1. INTRODUCTION

1.a. Background

Hypertension (HTN) is a major problem in the United States, affecting approximately 60 million people. It is associated with significant morbidity and mortality due to both cardiovascular and renal diseases (1,2). Improvements in the treatment of hypertension have reduced cardiovascular and cerebrovascular sequelae such as congestive heart failure and stroke, but it is unknown to what extent, if any, such improvements in treatment have had on progressive renal failure attributed to hypertensive nephrosclerosis. A number of large-scale national trials have been conducted to control blood pressure (BP); however, the intent of these studies was to evaluate their ability to decrease the incidence of cardiovascular and cerebrovascular events. These studies were not designed to examine the effect of long-term blood pressure control on renal function, prospectively. Currently there are no prospective large-scale, long-term trials which specifically evaluate the effects of blood pressure control on renal function in patients with hypertension and renal insufficiency (3).

1.b. Scope of the Problem

End-stage renal disease (ESRD), attributed to hypertensive nephrosclerosis, is the leading cause of ESRD in African Americans (4). Although African Americans make up only 12% of the U.S. population, 28% of the patients on hemodialysis are African Americans, with the rate of developing ESRD four times greater for African Americans than for Whites (5). The rate of ESRD due to hypertension is 20-fold higher in African Americans versus whites in the 25 to 44 year age group (4). Although it is not clear what accounts for this increased susceptibility to renal failure in African American hypertensives (6-12), it is evident that it is not accounted for solely by higher prevalence of hypertension (13-14) or by socioeconomic factors (15). The healthcare costs for the increasing number of African American hypertensives reaching ESRD was 1.24 billion/year in 1990 (16). Furthermore, the cost of morbidity and mortality to the individual with hypertension transcends the dollar cost.

1.c. Unique Aspects of Hypertensive ESRD in African Americans

The Hypertension and Detection Follow-up Program revealed that the five year mortality for African American hypertensives exceeded that for Whites even for those in the stepped-care group (17). African Americans with HTN have a higher incidence of left ventricular hypertrophy, strokes and ESRD when compared to White hypertensives (18). Risk factors which have been demonstrated to contribute to an increased incidence of ESRD include diagnosis at a younger age of HTN, lower income levels, presence of diabetes, history of smoking, or higher diastolic blood pressure (DBP). However, the African American race remains a strong independent variable associated with hypertensive ESRD (15).

There are differences between African American and White hypertensives, some of which may be important in the increased risk of ESRD. Normotensive African Americans have a systolic BP 5.6 mmHg higher and a diastolic BP 5 mmHg higher than Whites (19). Compared to hypertensive Whites, hypertensive African Americans have: increased salt sensitivity, decreased potassium intake, lower plasma renin levels, decreased kallikrein excretion, decreased sensitivity to β-blockade, increased responsiveness of their HTN to diuretics, increased vasopressin levels, increased intracellular calcium and decreased dopamine responses to salt loads (20-23). There is also evidence for racial differences in the renal vasculature among hypertensives, with African Americans having decreased renal blood flow and increased vascular resistance at all levels of systemic pressure relative to Whites (24). Which, if any, of these differences explain the discrepancy in development of ESRD in African American versus White hypertensives remains to be determined.

Among African Americans 45% of ESRD patients are women whereas only 33% of White ESRD patients are women (5). The limited data which exist suggest that gender, like race and age, significantly influences the natural history of HTN, the selection of antihypertensive agents and the treatment response (25). An important element of any study of HTN and treatment outcome will be the recruitment of a significant number of women.

1.d.Renal Structure in Relation to Function in African American Hypertensive Nephrosclerosis

Much of the published data on the incidence and prevalence of ESRD due to HTN in the U.S. population is derived from ESRD registries which use clinical diagnosis unsubstantiated by biopsy or autopsy data (26-27). In a recent report of 27 white patients with hypertension but without nephrotic syndrome (1.2-4.3 gm/day proteinuria) biopsied six were found to have occult glomerular disease (3 IgA, 2 membranous and 1 membranoproliferative glomerulonephritis) (28). Thus, cases of hypertensive ESRD may be mislabeled thereby resulting in a spurious, overestimation of the true incidence and prevalence of this cause of ESRD. Of patients newly admitted to ESRD programs with a clinical diagnosis of hypertensive nephrosclerosis 41% are African American. Since presumptive hypertensive nephrosclerosis is the most common cause of ESRD in African Americans, this mislabeling was thought to be particularly relevant to African Americans. Indeed, misclassification bias based on the racial characteristics of the patients may account for some of the excess diagnosis of clinically defined hypertensive nephrosclerosis in African Americans. However, the AASK pilot study did not show a need for biopsies, so they are excluded for the full-scale study.

1.e.Evidence for the Renoprotective Effects of Blood Pressure Control

Several human studies have evaluated the effect of BP control on the development or progression of renal insufficiency attributed to hypertensive nephrosclerosis. A retrospective study found that despite control of diastolic BP African Americans were still twice as likely as Whites to have elevations in serum creatinine. Sixteen percent of patients with good BP control developed progressive renal insufficiency (29). Several possibilities exist for the

failure of these human studies to demonstrate a clear beneficial response to BP control (30). The degree of BP control, duration of the intervention and population size vary from one study to another. Some of the patients included in these studies may have had diseases other than hypertensive nephrosclerosis. Progression of renal insufficiency may also have occurred secondary to aging. Finally, and perhaps most importantly, newer agents such as calcium channel blockers (CCB) and converting enzyme inhibitors (CEI) were not part of the antihypertensive regimens in early studies.

Alternatively, it has been demonstrated that long-term BP control with conventional antihypertensive medications (including ganglionic blocking agents, reserpine, diuretics, vasodilators and β-blockers) can preserve renal function (17, 31-36). However, such analyses have been limited for two major reasons. First, large-scale trials were not specifically designed to assess renal function in relation to BP control. Consequently, little or no information on precise measurements of GFR is available from these studies. Second, patient selection criteria was such that in some of the studies large numbers of patients were followed with normal baseline renal function.

The Hypertension and Detection Follow-up Program reported that in hypertensive patients with serum creatinines between 1.5 and 1.7 mg/dl there was a significant decrease in the rate of decline of renal function in patients with better BP control (17). In a smaller study of 79 hypertensive patients (89% African American) with nephrosclerosis, BP control improved renal function as measured by glomerular filtration rate (iothalamate) and serum creatinine (37). Several other retrospective studies confirmed the beneficial effect of BP control on slowing the rate of decline of renal function (38). In a retrospective review of the data from the Multiple Risk Factor Intervention Trial it was found that some subjects with mild to moderate hypertension had a progressive loss of renal function (estimated by serum creatinine). Importantly, effective blood pressure control was associated with stable or improving renal function in non-African Americans but not in African Americans (39). This retrospective study not only emphasizes the importance of mild and moderate hypertension on loss of renal function, but also raises important questions about the relationship of blood pressure reduction and renal function changes in African Americans. Also, in multiple experimental models in rats lowering BP with a variety of agents has been shown to be renoprotective (40-47). Thus far, no prospective, large study has adequately addressed the issue of whether or not BP control will slow the rate of decline of renal function in African Americans with presumed hypertensive nephrosclerosis or what level of blood pressure control is best.

1.f. <u>What Degree of BP Control is Beneficial?</u>

Important to note is that although severe diastolic HTN has a greater risk of azotemia than mild HTN, many cases of renal dysfunction will develop in those hypertensives with only mild to moderate elevations of diastolic BP (90-104 mmHg) (39,48). This is because the number of patients with mild to moderate HTN far exceed those with severe HTN (49). Thus, the control of BP even in patients with mild HTN must be addressed. In the Modification of Diet and Renal Disease (MDRD) Study, there was a significant correlation between BP

levels and the rate of decline in the GFR in proteinuric patients. Renal function was better preserved in those patients who had better BP control. This correlation persisted even in patients with BP levels below 140/90 mmHg (49). This suggests that it may be necessary to reduce BP below this widely accepted target level to preserve renal function.

In a preliminary report of a retrospective study of subjects with hypertensive renal disease, it was demonstrated that control of BP over a period of 3 years resulted in stabilization of GFR (iothalamate) (55). Of the 94 patients studied, 63% were African American but only 20% were female. Interestingly, this preliminary report described an improvement in mean GFR in 22 patients (89% were African American and 79% were male), of which 14 were randomized to strict BP control and 8 randomized to usual control. Mean GFR increased in patients assigned to both BP control groups. These results provided important evidence that renal function can not only be preserved with an intensive, persistent effort to maintain lower BP, but in fact can improve over time. Unfortunately, in this small group significant differences in diastolic BP control were not maintained over the 36 months of follow-up. Thus, with respect to BP control level, overall there were no discernible differences in GFR preservation (50). Although there is preliminary evidence to suggest that renal function is better preserved with BP control at levels even lower than the traditionally accepted 140/90 mmHg, cardiologists have expressed concern over the "J-curve phenomenon" in patients with underlying coronary artery disease (51). The concern is that if arterial BP is reduced too much through antihypertensive therapy, patients will have an increased risk of myocardial infarction. Similar concerns about underperfusion of the kidney at too low BP's exist. This may be a relevant concern in the renal vasculature as well, particularly if occult bilateral renal artery occlusion is present. Although it has not been studied, ischemic renal disease may be prevalent in African Americans. In the setting of ischemic renal disease lowered systemic pressure may result in a further decrease in renal blood flow and a "renal J-curve phenomena." More investigation with a broader range of BP goals is required to resolve this controversy.

1.g. Are Specific Antihypertensives Selectively Renoprotective?

The choice of antihypertensive drug may impact on preventing progression of renal failure. Data from animal studies on the protective effects of CEI and CCB have suggested that two major mechanisms may contribute to progressive renal failure, namely glomerular capillary hypertension and glomerular hypertrophy (41-42). These animal experimental models have shown that not all hypertensive regimens are equally renoprotective. Thus, agents such as CEI and CCB have been shown to protect the kidney from progressive glomerular sclerosis independent of their effect on systemic blood pressure (40, 42). These studies have formed a basis for testing the hypothesis in humans that CEIs and CCBs may offer a therapeutic advantage over conventional agents by being renoprotective in patients with renal insufficiency attributed to hypertensive nephrosclerosis.

The actions of CEI are well known (52). These agents decrease the production of angiotensin II and, in turn, aldosterone, by binding to active sites of converting enzyme. In addition, the antihypertensive mechanisms of CEI include non-renin mediated pathways. The reactivity

of the vasculature to norepinephrine may be reduced by this class of agent. CEI's may also exert a renoprotective effect by modulating growth factors or inhibiting matrix formation. CEI can block converting enzyme from breaking down the vasodilator, bradykinin, into inactive peptides. CEI, working through maintaining bradykinin, may stimulate the synthesis of vasodilatory prostaglandins, PGE_2 and PGI_2. It is important to note that the generation of both systemic and intrarenal angiotensin II is inhibited by CEI. The latter action of CEI may account in a major way for the renoprotective effect of this class of antihypertensive agent. As clearly shown in the remnant rat model of kidney failure, inhibition of angiotensin II generation has a greater vasodilatory effect on the efferent arteriole, which results in normalization of intraglomerular pressure, while improving renal blood flow and raising the glomerular ultrafiltration coefficient (40). It was demonstrated in this rat model that lowering the systemic BP with captopril better preserved renal function than lowering the systemic BP to an equal level with a combination of hydralazine, hydrochlorothiazide and reserpine (40). One possible explanation of these results is that elevated intraglomerular pressure is critical in the pathogenesis of glomerular sclerosis and progressive renal injury and CEI's, by lowering intraglomerular pressure, protect the kidney from glomerulosclerosis. However, whatever the mechanism, these studies have clearly demonstrated that CEI's preserve renal function better than the other antihypertensives tested, independent of their effects on systemic blood pressure. Short-term uncontrolled studies utilizing CEIs alone or in combination with a diuretic in humans with chronic renal disease have provided evidence that these agents may slow the rate of progression of renal disease and may be more efficacious than conventional agents (53-59). Unfortunately, these studies were limited by small numbers of patients, the use of retrospectively defined control periods, and the lack of randomized double-blind controlled design. Thus, there is a clear need for a prospective, randomized trial to determine if treatment of hypertension with CEIs can prevent progression of renal insufficiency attributed to hypertensive nephrosclerosis. This remains true despite the suggestion that when this class of agent is used as monotherapy in African Americans, it is less effective and may in certain circumstances (such as with intravascular volume depletion) contribute to an increased risk of acute renal failure (60). Furthermore, CEIs become effective antihypertensive agents in African Americans when a diuretic is added (61). Also, if significant prevalence of ischemic renal disease exists CEI's could lead to an episode of reversible acute renal failure.

Animal studies have also suggested that CCBs may also be renoprotective. Yoshida et al demonstrated by serial micropuncture studies in the remnant rat kidney model that the degree of glomerular capillary HTN did not correlate well with the subsequent development of glomerular sclerosis. Instead, glomerular sclerosis was better correlated with glomerular size (62). These studies suggest that glomerular hypertrophy, induced as an adaptive response to a reduction in functioning renal mass, is an important precursor to glomerular sclerosis. This may also explain why CCBs have been shown to prevent progression without necessarily lowering glomerular pressure, since they may inhibit glomerular hypertrophy (63). It has demonstrated that renal function in rat models is preserved specifically by nifedipine (42, 44, 49). In humans, preliminary data also suggest that CCB prevent progressive renal injury independent of their effect on systemic blood pressure and in contrast to other antihypertensive agents (64). Not all CCB's appear to have the same

effects on the kidney (42,43). CCB's are currently being recommended as an initial therapy in African American hypertensives. Thus, to answer the question whether in humans with clinically defined hypertensive nephrosclerosis either CCB's or CEI's, agents which in animal models and small studies in humans have been proposed to preserve renal function independent of their effect on systemic blood pressure, preserve renal function a clinical trial comparing CCB's to CEI's and to therapy excluding these agents (β-blocker arm) should be conducted.

In summary, ESRD attributed to presumptive hypertensive nephrosclerosis is a major national health problem. African Americans with HTN are clearly at greater risk for the development of ESRD than hypertensive Whites. This study proposes to explore both the specific antihypertensives and the different levels of BP control that might slow the rate of decline of renal function in hypertensive African Americans.

1.h. Effects of Specific Antihypertensive Agents on Renal Hemodynamics

Different classes of antihypertensive agents result in renal hemodynamic effects that may have a bearing on the natural history of renal disease. Specifically, ACE inhibitors reduce GFR by two to six percent below baseline within the first three months of initiation (65-67). This initial reduction in GFR has been documented to persist for up to seven years following initiation of drug (68). Moreover, it has been shown that termination of the drug is associated with an increase in GFR (68, 69), suggesting that the initial reduction may be reversible. Similarly most B-blockers also reduce GFR but only from one to two percent below baseline (70-71). However, there are no data on long term effects of this class of drugs on GFR. Conversely, CCBs increase GFR from two to seven percent above baseline (72-73). These estimates are based on the existing literature that is predominately in diabetic patients and very limited in African Americans.

The impact of these initial persistent effects on the overall slope of GFR over time is not fully understood. Two recent studies, however, exemplify the fact that if these initial and persistent hemodynamic effects are ignored one may reach a misleading conclusion. In a study by Bakris et al, predominately black hypertensive Type II diabetic subjects with a mean GFR of 64 ml/min were randomized to either an ACE inhibitor or CCB and followed for one year (65). The ACE inhibitor group had a 7% decline in GFR within the first three months of treatment, whereas the CCB group had an increase of two percent. An analysis of the total GFR change using a two slope model revealed that the ACE-inhibitor worsened renal function while CCB preserved renal function. However, an analysis of chronic slopes, that is the slope from three months to the end of the study, showed no significant differences between the two agents (65). This is further supported by a recent report by Bauer, et al (67).

Given that we are studying a chronic disease and that these antihypertensive agents have different initial effects on GFR which persist in spite of blood pressure reductions, it is essential that the rate of change in GFR in the "chronic phase" following the initial effects be considered in analyses of the effects of interventions involving these agents. A single slope analysis,

done by the traditional method, would not take this acute persistent effect into account and may not reflect the "true" rate of decline in GFR. Conversely, a two slope analysis, focusing on the total GFR change from baseline to the end of the study, accounts for any initial and persistent hemodynamic effect, but is dependent on the duration of the study. Given the fact that most studies are much shorter in duration (< 10 years) than the total clinical course of renal disease progression (> 20 years) a total GFR change analysis may be underpowered if the initial GFR reduction is in the opposite direction of the hypothesized beneficial effect. A chronic slope analysis, however, discounts any initial change in GFR and is thus more sensitive to effects of the interventions in the chronic phase. Moreover, if a "steady state" is assumed for the chronic phase, the rate of GFR change during this phase may be a more reliable indicator of the long term effects of the interventions. It is noteworthy that no data exist from clinical studies that address the issue of how the initial persistent reduction in GFR interacts with the natural history of the rate of decline in GFR. Studies from hypertensive animal models with ACE is to demonstrate preservation of renal morphology in spite of this initial and persistent effect on GFR (74-75).

The rationale for considering the chronic slope as a key component of an assessment of the effects of the interventions on progression of renal disease are clear. However, if the total change in GFR from baseline to the end of the study is not different between two treatment interventions, it is not clear that a difference in chronic slopes alone would provide convincing evidence that an intervention will ultimately delay the onset of renal failure. In particular, it is possible that a difference in chronic slopes may by due, in part, to a slow attenuation of the initial acute GFR reduction (76). Consequently, we will examine both the total GFR change and chronic slope of GFR to assess change over time. This is described more fully in the analysis chapter.

