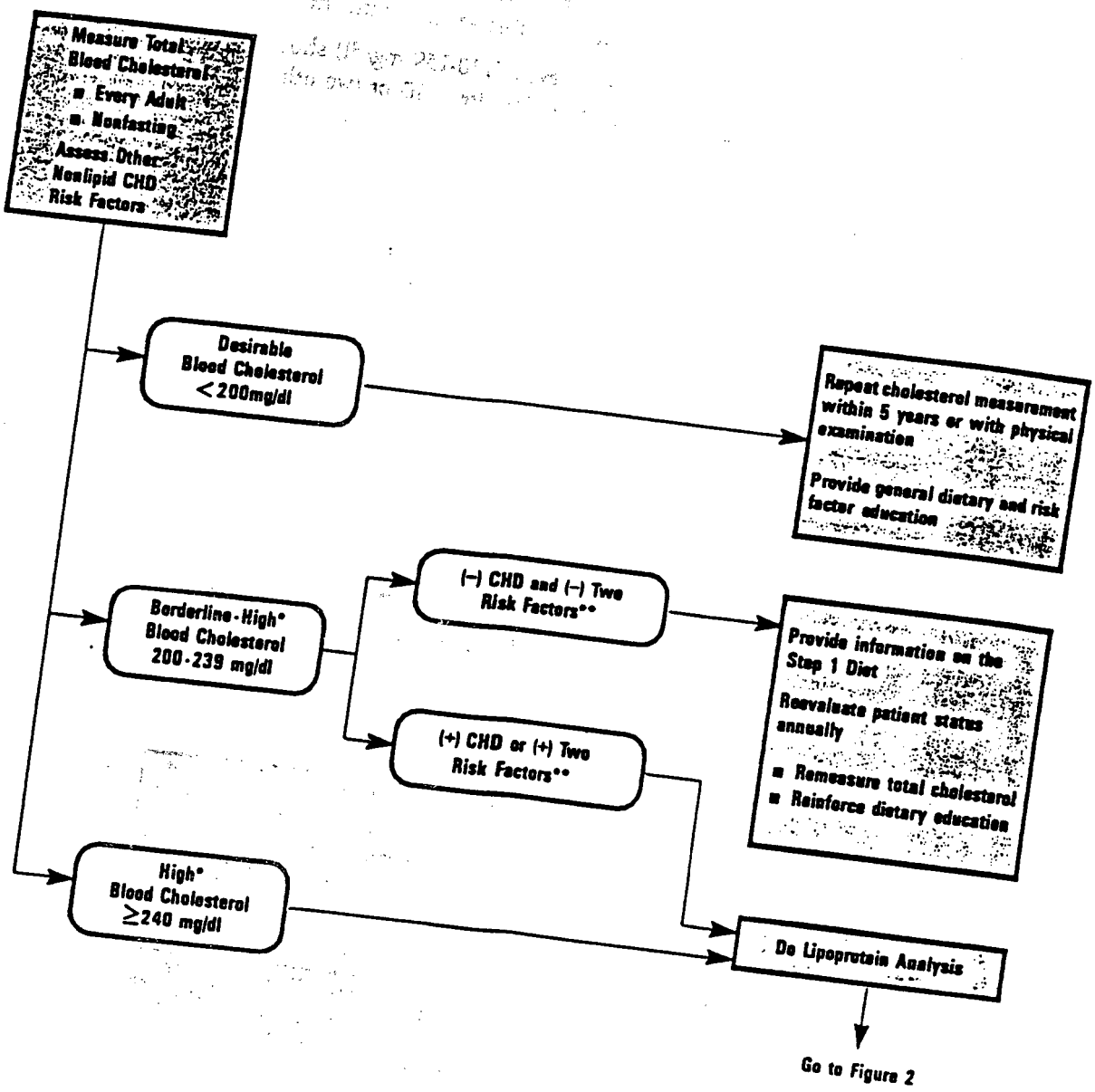
National Cholesterol Education Program
National Heart, Lung, and Blood Institute
National Institutes of Health
C-200
Bethesda, MD 20892.