1.i. Goals of the AASK Full Scale Study

The goal of the AASK Full-Scale Study is to conduct a randomized trial to evaluate the efficacy of different treatment regimens and different levels of BP control in slowing the progression of renal disease in African American hypertensive patients with chronic renal insufficiency.

The Full-Scale Study has the following goals:

1)To determine whether antihypertensive regimens including ACE or CCB as a first step will be more effective in slowing the progression of renal disease than a regimen with BB as a first step at the same level of control of blood pressure. (That is, are ACE and/or CCB renal protective?)

2)To determine whether moderate blood pressure control or low blood pressure control will be more effective in slowing the progression of renal disease in African Americans with hypertensive renal disease.

3)To determine whether these regimens are safe and acceptable to the participants.

1.j. Timeline: Month 1 to 88

The timeline from Month 1 (March 1995) to Month 81 (November 2001) is as follows:

Study Calendar Timeline:

Month 1Start enrollment
Month 38.5Initial Enrollment ends. Last SV2 Visit (May 15, 1998).
Month 78Last patient's Close Out Visit
Month 81 Last patients' Post Close Out Visit

1.k. <u>Patient Timeline</u>

The patient timeline for baseline and for the first month of follow up is as follows. A complete patient timeline through FV81 is outlined in the Forms Completion Schedule.

TIME LINE	**VISIT NUMBER**	**FORMS**
Chart Review	None	Form 1
Primary Screening (one or two visits)	SV-1	Form 2 (For patients not on meds, you may consider completing a Form 10 at SV-1)
	SV-2	Forms 4, 10, 12, 13, 14, *18*, 22 & 80
Informed Consent #1 (Consent to two GFR's and to back titration)		Consent Form #1 (This can be done at SV2 or at a separate CV1 visit)
Baseline 24-Hr. Urine	B1	*19* & 23 (can be completed at either SV2 or G1)
Back Titration (if necessary)	BT-1 to BT-99	Forms 10 & 11
GFR 1	G-1	Forms 10, 11, 13, *18,* 22 & 24
GFR 2 (at least one week after G1)	G-2	Forms 10, 11 & 24

TIME LINE	VISIT NUMBER	FORMS (continued)
Secondary Screening	None	Form 53
Informed Consent #2 (for Randomization)		Consent Form #2 or Sincere Discussion (This can be done at G2 or at a separate CV2 visit)
Randomization	None	Form 52
Pt. Receives Drug	FV0-0	Forms 5, 10, 11 & *40*
Special Visit	FV0-1	Forms 5 (if change to meds), 10 (optional), 11, 13, 18 (K and Cr only), 22 & 40

All Interim Visits require a Form 11 and any other forms which are specified by the Protocol (Section 10.j.)

Follow-Up Visit 1	FV1-0	Forms 5, 10, 11 & *40*

Follow-Up visits continue monthly to FV6 and every other month thereafter.

1.l. Documentation: Protocol, Manual and Forms

1.l.1 Purpose of the Protocol

The protocol describes the study, explains which procedures will be done, why they will be done and how the results will be utilized and interpreted.

1.l.2 Manual of Operations

The Manual of Operations includes the detailed instructions for performing the procedures required by the protocol. Sections of the Manual of Operations will be aimed toward the Study Coordinator, the Data Entry Specialist, the GFR Technician, the Blood Pressure Technician, and the Principal Investigator.

1.l.3 Forms and Reports Manual

The Forms and Reports Manual includes forms to be used for study data collection with instructions for their use.

1.m. Training and Certification Plans

Quality data collection and appropriate conduct of the study will require careful attention to the training of clinical center personnel.

Training and certification sessions for GFR Technicians, Blood Pressure Technicians, Study Coordinators, and key entry personnel will be held prior to the initiation of patient recruitment. The protocol, forms and other materials will be distributed to the appropriate clinical center personnel prior to the training session. Each center's personnel will be trained centrally in the study requirements such as blood pressure monitoring by random zero sphygmomanometer and GFR performance by iothalamate, counseling for adherence and the eliciting of information from study participants in a uniform reproducible manner. During the training session, presentations will be made by staff members of the Data Coordinating Center, Central GFR Lab, Central Biochemistry Lab and Drug Distribution Center. This training session will cover patient recruitment and patient eligibility and exclusion criteria. The clinical centers will be shown how to enroll patients as uniformly as possible over time and ways to reach the recruitment goals in the allotted time period. The data to be collected and the procedures to be done at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item by item basis. The Coordinators will also be trained in the use of the SF-36. The coordinators will learn how to code the patients medications and do pill counts. The methods for distribution of study antihypertensive medication and monitoring compliance to medication regimens will be discussed. The training sessions will include presentations regarding enhancing compliance to medications and helping the patients reach blood pressure goals and other goals.

Entering data forms, responding to data discrepancy queries and general information about obtaining research quality data will also be covered during the training session. Use of electronic mail will also be covered.

At the initial training session, the following certification sessions will be held: 1) data entry and correction, 2) random zero blood pressure measurement and 3) GFR test administration.

Recertification will be done annually for the random zero blood pressure trainers from each center and for GFR measurement.

2. OBJECTIVES AND DESIGN

2.a. Objectives

The objective will be to conduct a multi-center, prospective, randomized trial to determine the effects of blood pressure control and the use of specific antihypertensive regimens on the progression of renal insufficiency which has been clinically attributed to the effects of hypertension on the kidney. Two levels of BP control and 3 different antihypertensive regimens will be tested for their efficacy in slowing the rate of decline of renal function. The primary outcome to be measured in the full scale trial is the change in GFR as determined by iothalamate clearance. Details are included in the analysis plan (Chapter 12).

2.b. Design

The experimental design is a multi-center, prospective, controlled, blinded randomized study examining the impact of two different levels of blood pressure control and the impact of three antihypertensive regimens with different randomized agents (CCB, CEI, and conventional therapy with β-blockade) on the rate of change in GFR in African American subjects with hypertension and established renal insufficiency. The study will follow a two by three factorial design with stratification by clinical center. The first factor will be two levels of goal BP as defined by mean arterial pressure (MAP). One group will have a goal MAP $\leq$ 92 mmHg and the other group will have a MAP between 102-107 mmHg inclusive. BP will also be treated to < 160/90 in all participants. A MAP of 107 reflects good blood pressure control based on all currently available information. The MAP goal of $\leq$ 92 mmHg represents a lower goal of unknown but potential benefit. There will be a 10 mmHg separation between these two groups. This 10 mmHg difference is considered critical so that clear separation between the two BP groups is achieved.

The second factor will consist of three drug regimens, each initiated by a different agent. The three initial drugs used in these regimens will be a calcium channel blocker (amlodipine), an angiotensin converting enzyme inhibitor (ramipril) and conventional therapy with a β-blocker (metoprolol). The 3 X 2 factorial design is depicted below:

	Angiotensin CEI	β-BLOCKER	CCB
MAP $\leq$ 92	A1	B1	C1
MAP 102-107	A2	B2	C2

There will be six groups of participants, A1 and A2, B1 and B2, and C1 and C2.

2.c. Antihypertensive Medication Treatment Arms

The three regimens will be initiated by converting enzyme inhibitors, calcium channel blockers, and β-blockers with or without other agents as needed to achieve blood pressure goal. The CEIs lower peripheral arterial resistance, tend to raise cardiac output slightly, increase renal blood flow, decrease intraglomerular pressures (in some animal models), decrease efferent arteriolar resistance and decrease blood pressure. These affects accumulate over the first weeks of treatment. Adverse effects may include hypotension, rash, fever, eosinophilia, upper respiratory problems, cough, proteinuria in excess of 1 gram per day, neutropenia with or without agranulocytosis, hyperkalemia, and rarely angioedema. In the presence of bilateral renal artery stenosis, acute deterioration of renal function can occur and may lead to renal failure. This phenomena occurs usually within 14 days of beginning CEIs and is reversible if detected quickly. This implies that monitoring of the drug's effects for individuals will need to be done shortly after initial therapy. Ramipril is a CEI that has the advantage of being a once a day drug. This will potentially allow better compliance rates.

Calcium channel blockers dilate the main coronary arteries and arterioles, reduce arterial pressure and total peripheral resistance, decrease myocardial energy consumption, decrease A-V conduction, and decrease glomerular hypertrophy (in some animal models). These effects are generally additive when used with other antihypertensive agents. Potential adverse effects from CCBs include headache, first degree A-V block, dizziness, peripheral edema, elevation of liver enzymes, bradycardia, ECG abnormalities, nausea, sexual dysfunction and rash. Amlodipine has been chosen since it is a once a day CCB, again allowing better compliance rates.

The β-blocker regimen is intended to represent an older, less expensive, usual care arm for comparison with the CCB and CEI regimens. Also, there is little evidence that β-blockers have any benefit to preserve renal function independent of their effect on systemic blood pressure and so participants randomized to this regimen could be compared to proposed renoprotective regimens (CCB or CEI). Beta-blockers have a negative chronotropic effect due to blockade of the sinoatrial node and also have negative effects on inotropic and vasodilator responses. Conduction in the A-V node is lengthened and stroke volume shows a moderate increase both at rest and during exercise. Mechanisms for antihypertensive activity of the β-blockers are not well understood but may include competitive antagonism of catecholamines and peripheral adrenergic neuron sites, suppression of renin activity, and a more central effect with reduced sympathetic outflow to the periphery. Use of these drugs is contraindicated for patients with bronchospastic disease or second or third degree heart block. Also, when it becomes necessary to withdraw β-blockers they should be tapered in order to avoid a rebound effect unmasking previously occult angina. Common adverse effects include dizziness, fatigue, depression, wheezing, cold extremities, skin rashes, worsening claudication, impotence and sleep disturbances. More severe potential problems include bradycardia, congestive heart failure or second or third degree heart block. Metoprolol is β_1-selective

agent, producing a lesser effect upon bronchial and vascular smooth muscle than do the

non-selective agents such as propranolol. The Toprol form of metoprolol can also be prescribed in a once a day fashion, again potentially increasing compliance rates.

Although the goal of the full-scale study is to test whether one of these treatment arms helps preserve renal function better in African Americans with the clinical entity that is now attributed to hypertensive renal disease, a second goal is examining whether one of two levels of BP control ($\leq$ 92 mmHg vs. 102-107 mmHg) will also better preserve renal function. To achieve the BP goals, other antihypertensive medications will be used with the following guiding principles. The participants will be assigned to one of the above three randomized regimens, used alone in patients not on other classes of antihypertensive therapy at randomization, or as add-on therapy for those receiving other classes at the time of randomization. Subsequent to that assignment, *no other CCBs, CEIs, or β-blockers will be used in any of the participants to achieve BP control. If the BP goal is not reached in a given participant on maximal tolerated doses of the drug assigned, additional antihypertensive medications will be added. The recommendations are that antihypertensive medications will be added in the following order: 1) diuretics (furosemide); 2) α-blockers (doxazosin); (3) centrally-acting$_2$ agonist (clonidine); (4) minoxidil or hydralazine. It is recognized that in some participants any one of these additional antihypertensive medications may be contraindicated, may produce unacceptable adverse effects, or may be demonstrated to be or known to be not efficacious. However, where feasible, all attempts will be made to add additional antihypertensive medications in the above sequence and to maximize the dose of medications at one level before progressing to a new agent to enhance uniformity in the additional antihypertensives utilized.

It is the intent of this protocol to test whether any of the randomized drug regimens (β-blockers, CEIs, or CCBs) better preserve renal function in African Americans with renal insufficiency attributed to hypertensive renal disease independent of their effect on blood pressure. It is not the intent of this protocol to examine the efficacy of the randomized drug regimens (β-blockers, CEIs, or CCBs) in controlling BP, but rather their impact on preserving renal function. It is anticipated that the use of additional antihypertensive medications in the different treatment arms will be similar, allowing a post hoc analysis of their use.

2.d. Length of Time for Screening/Baseline in the Full-Scale Study

It is anticipated that there will be a 24-month period for recruiting, screening and entering patients into Baseline in the Full-Scale Study. This 24-month period will begin on March 1, 1995, approximately 2 weeks after the central training session, at the time when study data flow begins.

2.e. Sample Size in the Full-Scale Study

The sample size for the Full-Scale Study will be 1176 patients. Details on sample size and power are included in the Analysis Plan, Chapter 12. Sample size per center is in Table 5.1.

3. PARTICIPANT SELECTION/ELIGIBILITY AND EXCLUSION CRITERIA

3.a. Inclusion Criteria

1.African-American men and women (including Black individuals born in the Caribbean, Africa, Canada, etc.) age 18-70 years. Each center will attempt to include both men and women, at least 1/3 of each.

2.Hypertension is defined as a sitting diastolic blood pressure of 95 mmHg or more. The average of the last two of three consecutive readings on an random zero sphygmomanometer machine at any visit is the level used. Hypertensive participants on antihypertensive therapy at Baseline need only one qualifying clinic visit. Those not currently on medications at Baseline must qualify on each of two consecutive clinic visits.

3.Reduced renal function, defined as a pre-randomization (G1 visit) ^{125}I-iothalamate glomerular filtration rate between 20-65 ml/min/1.73m^2.

4.Willingness and ability to cooperate with the protocol.

3.b. Exclusion Criteria

1.History of malignant or accelerated hypertension within 6 months prior to study entry; previous chronic peritoneal or hemodialysis or renal transplantation.

2.Known secondary causes of hypertension.

3.Any known history of diabetes mellitus type I and II or fasting (8-12 hrs.) glucose > 140 mg/dl on two occasions or glucose > 200 mg/dl on one occasion prior to randomization.

4.A ratio of urinary protein (mg/dl) to creatinine (mg/dl) exceeding 2.5 in a 24-hour urine sample collected at or shortly before the initial GFR visit. (This ratio is used as an estimate of > 2.5 g/d proteinuria without needing to factor for validity of the collection.)

5.Clinical or renal biopsy evidence of any renal disease other than hypertensive nephrosclerosis. Persons with arteriographically documented renal arterial atherosclerotic disease less than 50% stenosis of the renal artery should be considered eligible for study participation if the PI at the center feels the disease is not clinically significant.

6.History of drug abuse in the past 2 years, including narcotics, cocaine or alcohol (> 21 drinks per week).

7.Serious systemic disease that might influence survival or the course of renal disease. (Chronic oral steroid therapy is an exclusion, but steroid-containing nasal sprays are

not. Inactive sarcoidosis is not an exclusion.)

8.Clinical evidence of lead intoxication.

9.Arm circumference > 52 cm, which precludes measuring blood pressure with the "thigh" blood pressure cuff.

Arm length such that if the cuff that is appropriate for the arm circumference extends into the antecubital space so that the cuff would interfere with placement of the stethoscope over the brachial artery for blood pressure measurement.

10.Clinical evidence of congestive heart failure, current or within the preceding six months. Ejection fraction below 35% measured by any method. Heart block greater than first degree or any other arrhythmia that would contraindicate the use of any of the randomized drugs.

11.Reactive airway disease, current or in the preceding six months requiring prescribed treatment for more than two weeks.

12.Impairment or difficulty in voiding, precluding adequate urine collections.

13.Intake of nonsteroidal anti-inflammatory agents (NSAIDs) more than 15 days/month, excluding aspirin. Inability to discontinue NSAIDs or aspirin for 5 days prior to GFR measurement.

14.History of severe adverse reaction to any of the randomized drugs required for use in the protocol or contraindication of their use.

15.Pregnancy or likelihood of becoming pregnant during the study period; lactation.

16.Serum potassium level > 5.5 mEq/L at the SV2 and confirmed at G1 for those <u>not</u> on ACE inhibitors during Baseline, or serum potassium level >5.9 mEq/L at the SV2 and confirmed at G1 for those on ACE inhibitors during Baseline.

17.Leukopenia < 2,500/mm^3 at SV2 and confirmed at the end of Baseline.

18.Medically-indicated need for any of the randomized drugs for any other reason (including angina pectoris, migraine, arrhythmia).

19.Allergy to Iodine.

20. Suspicion that the participant will not be able to adhere to medications or comply with the protocol visit schedule.

21. Participation in another intervention study.

4. INFORMED CONSENT

4.a. General Principles of Consent

In order to be eligible for the study, each participant must be willing to sign 1) a statement of informed consent consenting to Baseline and potential later randomization and follow up prior to the Baseline Period, 2) a statement of informed consent for randomization and follow up prior to randomization. This will document the agreement of the participant to participate in the study activities. These two consent forms may be combined. However, the participant will be queried in a sincere discussion prior to randomization to insure continued willingness to be randomized and comply with the study protocol and follow up visit schedule. The date that the second consent was signed (or the sincere discussion was held) is documented on Form 52. Copies of the signature of the 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 participants' names.

4.b. Participation in Other Studies

Participation in the AASK Study is expected to be time consuming. Participants will be asked by AASK Study personnel to not participate in any other research studies during their participation in the AASK Study unless it is an AASK ancillary study reviewed by the Publication, Ancillary Studies and Recruitment Subcommittee and approved by the Steering Committee.

4.c. Sequence of Consent Procedures

It is recognized that Clinical Center Institutional Review Boards (IRBs) 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.

Consent occurs at two stages of the study. 1) Consent should be obtained around the time of the Screening Visit, and will include description of the interaction with members of the study team, a complete physical examination, blood and urine tests, control of blood pressure pre-randomization; assessing GFR twice; to assess compliance with study procedures; and to agree later to follow the regimens selected by random assignment. 2) Consent for the Follow-Up Period will include a confirmation of consent to be randomized to treatment regimens, blinded medication and blood pressure goal. Centers may use a form for consent for Follow-Up and randomization. This form will include consent for blood pressure goal, blinded medications, follow-up visits and follow-up GFR's and is signed after a patient has experienced Baseline visits and one or both Baseline GFR.

In the place of a second consent, a member of the study team may have a sincere discussion with the patient at the end of Baseline to be sure he or she still wants to be randomized.

4.d. Privacy

At the beginning of the study, each participant is 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 participant data are published, no identifying information will be included. The medical records of participants in the AASK Study will be confidential. Specific study related information may be made available to the Food and Drug Administration, the study sponsors, and National Institutes of Health.

5. SCREENING PERIOD EVALUATION

5.a. General Principles of Screening

The study is designed to test whether or not the rate of decline of renal function in African-Americans with a primary **clinical** diagnosis of hypertensive nephrosclerosis is affected by: (1) the level of blood pressure control, and (2) the choice of antihypertensive drug regimen. Therefore, the objective of the recruitment process is to identify hypertensive participants with some evidence of renal damage who will be likely to benefit from antihypertensive therapy, who will be available for the entire follow-up period, and who are likely to be compliant to the treatment protocol and visit schedule. Participants with known other diseases, e.g. diabetes, which might influence survival or kidney function are not considered to be candidates, as are participants likely to be noncompliant. Participants for whom any of the randomized drugs are medically necessary for the treatment of other conditions are considered ineligible for enrollment and will not be further evaluated for participation in this clinical trial.

5.b. Recruitment Strategy

Recruitment strategies for the full-scale study include: surveys of local hypertension and renal disease clinics; radio and television programs; mass mailings of promotional brochures; laboratory value screening; referrals from other physicians; contacts with HMOs; screening of computerized medical records databases; contacts with African American organizations (physicians, fraternities, sororities); community screening programs; health fairs; and working with African American community organizations. National approaches include: contacts with organizations such as the NAACP and The Urban League; the solicitation of an African American public figure who will serve as a spokesperson; and public service announcements.

5.c. Screening Period Eligibility Requirements

Participants who are African-American with a history of hypertension, treated or untreated, aged 18-70 years of age and who express interest in the trial will be eligible for screening. Patients who were screened and excluded from the AASK Pilot Study are eligible. Patients who have attended a G1 or beyond and were subsequently excluded from the Full-Scale Study are not eligible for re-entry to screening unless at least six months have passed and there has been a significant change in the medical condition.

5.d. Screening Procedure

The majority of potential study participants will be identified at the local clinic level, and a Chart Review Screening Form 1 used to assist in this process. The inclusion and exclusion criteria have been listed, and forms will be completed where information is available from existing records. Where information is unavailable, clinic visits for the appropriate tests will be scheduled for the participant by the Study Coordinator. Participants will be asked

to sign consent form(s) indicating their interest in the trial and their availability to undergo tests. Participants who meet all of the inclusion criteria and who are free from all of the exclusion criteria will be admitted to the Baseline Period.

The patients will be screened in the first 31 months. The last patient will be randomized within 32 weeks of the last day of Month 31.

5.e. Restarting Baseline

A patient can restart the screening process 6 months after they have been identified as ineligible. Since patients can become ineligible at different points in time during the screening/baseline period, and since they become ineligible for different reasons, rules have been implemented in determining the earliest date a patient can restart the screening process. (See Form 47 instructions in the Forms Usage Manual for details.)

A patient can restart the screening process after one month if the Principal Investigator believes that the patient was excluded due to a problem in laboratory measurement, clinical center test procedures or clinical center sample preparation procedures. The Quality Control Subcommittee, after receiving the Principal Investigator's written explanation, will inform the Data Coordinating Center if the patient is eligible to re-enroll in writing. The date of restart is one month from the date the Quality Control Subcommittee approves the restart. (See Form 47 instructions located in the Forms Usage Manual for details.)

A patient can restart the screening process after one month if the patient was enrolled in baseline and was excluded for a logistic rather than a medical reason. This applies to all who are eligible on the basis of SV2, have no medical exclusions and are not randomized during the allotted time. (See Form 47 instructions located in the Forms Usage Manual for details.)

An excluded patient is also eligible to restart the Screening/Baseline process after one month if the patient was G1 GFR Eligible and met all other biochemical and clinical eligibility criteria but was not randomized during the allotted time. This includes those situations in which the G2 GFR was not done within 24 weeks of the SV2 visit or in which the person was not randomized within 8 weeks of the G2 GFR. (See Form 47 instructions located in the Forms Usage Manual for details.)

All patients who restart Baseline do not have to re-qualify for blood pressure (back titration) as long as they met the blood pressure criteria the first time in Baseline.

5.f. Creatinine Eligibility When Entering Baseline

Patients will be eligible for the baseline period if they meet all the inclusion criteria as written in Protocol Section 3. Also, as a guideline, it may be helpful to check to see if the patients have a serum creatinine between 1.3-4.5 for females, 1.4-5 for males or a measured creatinine clearance between 20-65 ml/min/1.73m^2 or a calculated (Cockroft-Gault formula) creatinine clearance between 20-65 ml/min.

Cockroft-Gault Formula:

$$\text{Creatinine clearance (ml/min)} = \left(\frac{[140\text{-age}] \times [\text{body wt in kg}]}{[72] \times [\text{Serum cr in mg/dl}]}\right) \times 0.85 \text{ (female only)}$$

To correct a measured creatinine clearance (ml/min) for body surface area (BSA), use the following formula:

$$\text{Creatinine clearance (ml/min/1.73 m}^2\text{)} = \frac{\text{Creatinine clearance (ml/min)} \times 1.73}{\text{BSA}}$$

To calculate BSA, use the following formula:

$$\text{BSA (m}^2\text{)} = [W^{0.425} \times H^{0.725} \times 71.84]/10{,}000 \quad ,$$

where W = weight in kilograms, and H= height in centimeters.

5.g. Evaluation of Recruitment, Screening, Retention and Compliance

Patients will be entered into the 21 clinical centers as shown in Table 5.1.

Table 5.1
Randomization Goals

Center #	Randomization Goal
#00 - University of San Diego	40
#01 - CWRU	85
#02 - Emory University	50
#03 - Harbor UCLA	24
#04 - Howard University	50
#05 - Johns Hopkins	65
#06 - MLK-Drew Medical College	39
#07 - Medical University of South Carolina	75
#08 - Meharry Medical College	20
#09 - Harlem Hospital	20
#10 - Morehouse School of Medicine	20
#11 - Mt. Sinai School of Medicine	60
#12 - Ohio State University	80
#13 - Rush Presbyterian	80
#14 - University of Alabama	65
#15 - University of Florida	65
#16 - University of Miami	75
#17 - University of Michigan	85
#18 - University of Southern California	43
#19 - Texas Southwestern Medical Center	75
#20 - Vanderbilt University	60

Screening forms have been designed to provide information on the success rates (yields) of the various recruitment strategies. All forms used in the study are coordinated to provide information on the retention rates of recruited and randomized participants and the reasons for drop-out and non- compliance with the prescribed regimen. The DCC will provide weekly electronic recruitment reports over electronic mail. This weekly report will list by clinical center the number of patients found eligible and ineligible on the Form 1 Chart Review, the Form 4 SV2 Visit, and the G1 GFR Measure, and will list by Clinical Center the number of patients randomized. Detailed summaries of recruitment will be given in the monthly report.

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

6.a. General Procedures

The purpose of this section is to describe the procedures that are to be used for measurements critical to the goals of this study and which must, therefore, be carefully standardized across the clinical centers. These will be taken during the screening, pre-randomization baseline period and during the follow-up period. They include the measurement of the glomerular filtration rate, the 24-hour urine samples, the measurement of blood pressure by random zero blood pressure devices and the central measurement of biochemical profiles. Included in this section for completeness are also the electrocardiogram data (which will be obtained and read at the individual clinics and are necessary to the maintenance of participant safety) and questionnaire data to be obtained by interview.

6.b. Glomerular Filtration Rate

The purposes of measuring glomerular filtration rate (GFR) are as follows:

1. To determine eligibility for the study.
2. To determine the change in renal function during the full-scale trial.

Glomerular filtration rate is measured by the renal clearance of ^{125}I-iothalamate administered by subcutaneous injection at G1 baseline, G2 pre-randomization, 3 months post-randomization and at six-month intervals thereafter. Ideally, GFR measurements should be performed within two weeks of the target visit date.

Non-steroidal medications, including aspirin, are discontinued or withheld at least 48 hours prior to the GFR determination. GFR's are not to be completed if the patient has started taking hydrochlorothiazide within the past 14 days of the GFR. Participant's usual antihypertensive medications, including diuretics, are not withheld prior to the study. The study is not postponed on the basis of a specific blood pressure level obtained at the time of the clearance study, however it may be postponed if, in the judgment of the investigator, there is a mitigating medical reason (such as a short term illness, see 11.d.).

6.c. Twenty-four-hour Urine Collections

The purpose of measuring renal excretion of the following substances is as follows:

1)Sodium and potassium: To estimate dietary intake.

2)Creatinine:(a) To estimate glomerular filtration rate.
(b) To estimate adequacy of urine collection.

3)Protein:To exclude participants with a protein/creatinine ratio of > 2.5, and to monitor changes

in urine protein excretion during therapy.

The 24-hour urine collections are performed prior to the first pre-randomization GFR determination as shown in the flow sheet (Table 18.1). Participants are provided with urine receptacles containing 250 ml of acetic acid for preservation of urea. Ideally the urine container is given to the participant on the visit immediately preceding the GFR determination and the 24-hour urine collection is started the day before the GFR measurement during pre-randomization. Post-randomization urine collections will be performed every six months. The participants receive specific instructions for obtaining a valid urine collection. The total volume of the urine is measured and the urine is aliquoted and shipped to the Central Biochemistry Laboratory at the Cleveland Clinic for determination of creatinine, and protein. The specimen is shipped to the Central Biochemistry Laboratory within one week of collection. Drugs that interfere with creatinine excretion (e.g., pyridium, most cephalosporins (except cephalexin), bactrim/septra, H-2 blockers) are withheld for 48 hours prior to 24-hour urine collection; and NSAIDS are withheld for 2 days prior to urine collection.

6.d. Arterial Blood Pressure

As the major variable that we are trying to bring to a standardized goal of control in this study, it is critical that blood pressure measurement be taken by trained and certified personnel who use accurate equipment and perform the technique according to the guidelines of the American Heart Association. Although blood pressure is considered a skill mastered by all health professionals, recent research has demonstrated that in both clinical care and pharmaceutical research, blood pressure is rarely measured in the recommended manner and equipment is frequently not accurate. Some problems in accurate measurement stem from personnel: not knowing or performing the recommended steps needed to get an accurate blood pressure, not being able to read the manometer correctly, not being able to remember the actual readings, and not being able to hear well enough to detect the Korotkoff sounds accurately.

These problems can be minimized by initial standardized training and certification of all who measure blood pressure, and by frequent monitoring that observers are: 1) following the proper technique, 2) do not have biases in their readings, 3) can read blood pressure accurately as documented by double stethoscope testing, and 4) by testing with videotape examples. Personnel who have problems with accuracy or biases during the study should be retrained, and if the problems persist they will be decertified. Annual recertification is required, and blood pressure should only be measured by personnel who hold a current certificate of accuracy. All new personnel who are added after the study begins will be required to attend training and certification sessions provided either at a central location or by the blood pressure trainer at each site who has been trained and certified as a trainer by the Coordinating Center.

6.e. Blood Tests

Blood tests are required both as an additional assessment of renal function (e.g., serum creatinine and blood urea nitrogen) and as measurements to help assure participant safety (e.g., serum potassium). Protocol blood tests to be obtained include:

CBC and HCG (all local) Human Chorionic Gonadotropin (pregnancy test)
SMA-18 (all central--shipped within one week of collection) which includes:
Sodium, potassium, chloride, bicarbonate, urea nitrogen, glucose, creatinine, total protein, albumin, aspartate transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, calcium, phosphorus, uric acid, magnesium and GGT.

In addition, fasting total cholesterol, total triglyceride, LDL-cholesterol, and HDL-cholesterol are performed at Baseline and annually during the study. Serum creatinine is measured at GFR visits. HCG (women only) tests are done before each GFR in women of childbearing potential (post-pubertal, pre-menopausal, not surgically sterilized). The timing of each test is outlined in Tables 18.1 and 18.2.

Additional local blood work is done as clinically indicated to monitor electrolytes and hematocrit for participant safety. These data are <u>not</u> sent to the DCC.

During Follow-Up, if a sample which is collected according to the "Completion Schedule" and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the sample may not be re-drawn. In this case, the Central Biochemistry Laboratory will analyze what they can, and the remaining values will be missing. However, if a serum sample is collected due to an Action Item or at the FV0-1 Safety Visit and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the serum should be recollected.

6.f. <u>Electrocardiograms</u>

Customary techniques are used by clinical center personnel to obtain 12-lead ECGs on the participants periodically. The ECG is used to evaluate cardiovascular status and, especially, in support of participant safety. Analysis of the ECG is done to identify arrhythmias, conduction defects, myocardial infarction, left ventricular hypertrophy, and abnormalities of P wave, the T wave and QRS complex. Because these readings are obtained to document the participants' status and for reasons of participant safety and are not themselves end-points in this study, the ECGs are read by the local center investigator. All personnel who obtain ECGs should have had formal training in proper technique.

6.g. <u>Questionnaires</u>

The questionnaires to be used in this study are the initial participant contact forms, a patient

symptom check list which is used both initially and at subsequent visits, a quality of life instrument (AASK Form 80, the standard SF-36), and an adherence review form (AASK Form 16). Form 80 is self administered. The responses to the Form 16 are elicited by interview in order to handle anticipated differences in the reading comprehension levels of the participants. The interviewers are trained in the proper and reproducible eliciting of such information.

7. ANTIHYPERTENSIVE REGIMENS

7.a. Introduction

The comparative effectiveness of various antihypertensive regimens to slow or prevent progressive renal dysfunction in African-American hypertensives with the clinical diagnosis of hypertensive renal disease has not been carefully evaluated. Recent animal studies suggest that either angiotensin converting enzyme inhibitors or calcium channel blockers may be classes of agents which slow the rate of glomerulosclerosis independent of their effect on blood pressure control. Long-term studies in humans of the impact of these drugs on progressive renal disease due to hypertension are not available or have been poorly controlled. Thus, it is important to examine the effects of regimens containing angiotensin converting enzyme inhibitors (CEIs) or calcium channel blockers (CCBs) on the rate of decline of renal function in hypertensive African Americans with renal insufficiency. The effects of regimens containing these agents will be compared to each other and to an antihypertensive regimen which is initiated with a beta-blocker (BB).

Similarly, an important unanswered question is what level of blood pressure control best preserves renal function in patients with declining renal function. Independent of the randomized drug to which the participant is assigned, they will be randomized to one of two levels of blood pressure control (MAP $\leq$ 92 mmHg or MAP 102-107 mmHg). All patients will also be treated to a systolic blood pressure $\leq$ 160 and diastolic blood pressure $\leq$ 90.

Since it is expected that blood pressure control may not be achieved easily with a single class of drug, additional medications will be added in a sequential fashion where indicated. These classes of drugs consist of a loop diuretic, a long acting alpha-blocker, a centrally acting alpha-2 agonist, and an arteriolar vasodilator, hydralazine or minoxidil. To enhance participant compliance, all drugs utilized in the study will be long-acting and will be administered no more often than a twice-per-day schedule. These additional drugs have been chosen for their effectiveness in lowering blood pressure, their sites of action and their safety.

7.b. Blood Pressure (MAP) Goals for the Follow-Up Period

For new volunteers entering the Baseline period, it will be documented that the diastolic BP is $\geq$ 95 mmHg by withdrawal or partial withdrawal of antihypertensive therapy if necessary. Those on antihypertensives at Baseline must show this once while off their antihypertensives. Those not on antihypertensives at Baseline must show this on two consecutive visits. In the post-randomization period, participants should have their medications titrated to remain within the limits of their randomly assigned blood pressure goals. The two blood pressure goals are MAP of 102-107 mmHg (labelled "moderate blood pressure control") and MAP $\leq$ 92 mmHg (labelled "low blood pressure control").

7.c. General Principles of Blood Pressure Management

It is anticipated that at the time of randomization, participants will be on a variety of antihypertensive agents with varying degrees of blood pressure control. On or before the initiation of the blinded randomized drugs, all calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors will be stopped; other antihypertensive drug classes can be continued. At the FV0-0 visit, the participant will begin one of the three randomized drugs (**Level I**).

7.c.1. Level I - Blinded Medications

The randomized drugs will be available in the following dosages: ACE inhibitor Ramipril 2.5, 5 and 10 mg; Calcium Channel Blocker Amlodipine 5 mg and 10 mg; and Beta Blocker metoprolol, 50 mg, 100 mg and 200 mg. The dose selected will be prescribed once-a-day. At the discretion of an AASK Study clinician, based on the participant's blood pressure at the time of randomization and on whether the patient is in the moderate or low blood pressure control group, any of the three doses of the randomized drugs can be started. If at the time of randomization, in the Principal Investigator's judgment, maximum tolerated doses of the randomized drugs alone will not be adequate to control safely the participant's blood pressure, the Investigator may also begin or continue post-randomization therapy with several levels of the subsequently outlined drugs in the Protocol (see below). If indicated, antihypertensive agents not provided by the study can be down-titrated or withdrawn as safely as possible as randomized medications are up- titrated over the next 2 months.