Initial Classification Based on Total Cholesterol

- The total blood cholesterol level is the basis for initial patient classification.
- All blood cholesterol levels above 200 mg/dl should be confirmed by repeat measurements, with the average used to guide clinical decisions.
- Other CHD risk factors should be taken into account in selecting appropriate follow-up measures for patients with borderline-high cholesterol levels.
- All patients with a level of 240 mg/dl or above, which is classified as high blood cholesterol, should receive a lipoprotein analysis. Patients with borderline-high blood cholesterol levels (200-239 mg/dl), who in addition have definite CHD or two other CHD risk factors, should also have a lipoprotein analysis performed.
- CHD risk factors as defined in the report include:
  - Male sex
  - Family history of premature CHD (definite myocardial infarction or sudden death before age 55 in a parent or sibling)
  - Cigarette smoking (currently smokes more than 10 cigarettes per day)
  - Hypertension
  - Low HDL-cholesterol concentration (below 35 mg/dl confirmed by repeat measurement)
  - Diabetes mellitus
  - History of definite cerebrovascular or occlusive peripheral vascular disease
  - Severe obesity (≥30 percent overweight)
- In public screening programs, all patients with a level above 200 mg/dl should be referred to their physician for remeasurement and evaluation.

FIGURE

1 — Initial Classification Based on Total Cholesterol

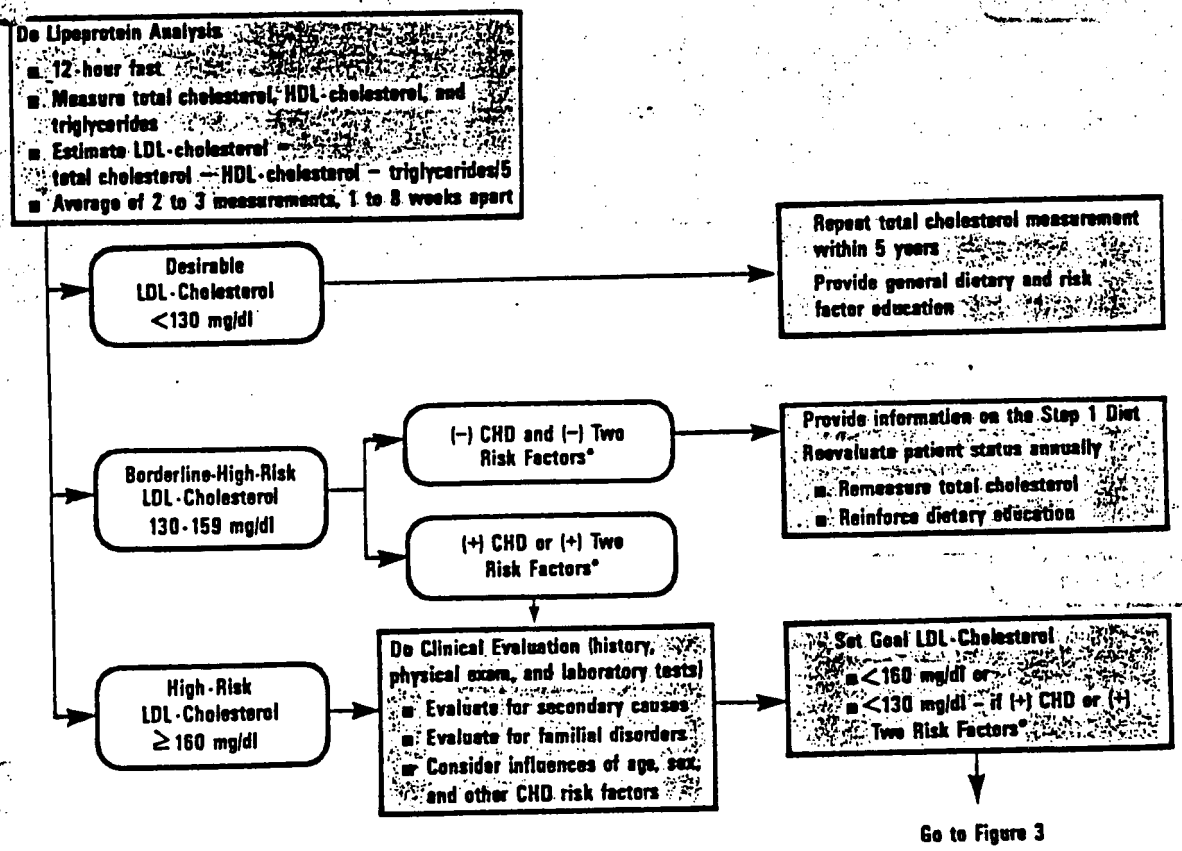


*Must be confirmed by repeat measurement; use average value.
**One of which can be male sex.