7.c.2. Level II - Diuretics

At Level II, all participants will receive furosemide. The exact dosage of furosemide used and the use of it as a once-per-day or twice-per-day drug as well as the time intervals between dosage change will be determined by the Principal Investigator. Furosemide can be added before the randomized drug is titrated to its maximum dosage if more rapid blood pressure control is needed, or if it is needed for volume control. The randomized drug will be titrated to the maximally tolerated dose within 2 months following randomization and the furosemide dose decreased to the minimum dose to achieve/ maintain goal MAP.

7.c.3. Level III - Alpha-Adrenoreceptor Antagonist

The alpha-adrenoreceptor antagonist, doxazosin, will be the third level non randomized antihypertensive used in the protocol. The dosage begun and timing of dosage increases will also be determined by the Principal Investigator; however, compliance with the package insert for the agent is recommended to avoid first dose orthostatic hypotension.

7.c.4. Level IV - Centrally-acting Alpha II Agonist

The Level IV medication will be clonidine. The Principal Investigator can use clonidine in either an oral or patch form. If the drug is used in the oral form, it will be administered in a BID dosage regimen. The starting dose of the drug and the intervals between changing doses of the drug will be determined by the Principal Investigator.

7.c.5. Level V - Vasodilators

If Level V medication is required, either one of the vasodilators, hydralazine or minoxidil, will be used. Hydralazine will be prescribed utilizing a BID dosage schedule. Minoxidil, however, can be used QD or BID at the discretion of the Investigator. The starting dose of these drugs and the time interval between dose changes will be determined by the Principal Investigator.

Level II-V agents will usually be added sequentially and titrated to the maximally tolerated dose. However, at the discretion of the Principal Investigator, if more rapid lowering of blood pressure is needed, multiple levels may be initiated at a time. Then, in order to simplify the regimen, back titration of higher level agents (e.g., minoxidil) is recommended as the dose of lower level agents (e.g., furosemide) is increased.

It is anticipated that after randomization there will be a time period of two months during which the participant's antihypertensive regimen will be titrated. During this titration period as outlined below, drugs will be altered and increased frequency of visits will occur to achieve the participant's blood pressure goal rapidly. Following the two month's titration phase, it is anticipated that the participant will enter a maintenance phase of blood pressure control during which infrequent alterations and non-protocol visits will be necessary.

7.d. Protocol Compliance

Compliance with the antihypertensive regimen is an important parameter in the study because the effect of blood pressure reduction by various regimens upon progressive nephrosclerosis is a primary purpose of the study. Furthermore, strategies to assure compliance developed during the pilot phase will be used for the main study.

In order to assure compliance, several general principles will be followed.

1. The local physicians who refer participants should understand the nature and requirements of the study so that antihypertensive medications are changed only by members of the study center.

2. Decisions to change a particular participant's antihypertensive regimen will be made consistently by the same individual from visit to visit at the clinical center. This fosters continuity of care.

3.Participants will be informed of their blood pressure goal and in some cases (where blood pressure is difficult to maintain in treatment range, see below) encouraged to measure and record their blood pressure at home and taught to calculate their MAP. Any use of home BP cuffs should be standardized at the participant's local center.

4.Unscheduled non-protocol visits should be used to achieve and maintain target blood pressure levels.

5.The DCC will maintain, for each center, an ongoing record of participants whose blood pressures are outside the goal MAP range.

6.Quality control measures will ensure that blood pressure measurement techniques are followed, and equipment is calibrated on a regular schedule.

7.Possible reasons that blood pressure is out of the goal MAP range will be documented.

8.Participants will be asked routinely about compliance with the medication prescription, possible side effects, and factors other than medications that may influence blood pressure. Pill counts will be performed for all study drugs and recorded on Form 5.

For participants whose blood pressure levels remain out of the goal MAP range for two months or more during the maintenance phase or after titration to maximum doses of medications, a standing compliance committee will be in place to work with the investigators at the participant's clinical center.

7.e<u>Blood Pressure Compliance: Management of Participants with MAP Above Randomization Goal</u>

7.e.1**Operational definition:** MAP > 107 mmHg for those randomized to the 102-107 goal, or MAP > 92 for those randomized to the $\leq$ 92 goal. Also, SBP > 160 or DBP > 90.

7.e.2**Assessment of Compliance:** With the help of the Form 16 adherence review, the degree of compliance with the antihypertensive regimen will be assessed with regard to:

A.Participant's knowledge of regimen including the type, quantity and timing of medication.

B. Pill count.

C. Adverse drug reactions as recorded on a standard questionnaire.

D. Problems at home or work that might limit compliance.

E. Assessment of stressful events that might affect blood pressure.

F. Change in sodium intake.

G. Addition or deletion of other medications that may affect blood pressure.

7.e.3 **Noncompliance with Antihypertensive Regimens**:

A. Advise and instruct participant if an error in administration is detected.

B. If an adverse drug reaction is responsible for noncompliance, attempt to modify regimen (excluding the discontinuation of randomized drugs).

C. Assess sodium intake by measuring 24-hour urinary sodium excretion.

D. Allow for flexible dosing schedule.

E. Involve the participant's family and significant others to encourage compliance.

F. Consider home blood pressure monitoring, medication diaries and/or other compliance enhancing measures and involve the participant in attempting to achieve the MAP goal.

G. Follow-up with the participant by telephone in one week and with a clinic visit within two weeks of any intervention or when clinic and home MAP differ.

7.e.4 **Blood Pressure Uncontrolled Despite Compliance**

A. If the in-center MAP is $\geq$ 10 mmHg above goal once or $\geq$ 5 mmHg above the goal on two consecutive visits, adjust medication per titration or maintenance protocols, increasing the medication in each level to its maximum dose or until an adverse reaction occurs.

B. If the in-center MAP is 1-4 mmHg above the goal and the participant is in the titration or maintenance phase of the protocol, leave the medications alone unless the participant has never reached goal. If the participant has achieved goal at previous visits, no change in meds is necessary. (If the participant has not achieved goal MAP at previous visits, proceed as in A.)

C. If the in-center MAP is 1-4 mmHg above the goal and overall antihypertensive pill count compliance is <80% and participant is in maintenance phase,

confirm at a non-protocol visit in two weeks. If the blood pressure remains elevated at next in-center visit, increase/add medication per protocol.

D.Home blood pressure monitors may be provided at the Investigator's discretion to any participant with difficult to control blood pressure.

E.Sodium intake should be assessed by determining 24-hour urinary sodium excretion. Excessive intake should be modified by dietary counseling.

F.Recommend and encourage additional lifestyle modifications to lower blood pressure.

G.As described in Chapter 11, the Compliance Subcommittee will receive summaries of participants whose blood pressure is more than 5 mm Hg above the goal (>97 for low or >112 for usual) for $\geq$ 2 consecutive visits after F6 (AASK Action Item 2).

7.f Blood Pressure Compliance: Management of Participant with MAP Below Randomization Goal

7.f.1 **Operational Definition**: MAP < 102 for those randomized to the 102-107 goal, or MAP < 92 with symptoms of hypotension for those randomized to the $\leq$ 92 goal.

7.f.2 **Assessment of MAP Below Goal**

A.Symptoms of hypotension will be recorded from a standard list of possible symptoms at each visit to the clinical center.

B.The investigators will reduce or discontinue antihypertensive agents per titration or maintenance protocols in order to achieve the blood pressure goal.

1.If the in-center MAP is $\geq$ 10 mmHg below the goal on a single visit or $\geq$ 5 mmHg below the goal on two consecutive visits, adjust medication per titration or maintenance protocols, decreasing the medication in each level to its maximum dose.

Drugs other than the randomized drugs will be the first agents to be discontinued. Home blood pressure recordings and/or non-protocol clinic visits within one week will be used to determine if blood pressure goal is achieved.

C.The reasons for any reductions in the antihypertensive regimen will be explained to the participant and the referring physician.

D.If the participant is only receiving the lowest dose of a randomized drug and has

symptoms of hypotension, the blood pressure will be repeated at weekly intervals without any change in medication. If the blood pressure remains below the goal for two consecutive weeks, the clinical center should consider temporarily having the patient take the drug every other day.

7.g. Early Termination of the Calcium Channel Blocker Arm

The Data and Safety Monitoring Board (DSMB) of AASK decided to terminate one part of the AASK, the Calcium Channel Blocker arm (amlodipine), before the trial's scheduled completion in the fall of 2001. This information was given to the AASK Principal Investigators on September 21, 2000, and the CCB arm was terminated immediately thereafter.

In view of the DSMB recommendations for patients randomized to amlodipine:

1. Participants whose latest AASK urine protein exceeds 1 gram per day, the patient should stop the AASK medication and placed on either open-label ACE inhibitor or beta-blocker in conjunction with higher order antihypertensives specified in the AASK protocol as necessary.
2. For participants whose latest AASK urine protein is under 1 gram per day, the clinical center staff should discuss the study results with the patient, and may place the patient on open label ACE inhibitor, beta-blocker or calcium channel blocker in conjunction with higher order antihypertensives specified in the AASK protocol as necessary.
3. The AASK target blood pressure goals remain in effect for all patients, including those randomized to the calcium channel blocker arm.
4. All regularly scheduled follow-up procedures should be continued, including collection of GFRs.

8. BASELINE PERIOD EVALUATION

8.a. General Principles of Baseline

The Screening and Baseline periods is expected to last about two months. Before entering Baseline, participants will be screened to ensure that they meet the inclusion criteria and that none of the exclusion criteria are present. Some of these will require confirmation by laboratory tests (e.g., SV-2 serum glucose must be less than or equal to 200; SV-2 WBC must be greater than equal to 2500). During the Baseline period, new participants' blood pressures will be documented to be in the qualifying range (DBP $\geq$ 95 mmHg). Those on antihypertensives at Baseline must show this once. This may require reducing or discontinuing antihypertensive agents they are currently receiving (back titration). Those not on antihypertensives at Baseline must show this twice. Blood pressures will then be controlled toward a MAP $\leq$ 107 mmHg either by using agents that the participant is currently receiving or by prescribing a regimen that excludes the three initial randomized drug classes (BBs, CCBs, or CEIs), if possible. If participants are currently receiving any initial randomized drug class, all efforts will be made to reduce or discontinue these agents, assuming satisfactory control of blood pressure can be achieved and maintained with other agents.

During Baseline, GFRs by iothalamate clearance will be obtained on two occasions separated by at least one week. Participants will qualify for the study based on the first baseline GFR (20-65 ml/min/1.73m^2). Other procedures done in the screening and Baseline period include a medical history, a physical examination, laboratory tests including 24-hour urines, biochemical profiles (SMA-18), documentation of patient symptoms, and quality of life assessment. Compliance with visit schedules, procedures, and the medication regimen will be carefully documented. Additional visits may be required when hypertension is being documented or blood pressure control is being established. The schedule of visits that follow are the visits at which data will be collected and transmitted to the Data Coordinating Center. Every effort should be made to promote adherence to this schedule. Following are Baseline visits and procedures.

Visit Period	**Visit Designation**
Screening	Screening Visit 1 (SV1)
	Screening Visit 2 (SV2)
Baseline	Back titration 1-99 visits (BT1-BT99)
	GFR Visit 1 (G1)
	GFR Visit 2 (G2)
Consent	Consent Visit*
Randomization	

* = If consent for follow-up is not obtained at G2

Suggested guidelines for Intervals Between Screening and Baseline Visits are indicated below:

Interval	Target Suggested Range
SV1-SV2 (if SV1 is done)	1 week 2 to 21 days
SV2-G1	1 week 1 to 3 weeks
G1-G2	1 week 1 to 3 weeks
G2-Randomization	1 week 0 to 10 days

The total length of the Screening and Baseline periods could be as short as 3 weeks. It is desirable for the G1 eligibility GFR to be as close as is feasible to the time of randomization. The interval between SV2 and G2 must be no more than 24 weeks. Also, the time from G2 to randomization must be no more than 8 weeks.

Follow-up visits during the first six months post randomization will be scheduled one month apart, with a window of ±15 days, starting with FV0-0 held as soon as possible after randomization.

8.b. Glomerular Filtration Rate

During Baseline, GFR will be measured on two occasions. The first measurement, G1, will be performed after screening and after the participant has been shown to meet blood pressure inclusion criteria. This measurement will determine GFR eligibility for randomization. Therefore, it must be within the range of 20-65 ml/min/1.73m^2 in order for the participant to continue in Baseline. The second GFR, G2, will be measured one week or more following the first GFR. The purposes of the second study are: 1) to provide information on the variability of GFR in the recruited population; and 2) to average with initial GFR, providing a reference point to compare to post randomization GFR's. The clinical center will be blinded to the absolute GFR values at baseline and during follow-up throughout the study.

If the CV for G1 is over 50%, the G1 may be repeated one time. If the repeat G1 is then in range with CV under 50%, the patient would continue to G2. Otherwise, the patient would be excluded. If the CV for G2 is over 50%, the G2 may be repeated one time unless the G1 had a CV over 50%. In this situation, the patient would be excluded. **There will not be a fourth baseline GFR**. If the repeat G2 was in range and had a CV under 50%, the patient would be eligible for randomization.

The consent for randomization or sincere discussion regarding randomization should be held no sooner than the G2 visits to guarantee that the patient has experienced at least one GFR before consenting to GFR's for the duration of the study.

8.c. Laboratory Tests from Screening through Randomization:

(See 10c for Lab Tests in Follow-Up.)

Laboratory tests will include both blood and urine analyses. Analyses will be done locally for CBC, HCG, and urinalysis; and centrally for SMA-18, lipid profile and 24-hour urine values. The buffy coat sample will be stored centrally but not analyzed. Following is information about when and where the required tests should be done.

8.c.1 **Baseline Laboratory Test Schedule**

Blood Tests (SMA-18, CBC)	Screening Visit 2 and G1 Visit
Lipid Profile (fasting)	G1
24-Hour Urine	Once at Baseline, at Screening Visit 2 or G1 Visit
Creatinine Clearance	G1
Urinalysis	Screening Visit 2
GFR Samples	GFR Visits 1 and 2
Buffy Coat (held)	G1
HCG (females of child bearing potential only)	G1 and G2 Visits

8.c.2. **Baseline 24-Hour Urine Collections**

Participants collect a 24-hour urine either at SV2 or G1 during Baseline. This urine collection is referred to as the B1 urine sample. Participants will be given urine collection equipment and instructions for collection prior to each collection. Participants will be queried about the completeness and accuracy of each urine collection. Urine should not be collected during a short term illness. (See Section 11.d.) Refer to the Manual of Operations for more detail about 24-hour urine collections.

24-Hour Urine (Urine analysis is done centrally)
- Total Volume (measured locally)
- U. Protein
- U. Urea Nitrogen
- U. Creatinine
- U. Sodium
- U. Potassium

8.c.3. **Baseline Blood Tests**

Serum chemistries will be analyzed centrally. Whole blood measurers will be done locally. Certain serum tests may also be done locally for patient care, patient safety reasons. Local analysis will provide a quick turn around, especially for serum electrolytes. Refer to the Manual of Operations for instruction on mailing specimens.

SMA-18:
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Urea Nitrogen
- Glucose
- Creatinine
- Total Protein
- Albumin
- Asparate transaminase (AST)
- LDH
- Alkaline Phosphatase
- Total Bilirubin
- Calcium
- Phosphorus
- Uric Acid
- Magnesium
- GGT

CBC:
- WBC
- RBC
- Hemoglobin
- Hematocrit

GFR samples will be processed at the Central GFR Lab.

HCG will be done locally on females of child bearing potential prior to GFR's.

The Central Biochemistry Laboratory will not accept repeat specimens for measurement unless an error in shipping or procedure has occurred. During Baseline, if a sample is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the sample may be redrawn.

During Follow-Up, if a sample which is collected according to the "Completion Schedule" and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the sample may not be re-drawn. In this case, the Central Biochemistry Laboratory will analyze what they can, and the remaining values will be missing. However, if a serum sample is collected due to an Action Item or at the FV0-1 Safety Visit and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the serum should be recollected.

8.c.4. **Electrocardiogram**

An electrocardiogram will be done at Screening Visit 2, then every two years thereafter at FV24 and FV48, etc. Refer to the Manual of Operations for more detail.

8.d. Screening Medication Status

During the screening visits, many of the participants may be taking a variety of medications including antihypertensive agents as well as drugs for other indications. During the screening visits, the Clinical Center study team will:

1) review the indications for all prescribed medication;
2) ensure that the participants are not receiving medication that would result in an exclusion;
3) ensure that there are no contraindications to discontinuing any of the randomized drugs that the participant is currently receiving (e.g., BBs for angina, CEIs for congestive heart failure, etc.)
4) screen for any condition that precludes the participant from being randomized to any of the study drugs.

Any medication that does not result in the exclusion of the participant may be continued as necessary during the study (e.g. for thyroid replacement). However, the participant must be able to withhold NSAIDs (for 2 days) prior to GFR measurement (see Section 7.2.).

8.e. History and Physical Examination

A full history and physical examination will be performed during the SV2 using Form 4. The physical examination will include evaluation of MAP, vital signs, height, weight, general appearance, funduscopic examination and grading of hypertensive retinal changes, chest, heart, and extremities (including pulses and bruits).