Classification Based on LDL-Cholesterol

- The LDL-cholesterol level is the basis for decisions about initiating dietary or drug therapy.
- Patients with LDL-cholesterol levels of 160 mg/dl or greater are considered at high risk for CHD. These patients should be given cholesterol-lowering treatment.
- Patients with borderline-high-risk LDL-cholesterol levels (130-159 mg/dl) should also be treated to lower their cholesterol if they have definite CHD or two other CHD risk factors (see page 1 for a list of risk factors).

FIGURE 2 — Classification Based on LDL-Cholesterol



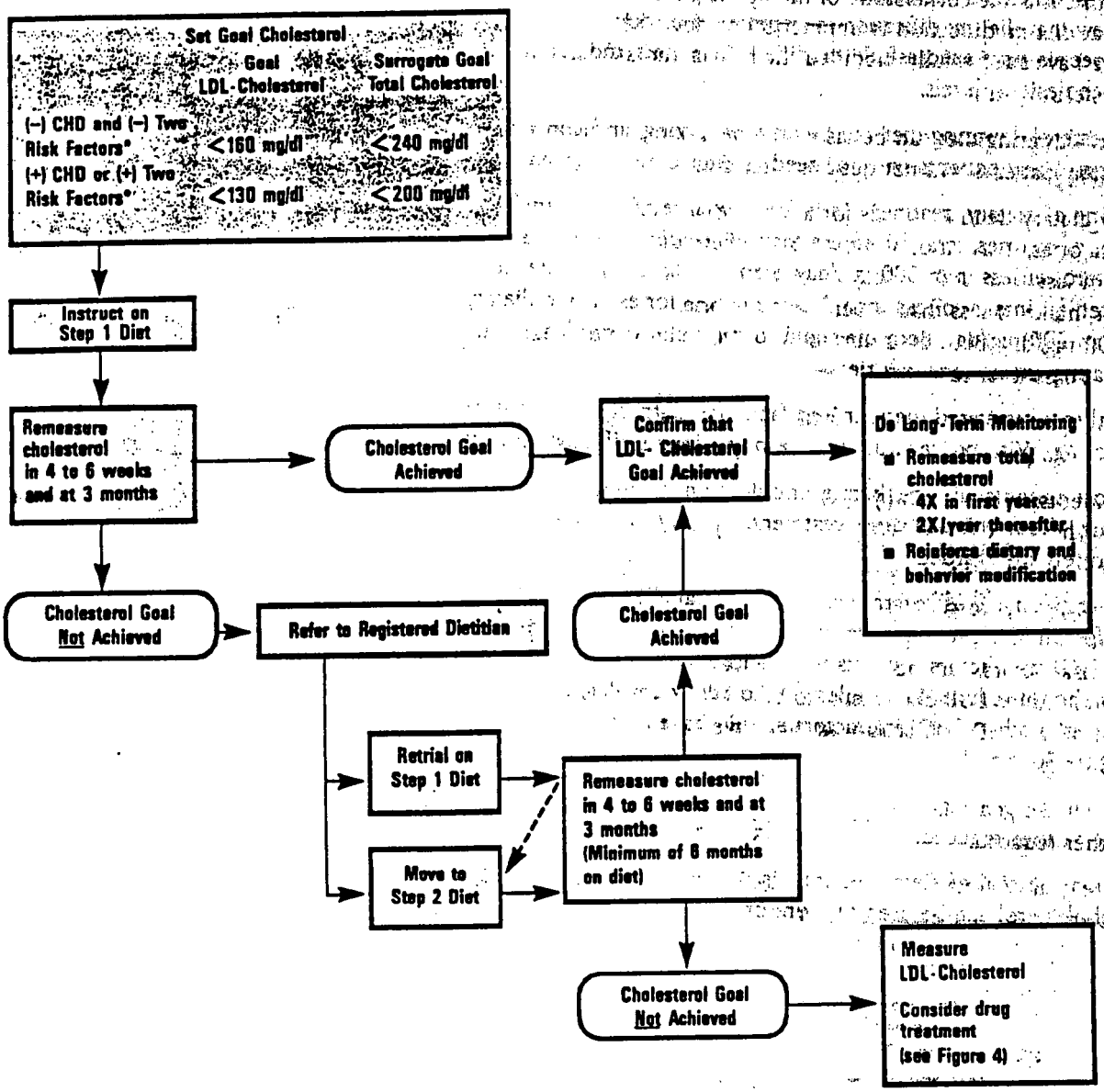
*One of which can be male sex.