At all other Screening and Baseline visits, a limited interval history and physical examination will be performed if there is a change in reported symptoms. It will consist of weight, vital signs, including MAP determined by an average of the last 2 of 3 measurements obtained in the sitting position with the random-zero sphygmomanometer; heart and lung examination; and a check for peripheral edema.

8.f Blood Pressure Measurement

Blood pressure will be measured by trained and certified personnel at each visit using the techniques and procedures listed in the Manual of Operations. Hawksley random-zero sphygmomanometers (MKII) will be used at each clinical center. Three consecutive readings will be recorded with the mean of the last two readings documented as the clinic visit measurement.

8.g Participant Questionnaires

Any symptoms of hypotension and any new symptoms volunteered by participants and since the last visit will be recorded at each visit. The check list on Form 11 will be used to record the responses. Reasons for missed visits will also be on Form 11.

Answers to questions related to compliance (such as lack of adherence to medication regimen) will be documented on Form 16.

Information regarding participants' quality of life will be elicited using the SF36 (Form 80) at Baseline and annually.

8.h Treatment of Hypertension during Baseline Period

The main goal of the treatment of hypertension during the Baseline period is to improve arterial pressure MAP toward normal (i.e., < 107 mmHg). In addition, agents belonging to the classes of the randomized drugs should be discontinued during this period if blood pressure control can be adequately maintained without their use. Adjustments in antihypertensive agents during screening will be dependent on two factors, namely 1) the medication status of participants at their first visit, and 2) the level of blood pressure.

8.h.1. Participants Not On Antihypertensive Therapy

For participants who are not receiving antihypertensive drug therapy or take antihypertensive medication sporadically (none within the week preceding the first visit), blood pressure will be measured off drug therapy at both screening visits (SV-1 and SV-2). Participants will be considered BP eligible if their average diastolic BP is greater than or equal to 95 mmHg on two consecutive visits. Participants with JNC Stage IV hypertension (SBP $\geq$ 210 or DBP $\geq$ 120) at SV-1 will be considered to have met the entry blood pressure criteria after only one visit and will be eligible for the initiation of drug therapy during Baseline. The purpose will be to improve BP toward a normal (i.e., a mean arterial pressure of $\leq$ 107 mmHg).

The AASK Study therapy consists of a regimen that includes the randomized drugs, diuretics, alpha blocker, central agonist and vasodilator therapies, sequentially added as needed. The medications will be provided free-of-charge to eligible and interested participants. (The clonidine patch cannot be provided free-of-charge because of its expense.) Only the blinded randomized medications and placebo will be provided centrally by the Drug Distribution Center.

8.h.2. Participants Already on Antihypertensive Therapy

At SV-1, participants taking antihypertensive medications will have their BP measured on current therapy.

A) Those with a diastolic BP $\geq$ 95 mmHg on their current medications meet BP eligibility. Antihypertensive agents will then be increased or added in order to improve mean arterial pressure towards normal (i.e., $\leq$ 107 mmHg). During the Baseline, whenever possible, attempts will be made to decrease and discontinue any of the initial randomized drugs that the participants are currently receiving. Agents other than BBs, CCBs, and CEIs should be used to control blood pressure. Thus, the latter agents may be continued to maintain blood pressure control, if deemed necessary by the investigator. To enhance BP control, participants will have the option, when possible, of either receiving antihypertensive therapy free-of-charge or continuing/augmenting their own therapy at their own cost but under the supervision of clinic center staff.

B) Those participants with well-controlled BP on treatment at the first visit will have medications back titrated/stopped in order to confirm hypertension. CEI, CCB or BB will be preferentially stopped. Once hypertension is confirmed, a regimen excluding BB, CCB or CEI will be implemented if possible in order to improve mean arterial pressure toward normal (i.e., $\leq$ 107 mmHg).

8.i Randomization

At randomization, the participants will be assigned to a blinded treatment bottle number. Each patient will receive a pair of bottles including either BB, CCB, or CEI in one and placebo in the other. All beta-blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors must be discontinued at least 24-hour prior to the first post randomization visit (FV0-0). Reduction of prior therapy dosages may accompany concomitant increases of the randomized agent. The investigators should also use level 1-4 agents as necessary to reach the blood pressure goal.

8.j Assessment of Compliance to Study Protocol

Participants will be considered compliant to study protocol and eligible for randomization if they:

1. Complete all of the following: Screening Visits 1 and/or 2 and two GFR visits. (Patients judged likely not to be able to follow the visit schedule are excluded.)
2. Complete required Screening and GFR visits in less than 24 weeks so the patient can be randomized within 24 weeks.
3. Agree to have blood drawn at the screening visits, and results of the blood work show no exclusions.
4. Take recommended antihypertensive medication per protocol, in the judgement of the study team. (Patients judged likely not to be able to adhere to medications are excluded.)
5. Agree to participate in study by signing the follow-up consent form or providing follow-up consent during a sincere discussion held at the G2 or Consent visit.

8.k Additional Assessments and Exclusions during the Baseline Period

Participants will not be considered for randomization if any one of the following conditions exist:

1. Suspected poor or doubtful likelihood of compliance to randomized protocol and/or randomized drug regimen on the basis of baseline experience.
2. If during the Baseline period the participant develops any of the exclusion criteria that would have prevented entry to the Baseline period.

9. RANDOMIZATION PROCEDURE

Treatment assignments for this study will be made using separate randomization schedules for each of the participating Clinical Centers (stratification by Clinical Center). Each participant will be randomized to a blinded treatment bottle number for the drug treatment arm and a blood pressure control goal.

The randomization schedules will be prepared by the Data Coordinating Center prior to the start of recruitment. Allocation to treatment groups will be equal and stratified by center. Randomly permuted blocks will be used to help balance numbers of participants assigned to each regimen and blood pressure control group. This method guarantees that at no time during randomization will the participants in the individual groups be grossly unequal.

Patients will be assigned in equal allocations to the Usual and Low MAP goals, so that half of the patients will be assigned to each goal. Due to expected differences in the initial acute effects between the CCB regimen and the ACE and BB regimens, an unequal 2/5 to 2/5 to 1/5 allocation will be used for the ACE, BB, and CCB regimens respectively, so that 2/5 patients will be randomized to the ACE and BB regimens, and 1/5 to the CCB regimen.

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 participant has signed the consent forms, and has met all eligibility requirements (including an acceptable level of compliance with study procedures), the Principal Investigator or the study coordinator shall access the interactive randomization program (Form 52). The program will verify through a defined set of questions that the participant is ready to be randomized and give the Clinical Center a randomized treatment assignment for that participant based upon his or her stratum.

Randomization of the participant to his or her treatment regimen and blood pressure control group marks the participant's official and irrevocable entry into the Follow-up Period. Once a participant has been randomized, efforts will be made to conduct all evaluations irrespective of the participant's compliance to the assigned drug regimen or blood pressure control group and protocol procedures and visits. These efforts should continue until termination of the Follow-up Period. Visits and procedures will continue after stop points.

10. FOLLOW-UP PERIOD EVALUATION

10.a General Principles of Follow-Up

The purpose for follow-up visits are: a) to ensure compliance with the protocol; b) to assess the participant's clinical status including BP control and the development of new symptoms or physical findings, c) to evaluate abnormal laboratory values, d) to assess progression of each participant's renal disease, e) to acquire data that ensures protocol adherence, f) to make changes in the medications to control BP as defined by protocol, and g) to identify participants who reach a Stop Point.

The FV0-0 is held as soon as possible after Randomization. At this visit, the patient receives two bottles (one bottle contains the randomized blinded medication and the other bottle a placebo). Protocol visits are held monthly for FV1, FV2, FV3, FV4, FV5 and FV6. Five to seven days after the FV0-0 (at which the patient receives his or her randomized medications) there will be a special FV0-1 visit to measure serum potassium, serum creatinine, and white blood cell count. After the sixth month of follow-up, protocol visits will continue every two months.

If a visit or procedure is missed, the visit should be rescheduled as soon as possible within the allotted interval. If that cannot be done within the allowable interval, the reason for the missed visit or procedure should be documented on Form 11 or 24 and transmitted to the Data Coordinating Center. (See Forms Manual for instructions for "Missed Visits").

10.b Glomerular Filtration Rate Details

During the post-randomization follow-up period, GFR will be measured after 3 months, 6 months, then at six-month intervals thereafter. In addition, all subjects reaching a GFR end point (> 50% decrease or 25 ml/min decrease since the previous GFR) will have a confirmation GFR within 2-4 weeks. The purpose of measuring GFR during these periods of time is to assess the effect of the post-randomization treatment and blood pressure goals on GFR.

During Follow-Up, if the CV for a GFR is >50%, the GFR does not need to be repeated.

10.cLaboratory Tests in Follow-Up (See Section 8.c for Screening through Randomization)

Laboratory tests during follow-up include SMA-18, CBC, lipid profile, 24-hour urines, GFRs, and pregnancy tests. Table 18.2 indicates when specific tests are done and whether the test will be analyzed locally or centrally.

Table 10.1. Schedule for Laboratory Tests

CBC	5 to 7 days following randomized drug, then at FV12 and annually thereafter
Serum potassium and creatinine	Measured 5 to 7 days following initiation of a randomized drug, then at FV3, 6, 12 and at 6 month intervals thereafter
SMA 18	FV12 and annually thereafter
Urinalysis	FV12 and annually thereafter
Lipid Profile (fasting)	FV12 and annually thereafter
24-hour Urine	FV6 and every 6 months thereafter
GFR samples	FV3, FV6, and at six-month intervals thereafter
Creatinine Clearance	FV6 and every six months thereafter
HCG tests (only for females of and child bearing potential)	Before each GFR

10.d <u>Follow-Up 24-Hour Urine Collections Details</u>

<u>Urine collections will occur near the time of each follow-up GFR visit (except FV3).</u> A reason for collecting urine just prior to the GFR is to better estimate creatinine clearance.

Total volume (measured locally)

Analysis for 24-hour urine collection (central analysis):

- U. Protein
- U. Urea Nitrogen
- U. Creatinine
- U. Sodium
- U. Potassium

10.e <u>Follow-Up Blood Test Details</u>

Blood chemistries will be analyzed centrally as well as locally. Table 18.2 and Section 10.c.1. indicates when blood tests are to be done.

Specific blood tests are as follows:

SMA-18, done centrally (no fast required)		Sodium Potassium Chloride Bicarbonate Urea Nitrogen Glucose Creatinine AST LDH Alkaline Phosphatase Total Bilirubin Calcium Phosphorus Protein Albumin Uric Acid Magnesium GGT
Lipid Profile (requires a 12-hour fast)		Cholesterol Triglyceride HDL-Cholesterol LDL-Cholesterol
Complete Blood Count (CBC)	WBC	
		RBC Hemoglobin Hematocrit

GFR Samples will be processed in the Central GFR Lab.

HCG (females of child-bearing potential) (local analysis)

Indication of fasting status prior to blood draw will be documented on the appropriate form. The Central Biochemistry Laboratory will not accept repeat specimens for measurement unless an error in shipping or procedure has occurred. During Baseline, if a blood specimen is received by the Central Biochemistry Laboratory and is hemolyzed, the clinical center may redraw the specimen.

During Follow-Up, if a sample which is collected according to the "Completion Schedule" and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the sample may not be re-drawn. In this case, the Central Biochemistry Laboratory will analyze what they can, and the remaining values will be missing. However, if a serum sample is

collected due to an Action Item or at the FV0-1 Safety Visit and is received at the Central Biochemistry Laboratory and is found to be hemolyzed, the serum should be recollected.

10.f Electrocardiogram (ECG) Details

A standard 12 lead electrocardiogram will be done at the SV2 visit and every two years thereafter, using a 10mm standard. These will be read locally.

10.g Drug Therapy

All participants will be questioned at each follow-up visit concerning the use of randomized drugs as well as other medications. Documentation of adherence to randomized drug prescription will be made on the pill count form. Participants will be instructed to call the Clinical Center if there are any changes or additions made in their medication regimen between follow-up visits. Participants will also be instructed not to take other antihypertensives or discontinue randomized drugs without first calling the Clinical Center.

Antihypertensive agents will be adjusted throughout the follow-up period as delineated in Section 7 of the protocol.

If new medications are prescribed for any reason during follow-up besides the randomized drug prescriptions, the investigator will assess the need and ensure that the medication is not contraindicated.

The AASK Study therapy consists of a regimen that includes the randomized drugs, diuretics, alpha blocker, central agonist and vasodilator therapies, sequentially added as needed. The medications will be provided free-of-charge to eligible and interested participants. (The clonidine patch cannot be provided free-of-charge because of its expense.) Only the blinded randomized medications will be provided centrally by the Drug Distribution Center.

Pill counts will be performed using Form 5 at each Protocol visit, and at interim visits if antihypertensives are changed or dispensed. Local counts may also be useful during non-protocol visits.

10.h History and Physical Examination

Blood pressure will be measured at each visit.

A limited history and physical will occur at each follow-up visit annually and a complete physical exam will be done annually.

Components of the complete evaluation are described in Section 8.e. The limited history and physical will include weight, vital signs, MAP, heart and lung examination, and a check for peripheral edema. MAP will be determined by the average of the last two of three

measurements obtained in the sitting position with the random-zero sphygmomanometer.

10.i Participant Questionnaires

Participants will be asked at each visit to volunteer symptoms experienced since the last visit including intercurrent illness and hospitalizations. An AASK symptom checklist on the Visit Form 11 will be used to record the volunteered responses. Quality of life (Form 80) will be assessed by a standard questionnaire, the SF 36, on an annual basis.

10.j Interim Visits

These visits will occur as frequently as necessary in between scheduled protocol follow-up visits. They may be for measurements for evaluation of protocol safety issues (e.g. Action Items, laboratory tests) or held electively. These visits will help ensure that participant's assigned MAP goals are achieved or maintained by adjustment of antihypertensive agents; that compliance with the protocol is achieved; that possible adverse events or symptoms related to adherence to the drug regimen are evaluated; that serum creatinine and potassium levels are measured; and that any causes of acute or subacute renal failure are evaluated and, if possible, corrected.

At each non-protocol visit not simply being held for obtaining laboratory tests, the evaluation will include but not be limited to blood pressure and the limited physical examination. The reasons for the non-protocol visits and the findings at these visits will be recorded on the Visit Form 11.

10.k Lifestyle Modifications

An important element of treatment and management of hypertension and kidney disease is diet and other non-pharmacological interventions.

Obesity and high sodium intakes may complicate the management of hypertension, in African Americans. Elevated serum lipid levels are common in persons with hypertension and kidney disease, thus dietary management to reduce elevated levels is encouraged. An integral part of the treatment of kidney disease, especially as kidney failure progresses, is diet. Protein, phosphorus, potassium, and calcium are nutrients that can be monitored and adjusted in the diet and/or with supplements to achieve improved biochemical goals. Protein reduction is routinely prescribed as kidney disease progresses to ameliorate symptoms of uremia. Whether a protein restriction imposed in the early stages of kidney failure will slow the rate of progression is still uncertain.

Since kidney disease and hypertension are characteristic of persons enrolled in AASK, modifications in diet should be encouraged to maximize medical care of these diseases as well as encourage a healthy lifestyle which is in keeping with the Healthy People 2000 Initiative. Diet, increasing exercise, avoidance of tobacco and ethanol are

non-pharmacological interventions considered cost effective for health improvement and maintenance.

While dietary modifications will be encouraged, intensive instruction and assurance of compliance is beyond the scope of this study. If the participant is on a prescribed diet at enrollment, then the participant will be encouraged to continue with the prescribed regimen if conflict does not exist with the study protocol or standard medical care as judged by the Principal Investigator. Goals established by the Joint National Committee (JNC) on the Detection, Evaluation and Treatment of Hypertension, the National Cholesterol Education Program (NCEP), and individualized medical needs will be encouraged. Referring physicians will be informed of the dietary recommendations, and if more intensive counseling is needed, then appropriate referral will be made through the referring physician or clinic or community resources.

Protein intake at the level of the Recommended Dietary Allowance (RDA) of 0.75 gm/kg/day is prudent for persons with kidney disease. Other dietary goals for AASK participants include: 1.5-2.0 g sodium, 1 meq/kg/day potassium.

When multiple dietary goals need to be achieved concurrently and/or when progress is not made in achieving goals, consultation with the referring physician is suggested and appropriate referral made for counseling with a registered dietitian should be considered.

10.l Educational Materials Regarding Diet

Educational material for the participant regarding diet may be provided. These could include simple guidelines for the following situations: increasing or decreasing calories; increasing or decreasing potassium; decreasing sodium intake; increasing or decreasing phosphorus; modifying fat intake; increasing or decreasing calcium and increasing or decreasing protein.

Multiple modifications include: decreasing calories and sodium; decreasing sodium and modifying fat; decreasing protein and phosphorus; decreasing calories, sodium protein and modifying fat.

For other dietary modifications or combinations, the participant will be encouraged to consult with a registered dietitian or their physician.

10.m Hypercholesterolemia

Participants with confirmed hyperlipidemia will be evaluated and referred for treatment in accordance with the National Cholesterol Education Program (NCEP) guidelines. A fasting lipid profile will be obtained during Baseline and annually in all participants. All participants will receive dietary information for a prudent AHA Phase I diet. Participants who meet criteria for lipid lowering drug therapy (LDL cholesterol > 190 mg/dl in any participant, > 160 mg/dl in participants with two or more cardiovascular risk factors, > 130 in participants with documented coronary heart or peripheral vascular disease) should be

referred back to their personal physician or clinic resources with a letter and copy of the laboratory results for treatment.

10.n Cigarette Addiction

Cigarette smokers will be counseled in smoking cessation at each clinic visit by clinic personnel. Participants who continue to smoke will be referred to available community or clinic resources for more intensive smoking cessation intervention.

10.o Ethanol Consumption

Participants will be encouraged to consume less than 1 oz of ethanol each day. Community or clinic resources will be used for more intensive counseling as needed.

10.p Missed Visit or Measurement

If a visit or measurement is missed repeatedly and cannot be rescheduled within the allowable range (window), the visit or measurement is "missed" and the participant is scheduled for the next regular visit. The reason a visit is missed will be noted on the Form 11. GFR windows will be the same as follow up visits; ±15 days through FV6 and ±30 days after FV6. For more information regarding requirements for "Missed Visits", see the Forms Manual.

10.q Patient Transfers

If study participants 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 participant moves into a geographic area served by a different Clinical Center, the participant (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 must be completed.

10.r Close Out and Post Close Out

Close out will take place over the last six months of the study. At the Close Out Visit, the patient will go off his or her blinded medications. Post-Close Out visits to evaluate participant safety upon discontinuation of the study regimen will be scheduled three months after each participant's Close Out Visit.

Participants should be encouraged to maintain their assigned regimen until the time of the Close Out Visit. Participants will turn in all leftover study medications, and will be asked to complete an anonymous Patient Evaluation Form. All participants will receive a certificate of appreciation, and will be directed to return back to their referring physicians.

10.s. Follow-Up After Confirmed Dialysis Stop Point

If a dialysis stop point is confirmed, Forms 28 and 29 are the only forms that are required. All other forms (Form 5, 10, 11, etc.) can be entered if information is recorded, but are not required by the database.

11. DEVIATIONS FROM ASSIGNED TREATMENT

11.a. Action Items

An action item is defined as an event that occurs to a participant or at a center after randomization and that prompts a change in the antihypertensive regimen, in the frequency or timing of a visit or measurement, or an intervention by a committee. Having defined action items will ensure that clinical events are responded to in a standard fashion at each Clinical Center. This section contains a summary and explanation of action items. Action Item Reports are included within the Forms and Reports Manual.

Clinical Center Action Items:

1. New Onset Nephrotic Range Proteinuria

Definition: Development of a 24-hour urinary protein (gl/L) to urinary creatinine (gl/L) ratio of ≥ 3.5.

Action: Repeat the 24-hour urine locally. (Data are not sent to DCC.)

Successful Resolution: Repeat local 24-hour urine on the next Protocol visit. Lab does not confirm nephrotic range proteinuria.

Unsuccessful Resolution: Repeat local 24-hour urine confirms nephrotic range proteinuria. Participant is referred to the community for further evaluation of nephrotic syndrome as dictated by usual medical care. The DCC will send summary reports for review by the Renal Function Subcommittee.

2. Persistent High Blood Pressure

Definition: MAP exceeds participant's goal by 5 mmHg (i.e. > 97 for the low group and > 112 for the usual group) on two consecutive visits after FV6.

Action: Participant will be scheduled for non-protocol visits every two weeks. The participant's randomized drug will be maximized, or if the randomized drug has already been maximized, the other subsequent antihypertensives outlined in the guidelines for blood pressure control will be added or dosage of those drugs will be maximized. The blood pressure goals will be reviewed with the participant in detail. The participant will also be counseled to intensify lifestyle modifications described in section 10.k.

Successful Resolution: Blood pressure declines to target levels.

Unsuccessful Resolution: The DCC will send a "persistent high blood pressure report" summary to the Adherence Subcommittee and the Clinical Management Subcommittee. If,

after the patients randomized drug plus every subsequent antihypertensive outlined in the protocol has been given at maximal doses for two consecutive visits with compliance documented by pill counts $\geq$ 80% at those two consecutive visits and the BP is greater than 160/100 on those two or more consecutive protocol visits, then a stop point may be declared.

3. Randomized Drug Noncompliance

Definition: Participant pill count reveals less than 80% of randomized blinded tablet or capsule has been taken on two consecutive visits.

Action: Principal Investigator (or his/her designee) will review the participant's record and take appropriate action.

Successful Resolution: Participant's pill counts reveal $\geq$ 80% compliance with randomized drug.

Unsuccessful Resolution: Participant's pill count continue to reveal less than 80% compliance. The action item reoccurs each subsequent month until 80% pill count is achieved. The DCC will provide a summary of the "Randomized Drug Noncompliance Reports" for review by the Adherence Subcommittee.

4. Visit Noncompliance

Definition: Participant misses two consecutive Protocol visits.

Action: The Principal Investigator at the Clinical Center takes appropriate action. DCC provides a Visit Noncompliance Report to the Adherence Subcommittee.

Successful Resolution: Participant comes to the next Protocol visit.

Unsuccessful Resolution: Participant continues to miss consecutive visits. Principal Investigator (or his/her designee). The Adherence Subcommittee will review summary reports.

5.GFR Noncompliance

Definition: Participant misses a GFR visit.

Action: The Principal Investigator at the Clinical Center takes appropriate action.

Successful Resolution: Participant comes to the next GFR visit.

Unsuccessful Resolution: Participant misses two or more consecutive GFR's. Principal Investigator or his/her designee at the Clinical Center will review summaries. Adherence Subcommittee will review a "GFR noncompliance" report.

6. Symptoms of Low Blood Pressure at MAP < 107

Definition: Symptoms potentially related to low blood pressure, such as orthostasis, lightheadedness, syncope reported to the DCC on the Form 11 symptom list on a visit at which the patients MAP was below 107.

Action: Evaluate the participant for any causes unrelated to their blood pressure or antihypertensive regimen which could be responsible for the symptoms as dictated by usual medical care. The antihypertensive medication should be reviewed and adjusted as needed. If participant's blood pressure is below goal then antihypertensive medications should be stopped or decreased until the MAP rises to the target level. Drugs other than the randomized drugs will be decreased or stopped first. If necessary, the randomized drug will be reduced to its lowest dose given every other day. All drug changes must be documented on Form 40. The participant will have non-protocol visits at the discretion of the study team. If participant is in the low MAP goal group and their blood pressure is at or above the $\leq$ 92 mmHg goal and no other cause for these new symptoms can be documented, the antihypertensive regimen will be altered allowing the blood pressure to rise until symptoms are resolved. If symptoms permit, waiting four to five days between drug dose changes are recommended.

Successful Resolution: Symptoms resolve.

Unsuccessful Resolution: Symptoms persist for greater than three months after the action item is first declared. DCC will provide a summary of "Low Blood Pressure with Symptoms" reports for review by the Clinical Management Subcommittee.

7. Low Blood Pressure without Symptoms

Definition: Participant's mean arterial blood pressure is below 102 mmHg (for those participants randomized to the 102-107 mmHg goal).

Action: Assess participant for any reversible cause of decreased blood pressure other than the antihypertensive drug. Decrease or stop antihypertensives (other than the randomized drugs) as needed. Decrease the dose of the randomized drug if needed but only if participant is off all other blood pressure lowering agents already. If necessary, give the minimum dose of the randomized drug every other day. Document all changes on Form 40. Recheck blood pressure at the discretion of the study team.

Successful Resolution: Blood pressure rises to within the goal of 102 mmHg to 107 mmHg.

Unsuccessful Resolution: Blood pressure does not rise to within the goal by the following month. The DCC will send a summary of the "Low Blood Pressure Without Symptoms" reports for review by the Clinical Management Subcommittee.

8. Low Serum Potassium

Definition: Serum potassium ≤ 3.0 mEq/L (Central Lab).

Action: Repeat measurement centrally within 48 hours (or less). If the serum potassium measured during the confirming visit is less than or equal to 3.0 mEq/L and there is an obvious reason for hypokalemia, the Principal Investigator or his/her designee at the clinical center should take corrective measures (including very cautious use of potassium supplements) and schedule a non-protocol visit soon after the institution of the corrective measures and followed the patient often. One corrective measure may include alteration of potassium intake (see Lifestyle Modifications, Section 10.h.).

Successful Resolution: Serum potassium ≥ 3.0 mEq/L on repeat central measurements.

Unsuccessful Resolution: Serum potassium < 3.0 mEq/L on consecutive protocol measures. Action item persists, usual medical care.

9. High Serum Potassium

Definition: Serum potassium ≥ 6.0 mEq/L (Central Lab).

Action: Repeat measurement centrally within 48 hours (or less). If the serum potassium measured during the confirming visit is greater than or equal to 6.0 mEq/L and there is an apparent reason for hyperkalemia (such as the use of potassium supplements) the Principal Investigator or his/her designee at the Clinical Center should take corrective measures and schedule a non-protocol visit one week or less after the institution of the corrective measures. One corrective measure may be to alter the potassium intake (see Lifestyle Modifications Section 10.k).

If the serum potassium is less than 6.0 mEq/L following the corrective measures, the participant returns to the standard protocol.

Successful Resolution: Serum potassium <6.0 mEq/L on repeat central measurement.

Unsuccessful Resolution: Serum potassium ≥ 6.0 mEq/L. Action item persists, usual medical care. Participant may reach a Stop Point related to blinded medication, as described in Section 11.b.

10. Leukopenia

Definition: Leukocyte count < 2,500/mm^3 (Local Lab on annual measure).

Action: Principal Investigator or his/her designee at the Clinical Center should stop the randomized study medication (and the other antihypertensives) and schedule a confirming non-protocol visit within 24 hours of receiving the clinical laboratory report.

Successful Resolution: Leukocyte > 2,500/mm^3 on local repeat measurement.

Unsuccessful Resolution: Leukocyte < 2,500/mm^3 on repeat visits. Action item persists, participant may reach a Stop Point (see Section 11.b.1).

11. Randomized Drug-Specific Side Effects

Definition: Adverse effects noted on the symptom form such as skin rash, cough, sinus bradycardia < 50 beats/min (or symptomatic sinus bradycardia < 60 beats/min), muscular weakness/fatigue, impotence, with no other apparent cause for these signs or symptoms other than use of the study medication.

Action: Evaluate the participant for any causes unrelated to their antihypertensive regimen that could be responsible for the symptoms and signs as dictated by usual medical care. Adjust medications other than the blinded randomized medication in an attempt to resolve symptoms or signs (e.g., clonidine dose if bradycardia). If symptoms of more than mild severity persist after the above actions are taken, and the randomized drug is at its lowest dose every other day, the randomized drug may be stopped for one week at the discretion of the Principal Investigator or his/her designee at the Clinical Center. The DCC should be notified of all medication changes. If the symptoms resolve after one week, the Principal Investigator or his/her designee may restart the randomized medication if medically indicated.

Successful Resolution: Randomized drug specific adverse effects of more than mild severity resolve or do not reoccur after reinstituting the randomized medication.

Unsuccessful Resolution: The participant has persistent randomized drug specific adverse effects necessitating stopping the meds on unblinding.

12. Worsening of Serum Creatinine

Definition: Increase in central serum creatinine of > 25% compared to most recent, previously measured central serum creatinine.

Action: Repeat measurement should be done centrally at the CBL as soon as possible. The participant will be evaluated for any causes unrelated to their blood pressure or antihypertensive regimen that could be responsible for the rise in their serum creatinine as dictated by usual medical care.

Successful Resolution: Repeat serum creatinine does not confirm the > 25% increase in serum creatinine.

Unsuccessful Resolution: Repeat serum creatinine confirms the > 25% increase. If the repeat serum creatinine has not increased further then the participant will return to their routine visits. If the serum creatinine on repeat continues to increase, then serum creatinine should be repeated again locally as soon as possible.

13. GFR Decline

Definition: A 25% reduction in GFR from one GFR to the next.

Action: The DCC will notify the clinic. All reversible causes of reduced GFR should be addressed.

Successful Resolution: The next protocol GFR measurement does not confirm a 25% reduction of GFR.

Unsuccessful Resolution: Repeat measurement at the next protocol GFR measure confirms. Stop point may be declared if there is a 50% reduction in GFR from one GFR to the next.

14. GFR "Event"

Definition: 50% decline or 25 ml/min/1.73m^2 or more reduction in the GFR value compared to the mean baseline GFR.

Action: The DCC will notify the clinic to perform a repeat GFR.

Resolution: The DCC determines if the repeat GFR confirms 50% reduction or 25 ml/min/1.73m^2 or more reduction in GFR value from baseline. If so, this will count as an "event" in the patient outcome time-to-event analysis. Patient continues to be followed according to protocol. Centers are not notified as to the results of the repeated GFR since the centers are blinded to the GFR results.

15.Worsening of Urine Protein/Creatinine Ratio

Definition: Onset of symptomatic diabetes requiring treatment with insulin or an oral hypoglycemic and the development of a protein/creatinine ratio of >1.5.

Action: The DCC will notify the clinic to repeat the 24-hour urine centrally.

Successful Resolution: The central repeated 24-hour urine does not confirm the protein/creatinine ratio of >1.5.

Unsuccessful Resolution: The central repeated 24-hour urine measurement confirms the protein/creatinine ratio >1.5. A stop point may be declared.

11.b. Adverse Events, Hospitalizations, and Deaths

Adverse events are defined as significant clinical events which are potentially related to the intervention, or death. Adverse events will be reported on the Hospitalization form. The DCC will electronically transmit patient hospitalization summaries to the Clinical Management Subcommittee. They will review the data documenting the event and, if thought to be indicated, request that the DCC request that Clinical Center provide primary documents such as the hospital discharge summary. The Clinical Management Subcommittee will then make appropriate recommendations to the Study Physician. The hospitalization data will be summarized for the External Advisory and Safety Monitoring Committee.

When, in the judgment of the AASK physician, a hospitalization is judged to be due to the patient's randomized study drug treatment, this will be documented on Form 45, Item 14.c. "Hospitalization due to randomized medication regimen." The Form 45 must be entered into the AASK database by the end of the day on which this judgment is made. This will generate a "Potentially Serious Adverse Reaction Report" which will immediately be electronically mailed to Drs. Kusek and Agodoa at the NIH. They will forward relevant information to industry sponsors by FAX by the end of the following business day.

When, in the judgement of the AASK Physician, a death is believed to be related to the patient's randomized study drug treatment, this will be documented on Form 48, Item 14.c., "Death related to randomized medication regimen." The Form 48 must be entered into the AASK database by the end of the day it is completed. This will generate a "Potentially Serious Adverse Reaction Report" which will immediately be electronically mailed to Drs. Kusek and Agodoa at the NIH. They will forward relevant information to industry sponsors by FAX by the end of the following business day.

Any adverse reactions suspected as being possibly or reasonably related to the randomized drug should be reported to the DCC. It is not necessary for Clinical Center staff to prove causality before reporting.

All deaths will require the Study Physician to notify the DCC immediately via the death form. The DCC will electronically send a report to the chair of the Clinical Management Subcommittee. Data describing the cause of death will be transmitted to the DCC within one week and will be transmitted to the Clinical Management Subcommittee designated review as soon as possible. This will be in the form of an electronic "death report" including all symptoms, hospitalization, GFR's biochemistry, and the clinical center's detailed description of the death. The clinical center will also send primary paper documents surrounding the death to the DCC. These include death certificates, autopsy reports, and hospitalization discharge summary if death occurred in the hospital. The subcommittee reviewers may request that the DCC send them the primary documents such as hospital records or autopsy forms. The External Advisory and Safety Monitoring Committee will receive detailed summaries of deaths.

11.c. <u>Stop Points</u>

A stop point can only occur after the patient is randomized and denotes the occurrence of an event which necessitates unblinding or altering one of the two interventions in the study (i.e., cessation of the coded medication or cessation one of the two levels of blood pressure control). The other intervention will remain as usual, except for pregnancy. Visits continue after stop points. GFR's continue after all stop points except pregnancy. Before a stop point is declared all possible measures will be taken to reverse the problem necessitating the stop point. If there is a necessary deviation from the randomized intervention, we will minimize the degree if at all possible. If possible the participant will resume the intervention at a later time.

A Stop Point is identified by the Principal Investigator after thorough review of the case with the relevant local staff Data Coordinating Center and the Clinical Management Committee. The local Principal Investigator and Study Coordinator will complete a Stop Point Form. The DCC and Clinical Management Subcommittee reviewers jointly complete a stop point confirmation form.

When it has been determined that side effects requiring unblinding have occurred, this will be documented on Form 31, Item 8 "Necessity of Unblinding." The Form 31 must be entered into the AASK database by the end of the day on which the decision is made. This will generate a "Potentially Serious Adverse Reaction Report" which will immediately be electronically mailed to Drs. Kusek and Agodoa at the NIH. They will forward relevant information to industry sponsors by FAX by the end of the following business day.

Nine types of stop points have been designated for the AASK. There are three general stop points related specifically to the blinded medications.

General Stop Points

1. GFR Decline
2. Pregnancy
3. Need for a new blood pressure goal
9. Dialysis

Stop Points Related to Blinded Medications

A. Need additional medication

4. Need additional medication for blood pressure control
5. Need additional medication due to a serious medical condition

B. Need to stop blinded medication

6. Need to stop blinded medication due to serious medical condition
7. Need to stop blinded medication due to hypotensive side effect
8. Need to stop blinded medication due to other side effects

Details are as follows:

1.GFR Decline. When there is a loss of 50% of GFR from one GFR to the next, the DCC will send a potential GFR stop point report and the GFR will be repeated as soon as possible. If the rapid drop is confirmed by a repeat measure of GFR, there is a stop point.