Dietary Treatment

- Dietary treatment is the cornerstone of therapy to reduce blood cholesterol levels. The view that diet modification is impractical or doomed to failure is not justified. Many people have successfully modified their diets and substantially reduced their blood cholesterol levels.
- A cholesterol-lowering diet can be tasty, satisfying, and consistent with good nutrition. Many patients will not need to alter their eating habits radically.
- Step One of dietary treatment calls for an intake of saturated fat of less than 10 percent of calories, total fat of less than 30 percent of calories, and dietary cholesterol of less than 300 mg/day. Step Two calls for further reduction in saturated fat intake to less than 7 percent of calories and in dietary cholesterol to less than 200 mg/day. Both diets aim to promote weight loss in the overweight by eliminating excess total calories.
- Referral to a registered dietitian can facilitate instruction for diet modification and monitoring. With proper training, the physician's staff may perform these functions.
- For most patients, dietary therapy should be continued at least 6 months before deciding whether to add drug treatment. Dietary therapy should not be prematurely disregarded.
- The therapeutic goals recommended in the panel's report, like the cholesterol levels for initiating therapy, are influenced by the presence of definite CHD or other CHD risk factors. Patients with neither definite CHD nor two other risk factors should reduce LDL-cholesterol to below 160 mg/dl. Patients with definite CHD or two other CHD risk factors should have a goal of reducing LDL-cholesterol to below 130 mg/dl.
- The recommended goals are minimal goals. If lower goals can be achieved, risk may be further reduced.
- Although the goal of dietary therapy is to lower LDL-cholesterol concentration, total cholesterol can be used to monitor response to diet for convenience.