2. Pregnancy.

3.Need for a new blood pressure goal. Can't stay on randomized BP goal anymore due to a concomitant condition. This is defined as onset of a serious medical condition that requires 1) that a person on the moderate goal switch to low or 2) that a person on the low goal switch to moderate.

4.Need additional medication for blood pressure control. A diastolic BP that remains at or above 100 mmHg or a systolic BP that remains at or above 160 mmHg on three consecutive post-randomization visits following maximally tolerated doses of the multiple drug regimen specified by the protocol and in spite of documented compliance. This requires unblinding and if the patient is judged to have been on an inappropriate drug, this requires cessation of the study medication and addition of other medications which may include one of the three first line randomized drug therapies.

5.Additional medication due to a serious medical condition: Development of the need for any of the three first-line randomized drug therapies for non-hypertensive indications (i.e.,

refractory angina, severe CHF). Development of the need for ACE Inhibitors subsequent to the onset of symptomatic diabetes requiring treatment with insulin or an oral hypoglycemic agent **and** the development of a confirmed protein/creatinine ratio of > 1.5 (i.e., two consecutive 24-hour urine samples with Central Biochemistry Lab protein/creatinine ratio results > 1.5).

6.Need to stop blinded medication due to serious medical condition. Can't take a randomized drug anymore due to a concomitant condition. Onset of concomitant medical conditions impacting blinded medication, defined as conditions that requires that ACEI, BB, or CCB stop. These require unblinding, and if the patient is on the drug which must be stopped, these require cessation of the study medication.

7.Need to stop blinded medication due to hypotensive side effects. Significant hypotension symptoms for participants who are receiving the lowest dose of a randomized drug every other day. This requires cessation of the coded medication.

8.Need to stop blinded medication due to other side effects. Onset of serious concomitant conditions that could represent adverse side effects of the randomized drug therapy. These may require unblinding and if the patient is on the drug which must be stopped, these require cessation of study medication.

8.1 Side effects requiring unblinding

If this patient is on the drug indicated, that drug must be stopped.

a. Heart block > first degree (B blocker)
b. Congestive heart failure (B blocker)
c. New onset asthma (B blocker)
d.Intolerable persistent new or worsening cough not apparently due to usual causes (ACEI)
e.Confirmed increase in serum potassium to 6 mEq/L or more for no other apparent reason except the blinded medication (ACEI)
f. Angioedema (ACEI)
g. Confirmed leukopenia < 2,500/mm^3 (ACEI)
h. Intolerable vasodilator symptoms (CCB)

When it has been determined that <u>side effects</u> requiring unblinding have occurred and the Clinical Center formally requests unblinding, the Clinical Management Subcommittee will confirm this on Form 31, Item 8 "Necessity of Unblinding." The Form 31 must be entered into the AASK database by the end of the day on which the decision is made. This will generate a "Potentially Serious Adverse Reaction Report" which will immediately be electronically mailed to Drs. Kusek and Agodoa at the NIH. They will forward relevant information to industry sponsors by FAX by the end of the following business day. Any adverse reactions suspected as being possibly or reasonably related to the randomized drug should be reported to the DCC. It is not necessary for a Clinical Center staff to prove causality before reporting.

8.2 Side effects not requiring unblinding

Since these can be a result of any of the drugs, they do not require unblinding. They requires cessation of the study medication.

a.Onset of sexual dysfunction.

b. Severe systemic rash

9. Need to begin dialysis

A stop point should be declared when a patient begins dialysis.

11.c.1. **Measurements at the Time of a Stop Point**

When a Stop Point has been confirmed by Clinical Management Subcommittee Review, an extra measurement of GFR will be obtained, except for pregnancy and for GFR decline.

11.c.2. **Follow-Up After Stop Point**

After reaching a Stop Point, the participant should be followed according to protocol including all visits and measurements. Outcome measures are documented in the same fashion as if there had been no Stop Point. If for example, the participant can no longer take a study drug but can still safely be in their assigned blood pressure group, every effort should be made to keep them at their assigned blood pressure goal. Also, every effort will be made to keep participants in their assigned groups even after unmasking. For example, if a participant has a myocardial infarction and the cardiologist insists a beta-blocker be used for treatment, Stop point 5 will be declared and confirmed. The study drug will be unmasked and if the participant is assigned to a beta-blocker it will be continued. In all cases, the participant's data will be analyzed in the group to which they were originally assigned whether or not the intervention was continued.

After the stop points, if possible, at a later time, the study drug will be restarted. The DCC will send an "Is it possible to restart" report every three months after a patient goes off his or her study drug or goal to remind the clinic to consider restarting the study drug or goal level.

12. ANALYSIS PLAN

12.a. Baseline Analyses

Demographic and clinical characteristics of patients who are randomized will be summarized to characterize the study population and contrasted with the characteristics of patients who were either screened or entered Baseline but who were not randomized. Baseline patient characteristics will be compared between the treatment groups to identify imbalances. In accordance with the 3x2 factorial design, these comparisons will be made using analysis of variance for continuous variables, and loglinear models for categorical variables.

12.b. Analyses During Follow-Up

The following analyses will be conducted during the follow-up period, and results presented in monthly reports to study personnel when blinding is not compromised.

Adherence. Each of these indicators of compliance described in Sections 7e-7f will be monitored, summarized by clinical center, and related to patient characteristics.

Retention. Frequencies of patients reaching stop points will be kept for each treatment combination. Characteristics of patients lost to follow-up will be compared to those not lost to evaluate possible drop-out bias.

Achievement of target blood pressure levels. The interpretation of the blood pressure control factor will be facilitated if i) attained blood pressure levels are well separated between the two levels of control, and ii) the amount of separation is similar over the three regimens. These issues will be examined using graphical summaries (e.g., box plots) of follow-up blood pressure measurements by treatment group. Separation in attained blood pressure will also be evaluated by examining the main effect of the blood pressure control factor in repeated measures analysis of follow-up MAPs. Consistency of separation will be assessed by the interaction between this factor and the randomized drug regimens.

Additional outcomes related to achievement of target blood pressure levels include frequencies of patients within target ranges, the proportion of desired reduction achieved, and the number of "steps" required to achieve control in the three regimens.

Adverse Effects. Detailed summaries of the frequency and severity of adverse effects will be provided by treatment group on an ongoing basis throughout the Study.

12.c. Primary Renal Function Analysis

STATEMENT OF HYPOTHESES

The objectives of the primary renal function analysis are to characterize the effects of the randomized treatment regimens on the pattern of change in GFR during follow-up, and to provide a basis for assessing the likelihood that one of the interventions will delay the onset of ESRD. This analysis will be based on the assumption that mean GFR declines at one rate during the initial three months after randomization (acute phase), and at a possibly different rate for the remainder of follow-up (chronic phase). Based on this 2-slope formulation, two separate sets of hypothesis are of fundamental clinical importance:

Null Hypothesis 1:There will be no difference between treatment groups in the mean rate of decline in renal function (assessed by GFR) during the chronic phase.

Research Hypothesis 1: There will be a difference between treatment groups in the mean rate of decline in renal function (assessed by GFR) during the chronic phase.

Null Hypothesis 2: There will be no difference between treatment groups in the level of renal function (assessed by GFR) at the end of the study follow-up period (5 years).

Research Hypothesis 2:There will be a difference between treatment groups in the level of renal function (assessed by GFR) at the end of the study follow-up period (5 years).

The first set of hypotheses addresses the question of whether the rate of loss of renal function is slowed following the initial acute effect. The second set of hypotheses addresses the question of whether the study was able to demonstrate that one intervention preserves renal function to a greater degree than another intervention.

PRIMARY RENAL ANALYSIS

If informative censoring [78, 79] is not a major confounder in the study (see below), the mixed-effects modelling approach of Laird and Ware [80, 81] will be used to analyze the change in GFR under a 2-slope model in which each patient is assumed to have one slope during the acute phase and a possibly different slope during the chronic phase. The effects of the treatment interventions will be tested on the mean acute slopes, the mean chronic slopes, and the estimated total mean change in GFR from Baseline to 5 years (the approximate end of follow-up). The analysis of the total mean change in GFR from Baseline to 5 years will be based on a time-weighted linear combination of the mean acute and chronic slopes.

The comparisons of the chronic slopes and the mean total GFR change to 5 years address the primary renal hypotheses, and will be used to draw conclusions about the likelihood that one of the interventions would delay the onset of ESRD. If the comparison of two treatment groups is significant in the same direction for both the chronic slopes and the total GFR change analyses, then it will be possible to conclude that the treatment group with the less steep slopes both reduced the rate of decline in renal function following the acute phase, and that this treatment was demonstrated to have preserved renal function by the end of the study. This result will be regarded as providing strong evidence that the treatment will delay the onset of renal failure.

The primary analysis of GFR slopes will be carried out with age, gender, history of cardiovascular disease, baseline MAP, and baseline urine protein excretion included as covariates. In accordance with the factorial design of the study, both the main effects and the interactions between the blood pressure level and anti-hypertensive agent factors will be tested. If an interaction is detected, the effects of each factor will have to be evaluated at each level of the other factor. It is recognized that the power to detect an interaction and for comparing individual cells in the design will be limited. However, it is expected that any effects of treatment to the low vs the usual blood pressure goal will be in the same directions for each anti-hypertensive agent arm. That is, if the low blood pressure goal reduces the rate of GFR decline relative to the usual blood pressure goal in the ACE arm, it is not likely that it will increase the rate of GFR decline in one or both of the other two arms. Hence any interactions that might occur between the anti-hypertensive and blood pressure goal factors are expected to be quantitative rather than qualitative in nature. In the event of a quantitative interaction, the main effect of one of the anti-hypertensive regimen/blood pressure goal factors can still be interpreted reasonably clearly as the effect of that factor averaged over the different levels of the other factor.

The primary main-effects comparisons are:

i) Low vs Usual MAP goals,
ii) ACEi vs Beta Blocker, and
iii) Calcium Channel Blocker vs Beta Blocker.

An intention-to-treat strategy [82] will be used in which patients are retained in the groups to which they are randomly assigned, regardless of whether they comply to their treatments or achieve their target levels of blood pressure control. However, patients who die or drop out of the study during the acute phase will have little impact on the chronic slopes analysis. Patients who subsequently reach stop points requiring modifications of the treatment interventions will continue to be followed for GFR, and will be retained in their original randomized group for the chronic slope analysis. Thus the primary analysis will compare blood pressure regimens; the effects of compliance and the effects of specific drugs included in the regimens will be investigated in subsequent explanatory analyses.

The baseline for the chronic slopes is effectively placed at 3 months follow-up, at which point the different intervention groups will differ systematically from one another because different treatments will have been applied during the first three months. In particular, the treatment groups are expected to be in different hemodynamic states and to have different levels of GFR. Therefore, the interpretation of the comparison of chronic slopes will take into account a confounding of i) the effects of the interventions on decline in GFR during the chronic phase, and ii) the effects of differences in the states of the patients at the beginning of the chronic phase.

The assumptions of the 2-slope model will be examined periodically as the study progresses. In addition to informative censoring, key potential deviations from assumptions include non-constant between-patient or within-patient variance of GFRs and/or nonlinearity of the mean decline in GFR during the chronic phase. The pattern of decline in mean GFR will be assessed by fitting a multi-slope spline model [84] with changes in slope allowed at the time of each protocol GFR measurement, and the validity of confidence intervals for major comparisons assessed by computing robust estimates of standard errors [85]. If major deviations from the 2-slope model are detected which impact the conclusions of the analysis, consideration will be given to generalizing the 2-slope model to incorporate them.

12.d Secondary Patient-Outcome Analysis

STATEMENT OF HYPOTHESES

The objective of the main *patient-outcome analysis* is to determine the clinical impact of the interventions based on a relatively "hard" endpoint which is primarily related to renal function but which is relevant to the patient. The statements of the null and research hypothesis for the statistical analysis of clinical aspect of the study are as follows:

Null Hypothesis:There will be no difference in rate of renal events ([i] and [ii] below) between the treatment groups, and no difference in mortality [iii] between treatment groups.

Research Hypothesis:The combined rate of renal events ([i] and [ii]) and death [3] will differ between the treatment groups.

MAIN PATIENT-OUTCOME ANALYSIS

The main patient-outcome analysis is a time-to-event analysis, with events including

[i]Reduction in GFR by 50% or by 25 ml/min/1.73m^2
[ii]ESRD
[iii]Death.

The reduction in GFR will be assessed relative to the mean of two baseline GFR measurements. GFR events defined by [i] must be confirmed by a repeat GFR within one month.

The time-to-event analysis will be carried out as a Cox-regression [86] with age, gender, history of cardiovascular disease, baseline MAP, and baseline urine protein excretion included as covariates. In accordance with the factorial design of the study, both the main effects and the interactions between the blood pressure level and anti-hypertensive agent factors will be tested. If an interaction is detected, the effects of each factor will have to be evaluated at each level of the other factor. It is recognized, however, that the power to detect an interaction and for comparing individual cells in the design will be limited. As in the primary renal function analysis, the primary main-effects comparisons for the time-to-event analysis are:

i) Low vs Usual MAP goals,
ii) ACEi vs Beta Blocker, and
iii) Calcium Channel Blocker vs Beta Blocker.

The main patient outcome analysis will employ the intention-to-treat strategy [82] in which patients are retained in their randomized groups, regardless of whether they comply to their treatments or achieve their target levels of blood pressure control. The effects of compliance and the effects of specific drugs included in the regimens will be investigated in subsequent explanatory analyses.

GENERALIZED PATIENT OUTCOME ANALYSIS

A broader time-to-adverse event analysis with adverse events including i) time to GFR reduction of 50% of 25 ml/min/1.73m^2, ii) ESRD, iii) death, and iv) hospitalized myocardial infarction and stroke will also be conducted. This will be the main analysis addressing the overall benefit of interventions to the patient, including effects on both relevant renal and cardiovascular events. Because the proportion of patients experiencing events will be increased, the power of this more broadly based time-to-adverse event analysis may be greater than that of the time-to-event analysis based on events (i) - (iii) alone.

12.e. <u>Explanatory Renal Function Analyses</u>

Randomized Comparisons:

A.An analysis of the full distribution of GFR slopes, including estimates of the effects of the treatment interventions of the variability of GFR slopes. If informative censoring does not turn out to be a major confounder in the study, this analysis will also be based on the 2-slope mixed effects approach described above. If a treatment intervention can be shown to significantly reduce the inter-patient variability in GFR slopes in association with a reduction in the proportion of patients with steep slopes, this will be regarded as suggesting a beneficial effect of this intervention on patients with comparatively rapid disease progression.

B.Time-to-event analyses of the effects of treatment interventions specifically on renal and non-renal events. These analyses will be carried out using competing risk Cox models with cause specific hazard rates [83]. Consideration will also be given to testing the effects of the treatment groups on the subdistribution functions associated with specific types of events.

C.The direct comparison of the Calcium Channel Blocker and ACEi arms will not be regarded as part of the primary analysis due to interpretational difficulties associated with the large differences in hemodynamic effects expected between these agents. However, there is expected to be sufficient statistical power to separately compare the mean acute GFR slopes and mean chronic GFR slopes between these arms. These comparisons will therefore be carried out as secondary analyses.

Non-Randomized Comparisons:

D."As-treated" analyses which model the relationship of achieved levels of MAP and the specific anti-hypertensive agents used with each of the outcomes described above. Mixed effects models will be used to relate the mean chronic and total GFR slopes to mean follow-up MAP and to indicator variables for the different classes of anti-hypertensive medications after controlling for baseline factors which are predictive of mean GFR slope. Due to the possibility of an effect of decline in renal function on the ability to control blood pressure, and other biases associated with differences between compilers and non-compilers in clinical trials, the results of these analyses will be interpreted with caution.

Additional analyses will also be conducted to evaluate the effects of specific anti-hypertensive classes and cumulative mean follow-up MAP as time-dependent factors.

E.An analysis comparing the effects of the randomized anti-hypertensive agent groups after controlling for follow-up blood pressure levels. This analysis will also be conducted based on the mixed-effects 2-slope model. If the achieved blood pressure levels turn out to differ between the anti-hypertensive regimens, this analysis will be essential to determine whether differences between the anti-hypertensive groups are due to different levels of blood pressure control or to renal protective effects of the agents.

F.The analyses described in [A], [C], and [D] will also be conducted based on reciprocal serum creatinine and for log transformed urine protein.

INFORMATIVE CENSORING

The Laird-Ware mixed effect model approach maximizes precision by giving more weight in the analysis to patients with longer follow-up. Because of this differential weighing, the estimates of GFR slopes will be biased if patients who become lost to GFR follow-up during the study tend to have either steeper or less steep slopes than those who remain for the full duration of follow-up (this phenomenon is referred to as *informative censoring [78, 79]*). If the rate of loss to follow-up is affected by the treatment interventions, informative censoring may invalidate the primary hypothesis tests comparing the treatment interventions under the Laird - Ware mixed effects model [78, 79, 80].

The major potential sources of informative censoring in the AASK are i) patients reaching end-stage renal disease, which would preclude further GFR measurements, or ii) patients dying or otherwise becoming lost to GFR follow-up. Informative censoring due to patients reaching ESRD is expected to have a minor impact because a relatively small proportion of patients are likely to reach ESRD during follow-up since baseline GFR > 20 ml/min/1.73m^2, and because those that do reach ESRD are likely to do so late in follow-up when the impact of subsequent missing GFRs on the Laird-Ware analysis is minimal. Informative censoring due to mortality may be a serious problem if the mortality rate turns out to vary substantially as a function of the patient's GFR. The strong correlation of serum creatinine with mortality rates in the HDFP Study suggests that this might be the case. Patient loss-to-follow-up may also be a source of informative censoring if there is a substantial loss-to-follow-up rate, and if patients who are lost to follow-up tend to have either a more or a less rapid decline in renal function.