FIGURE

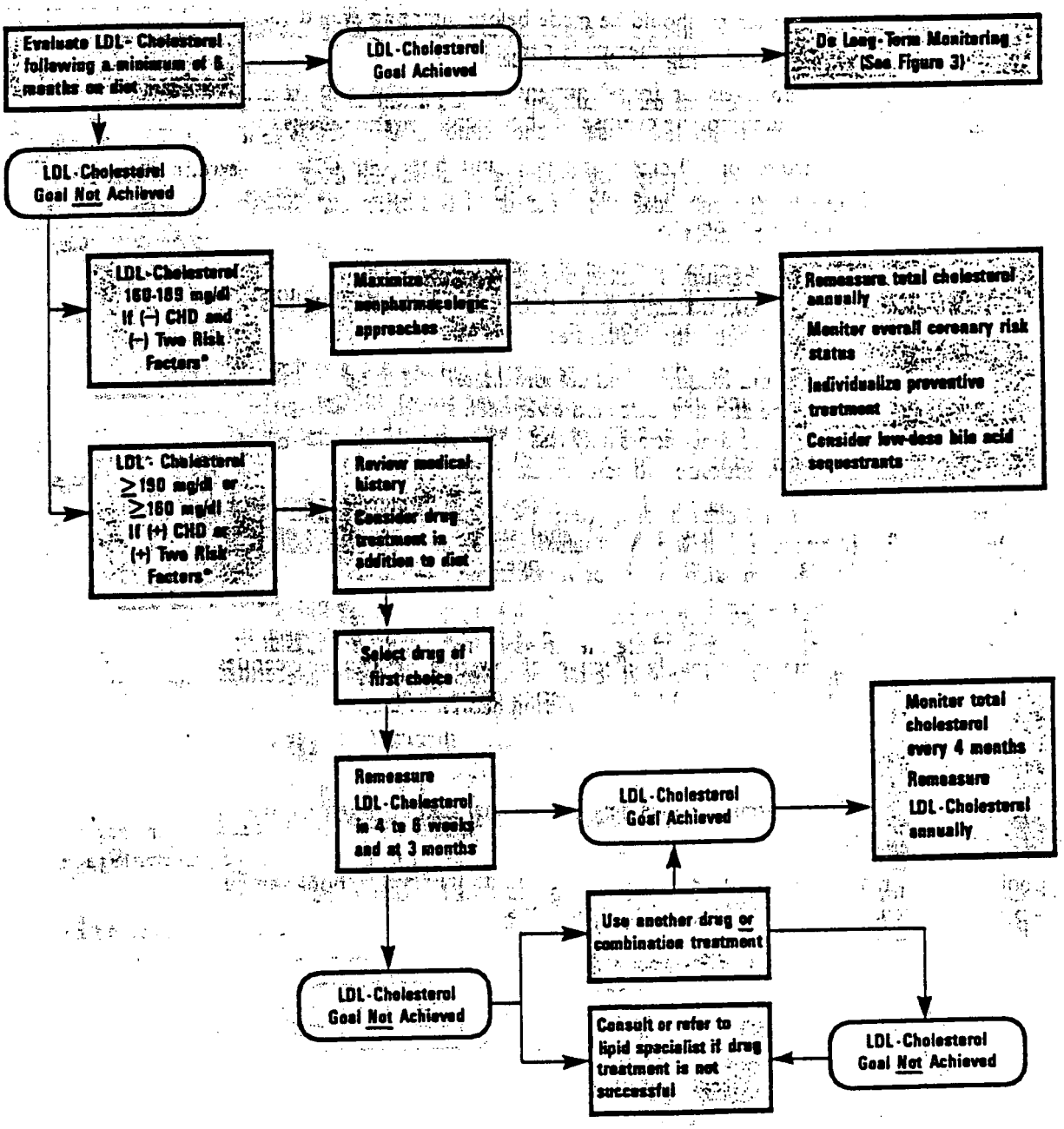
3 – Dietary Treatment



*One of which can be male sex.

FIGURE

4 – Drug Treatment



*One of which can be male sex.

Drug Treatment

- Maximal efforts at dietary therapy should be made before initiating drug therapy and should be continued even if drug therapy is needed.
- The panel set the initiation levels for drug treatment in such a way as to create a protective barrier to the inappropriate overuse of cholesterol-lowering drugs.
- Patients with LDL-cholesterol of 190 mg/dl or greater, and those with LDL-cholesterol 160-189 mg/dl who also have definite CHD or two other risk factors, should be considered for drug therapy.
- The drugs available for consideration include: bile acid sequestrants (cholestyramine and colestipol), nicotinic acid, HMG CoA reductase inhibitors (lovastatin), gemfibrozil, probucol, and clofibrate.
- The bile acid sequestrants and nicotinic acid are considered the drugs of first choice. Both cholestyramine and nicotinic acid have been shown to lower CHD risk in clinical trials, and their long-term safety has been established. These drugs require considerable patient education to achieve adherence.
- Lovastatin is the first of a new class of drugs (the HMG CoA reductase inhibitors). These drugs are very effective in lowering LDL-cholesterol, but their effect on CHD incidence and their long-term safety have not yet been established.
- The other available drugs -- gemfibrozil, probucol, and clofibrate -- are not as effective in lowering LDL-cholesterol as are the drugs of first choice or lovastatin. Gemfibrozil and clofibrate are primarily effective for lowering elevated triglycerides but are not FDA approved for routine use in lowering cholesterol.
- The goals of drug therapy are the same as those of dietary therapy (see page 4).
- Drug therapy is likely to continue for a lifetime. Thus, when dealing with the selection of bile acid sequestrants versus newer drugs that may be easier to take, safety must be emphasized.
- Cholesterol is an active area of research. Ongoing and future investigations can be expected to expand and refine drug treatment options.

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