The association of mortality and patient loss-to-follow-up with renal function measures will be examined periodically during the study. If a bias due to informative censoring is suggested, then the mixed effects model will need to be generalized to account for informative censoring. Since the development methods of carrying out analyses with informative censoring is currently in at state of rapid change, the determination of the optimal method for carrying out an informative censoring analysis will be reviewed periodically during the follow-up period. At present, we plan to use the approach of Schluchter [87] which expands the Laird-Ware mixed effects model by adding terms to account for the relationship between censoring time and the randomization groups and for the correlation between the censoring time and the true GFR slopes.

12.f. Explanatory Analyses Related to Time-to-Event

SECONDARY ANALYSES INVOLVING RANDOMIZED INTERVENTION GROUPS

Explanatory time-to-event analyses will be conducted to develop a better fitting model for the relationships of the events in the primary time-to-event analysis with the study intervention group and prognostic covariates based on interactive analysis of the data. In particular, a stepwise variable selection strategy [88] will be used to develop a multiple regression model relating the event hazard rate to the randomized treatment groups and an optimal set of

baseline factors including the covariates prespecified for the primary analysis as well as other potential prognostic covariates (i.e., baseline lipid levels, baseline creatinine). Interactions between the treatment groups and the prognostic covariates will also be investigated.

It is possible that the hazard ratios between the intervention groups may not be proportional throughout follow-up due to differences in the ratio of rates at which patients reach GFR events over time. For example, if the effect of the treatment interventions turns out to be multiplicatively related to the patient's mean rate of progression, then the hazard ratio in the time-to-event analysis will be greater early in follow-up than later in follow-up. The possibility of non-proportional hazards over time between different treatment groups and between different levels of the prognostic covariates will be investigated by various methods including log-log plots [89] and the model selection approach of Thall and Lachin [90]. In the event of substantially nonproportional hazards, consideration will be given to adding time-interaction terms into the Cox models for the secondary analyses. Alternatively, parametric survival analysis models which allow nonproportional hazards (i.e., lognormal or Weibul models) will be considered [91].

It should be noted that the issues addressed in this section, i.e, the possibility of a nonconstant hazard ratio over time or incorrect specification of the relationship of the hazard function to the covariates in the primary analysis, would reduce the power of the primary Cox analysis, but the nominal significance level of the tests of the study interventions would remain valid [92, 93].

SECONDARY ANALYSES OF COMPLIANCE

The Cox regression model described above will be extended to include time dependent covariates specifying whether the patient i) is currently on his/her randomized intervention, ii) has previously reached a stop point and is no longer receiving any of the first line anti-hypertensive agents, or iii) has crossed over to the first line agent of one of the other treatment regimens. This analysis will provide estimates of the effects of the respective treatment regimens while the patients are actually receiving the intended medications. Each of the explanatory renal function analyses described in [D] and [E] above will also be conducted using Cox regression models with time to substantial GFR reduction, ESRD, or Death as the outcome. Results of these analyses which involve factors other than the randomized treatment groups will be interpreted in the context of observational analyses since patients will not be randomized on these variables.

ANALYSES OF MORTALITY AND OF CARDIOVASCULAR EVENTS

Time-to-event analyses will also be conducted to specifically compare mortality and cardiovascular event rates between the randomized treatment groups. It is recognized that the power of these analyses will be low due to the relatively small number of patients in the AASK as compared to typical cardiovascular trials of anti-hypertensive regimens. Hence a non-significant effect of the blood pressure goal or anti-hypertensive regimen factors on

these outcomes will not be interpreted as demonstrating an equivalence of these interventions on cardiovascular endpoints.

12.g. Power of Primary Analyses

ASSUMPTIONS

There are limited data on the decline in GFR in African Americans. The assumptions of the power analyses are based largely on information obtained from the recently completed multi-center clinical trial, the Modification of Diet in Renal Disease (MDRD) Study A, the AASK Pilot Study, analyses of black patients in the HDFP, and unpublished results from a recently completed study of blacks with hypertensive nephrosclerosis at the University of Texas Southwestern Medical Center at Dallas (Toto, et al). Additional details of the results of these studies pertinent to the assumptions of the power calculations are provided in the document "Power Calculations and Design Issues in the Full-Scale AASK", which may be obtained from the Data Coordinating Center. The key assumptions are spelled out below:

Study Parameters:

1.The study will have 2 years of uniform patient accrual, with 4 additional years of follow-up.

2.Hypothesis tests will be 2-sided, with a 5% significance level and no adjustment for multiple comparisons [94].

3.There will be 2 baseline GFRs which are averaged for the time-to-event analysis. During follow-up, there will be GFRs at 3, 6, and 12 months, and every 6 months thereafter. A repeat GFR will be conducted within one month of GFR reductions defining GFR events in the time-to-event analyses.

Hypothesized Effect Size:

4.A 30% proportional reduction in GFR slope is hypothesized for the Low vs Usual blood pressure goal, for the ACEi arm vs the Beta Blocker arm, and for the Calcium Channel Blocker arm vs the Beta Blocker arm. No effect on GFR slope is hypothesized for patients with positive or 0 slopes.

For the time-to-event analysis, a 20% reduction in mortality is also hypothesized for the Low vs Usual blood pressure goal, for the ACEi arm vs the Beta Blocker arm, and for the Calcium Channel Blocker arm vs the Beta Blocker arm.

Mean Rate of Progression:

5.The limited published data regarding the rate of change in GFR in blacks leaves substantial uncertainty in the mean rate of progression. A mean GFR slope of -4.9 ml/min/1.73m^2/yr was observed among six non-proteinuric blacks with hypertensive nephrosclerosis randomized to the usual MAP goal in MDRD Study A. The mean GFR slope was approximately -1 ml/min/1.73m^2/yr among 56 blacks with hypertensive nephrosclerosis in the unpublished data of Toto et al. The mean GFR slope ranged from -2 to -3 ml/min/1.73m^2/yr in relevant non-proteinuric subgroups (which include whites) of patients randomized to the Usual MAP goal in the MDRD Study A with sample sizes of 46 to 188.

A more accurate estimate of mean progression rate will be assessed after the first two years of follow-up in the study cohort. For the primary power calculations, a mean GFR slope of -4 ml/min/1.73m^2/yr is assumed for the Usual MAP group in the comparison of MAP goals, and for the Beta Blocker group for the comparison of anti-hypertensive agent arms. However, due to uncertainty regarding the mean GFR slope, power is also considered for mean GFR slopes ranging from -2 to -4 ml/min/1.73m^2/yr.

Variability of GFR measurements and slopes:

6.Based on the AASK Pilot Study baseline GFRs, the within-patient variance of GFRs is assumed to be proportional to the patient's current GFR (within-patient variance of GFR measurements = 0.67 × current GFR).

7.Based on MDRD Study A data, after accounting for the individual patient's GFR regression lines, GFR measurements obtained more than 12 months apart are assumed to have a residual correlation of zero, while the correlation between GFR measurements obtained within 12 months of each other are assumed to increase linearly to +0.28 for GFR measurements obtained within 1 month of each other.

8.Between-patient variability of GFR slopes is assumed to be similar to that seen in the MDRD Study A (between-patient standard deviation of GFR slopes = 3.8 ml/min/1.73m^2/yr).

Loss to Follow-up:

9.A 4%/year loss-to-GFR follow-up rate is assumed due to patients leaving the study. The 4%/yr rate translates into about an 18% loss to GFR follow-up over 5 years.

10.Patients reach ESRD at a GFR of 7 ml/min/1.73m^2.

11.A 10% mortality over 5 years is assumed in the Usual MAP group in the comparison of MAP goals, and in the Beta Blocker group in the comparison of the anti-hypertensive agent goals.

Dropins and Dropouts:

12.Patients will "switch" from the treatment corresponding to the patient's assigned treatment to the other treatment being compared at a rate of 4%/year.

Acute Effect:

13.A mean acute effect of -2 ml/min/1.73m^2 is assumed in the Low MAP group in the comparison of MAP goals, and in the ACEi group in the comparison of the ACEi and Beta Blocker arms. A mean acute effect of +2 ml/min/1.73m^2 is assumed in the Calcium Channel Blocker group in the comparison of the Calcium Channel Blocker vs Beta Blocker arms.

Compliance:

14.Compliance is not explicitly modelled in the power calculations. Thus the assumed effect sizes are regarded as applying to comparisons of the randomized treatment groups at the levels of blood pressure control which are actually achieved and the amount of the anti-hypertensive medications which are actually taken.

RESULTS OF POWER ANALYSIS

The power of the AASK study under the assumptions specified above for the comparisons of the Low vs Usual MAP goals, the ACEi vs Beta Blocker arms, and the Calcium Channel Blocker vs Beta Blocker Arms is specified in Table 12.1 below.

Under the assumption of a mean GFR slope of -4.0 ml/min/1.73m^2/yr, a hypothesized 30% effect on GFR slope and assuming informative censoring is not found to be a major confounder during the study, the power of the analysis of chronic slopes is 99% for the comparison of the Low vs Usual MAP goals, 98% for the comparison of the ACEi vs Beta Blocker arms, and 87% for the comparison of the Calcium Channel Blocker vs Beta Blocker arms. The power of the analysis of estimated total mean GFR change to 5 years under these same assumptions is 84%, 76%, and 99% for the corresponding comparisons. If an informative censoring model must be used, the power of the analysis of chronic slopes is expected to be approximately 96%, 92%, and 78% for the same set of comparisons, while the power for the analysis of total GFR change is 77%, 68%, and 98%, respectively.

If a 20% effect on mortality is hypothesized in addition to the 30% reduction in mean GFR slope, the power of the time-to-event analysis is 88% for the comparison of the Low vs Usual MAP goals, 81% for the comparison of the ACEi vs Beta Blocker Arms, and 99% for the comparison of the Calcium Channel Blocker vs Beta Blocker Arms.

Table 12.1

Power of AASK 3 x 2 Design Under 412:412:206 Allocation to ACEi, Beta Blocker and Calcium Channel Blocker Arms

Assumed Mean GFR Slope (ml/min/1.73m^2/yr)	Analysis	POWER		
		Low vs. Usual MAP Goal	ACEi vs. Beta Blocker	Calcium Channel Blocker vs. Beta Blocker
-4.0	**Chronic Slope***	**96 - 99**	**92 - 98**	**78 - 87**
	Total GFR Change*	**77 - 84**	**68 - 76**	**98 - 99**
	Time-to-Event	88	81	99
-3.0	**Chronic Slope**	**89 - 94**	**81 - 88**	**63 - 72**
	Total GFR Change	**50 - 55**	**42 - 46**	**95 - 98**
	Time-to-Event	80	71	96
-2.0	**Chronic Slope**	**66 - 77**	**56 -67**	**38 - 49**
	Total GFR Change	**20 - 23**	**17 -19**	**84 - 91**
	Time-to-Event	67	57	88

*Power for the analyses of chronic slopes and total GFR change is provided for unweighted analysis of GFR slopes for patients with at least one year follow-up (left) and for weighted analysis using the mixed effects model (right).

May 3, 1999

12.h. Interim Analyses

At approximately 1 year intervals throughout the study the External Advisory Committee will review data regarding patient safety, recruitment, compliance, and efficacy of the MAP goal and anti-hypertensive agent interventions. Standard statistical stopping rules are not directly applicable due to use of two primary outcomes (both the chronic GFR slope and the total change in GFR over 5 years). A unambiguous demonstration of the superiority of one intervention over another will require significant differences in the same direction for both of these outcomes. Consequently, a formal stopping rule will be developed in which one intervention will be regarded as having been demonstrated to be more efficacious than another if both the chronic slope and total GFR change analyses are significant in the same direction based on a spending function [95] maintaining a total significance level of 5%. A spending function similar to the O'brien-Fleming rule [96] will be used with large critical values for the initial interim analyses in order to assure that the study is not halted prematurely, and to assure that the final study analysis requires only a small adjustment to account for the earlier interim analyses. If one arm of the study is demonstrated to be inferior to another at one of the interim analyses, consideration will be given to reassigning patients originally randomized to that arm and continuing the other interventions of the study.

The decision for an early termination of the study due to a demonstration of the superiority of one intervention will be complex, and in addition to the formal stopping rule will take into account the results of the time-to-event analyses and assessments of patient safety.

It is also possible that the primary analyses of the study will be underpowered depending on the size of the acute effect and mean rate decline in GFR which is observed during follow-up. As shown in Table S.1, the analysis of the mean change in GFR to 5 years is especially sensitive to the impact of a less steep mean slope. To address this issue, the interim analyses will also include assessments of the conditional power of the chronic and total GFR change analyses and of the time-to-event analysis. If the conditional power for the primary renal function analyses and/or the time-to-event analysis becomes inadequate during the course of the study, the External Advisory Committee will consider the option of ending the study.

12.i. Cardiovascular Analyses

A secondary composite cardiovascular outcome measure and a tertiary outcome measure are defined. The Cardiovascular Outcome/MAP Goal Achievement Committee will review potential cardiovascular hospitalizations using discharge summaries and lab reports from these hospitalizations. Clinical Centers will be required to send these discharge summaries and lab reports to the DCC for distribution to the Cardiovascular Outcome/MAP Goal Achievement Committee for their review.

12.i.1. **Secondary composite cardiovascular outcome measure**

The secondary outcome measure is a composite end point of time to any of the following:

1) Cardiovascular death

2) Cardiac revascularization procedure

3)Non fatal myocardial infarction (Non fatal myocardial infarction is defined as a clinical report of myocardial infarction from the investigator and the presence of one of the following:

•elevation of CPK greater than 2 times the upper limit of normal for the given hospital **supported** by the elevation of cardiac specific enzyme above the normal range such as MB fraction or cardiac troponin 1,

or, in the absence of cardiac specific enzymes

•determination of a typical evolutionary pattern defined as an elevation of CPK to 2 times the upper limit of normal for the given hospital followed by a fall of at least 50% or the appearance of new pathological Q-waves in two or more contiguous leads

or

•the appearance of a R-wave with R/S ratio in lead V1 greater than 1.0 in the absence of another explanation for these or a loss of progression of R-waves V2 through V5)

4)Heart failure requiring hospitalization and therapy with either an inotropic agent, vasodilator or ACE inhibitor or required an increase dose of a diuretic or required ultra filtration or dialysis;

5)Permanent neurological deficit of at least 24 hours duration attributed to a stroke and requiring hospitalization and confirmation by radiographic imaging.

12.i.2. **Tertiary outcome measure**

The tertiary outcome measure adds outcomes that are not as strictly defined as those included in the secondary outcome measure. The tertiary outcome measure is a composite end point of time to any of the following:

•Secondary composite cardiovascular outcome

•Non fatal MI and documented by a clinical report of a myocardial infarction from the

investigator but lacking confirmation of elevated enzymes or EKG changes

•Permanent neurological deficit of at least 24 hours duration attributed to stroke requiring hospitalization but lacking confirmation by radiographic imaging.

12.i.3. **Determination of Secondary and Tertiary Outcomes**

Each patient's first hospitalization that is noted by a clinical center to be potentially cardiovascular in nature will be reviewed by two members of the Cardiovascular Outcome Committee. If the two members of the Cardiovascular Outcome Committee are in agreement as to whether a secondary or tertiary outcome has been met, the case will be classified as such.

If the two members of the Cardiovascular Outcome Committee are in disagreement as to whether a secondary or tertiary outcome has been met, the case will then come before the full Outcome Committee for review and adjudication.

13. QUALITY CONTROL

13.a. Quality Control Introduction

In addition to the quality control methods and programs routinely used at clinical center laboratories and central laboratories, quality control mechanisms for the AASK Study are outlined in the following sections.

13.b. Quality Control of Clinical Centers

13.b.1. **Training and Certification of Study Personnel**

Clinical center personnel are trained and certified for the specific tasks they perform and undergo certification as to their competence. Individuals who have multiple titles and responsibilities with regard to this study must be trained and certified for each responsibility. The training and 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 unless they are responsible for performing study measurements or procedures. All investigators are expected to be actively involved in study activities at their center, in study-wide committees (as assigned), and in meetings of the Steering Committee. Any investigator who measures blood pressure must be initially trained and certified and must keep his/her certification up to date.

Study Coordinator

Study Coordinators must attend a Study Coordinator training session and complete training in: 1) Interviewing and Forms Completion, 2) Data Entry, 3) Error Corrections, 4) Recruitment Monitoring 5) Medication Coding, 6) Pill Counting, 7) Adherence strategies, and 8) Pregnancy tests. Coordinators must be **certified** in forms completion, data entry, error correction and medication coding.

Any study coordinator who measures blood pressure must be initially trained and certified and must keep his/her certification up to date.

Data Entry Specialist

Data entry personnel must be trained in and **certified** in forms completion, data entry, error correction and medication coding.

Blood Pressure Measurement Expert

The purpose of having a centrally trained blood pressure measurement expert is to assure that all blood pressure measurements are accurate and represent the patient's true blood pressure. It is expected that this person will have had experience in measuring blood pressure, can hear blood pressure sounds accurately, and can recall and record them accurately. Before

this person is selected, they should be screened for being able to see and hear well enough to measure blood pressure by taking the center's standardized video test and by being tested with the center's double stethoscope test. This can be administered by the investigator or study coordinator. The duties of the Blood Pressure Measurement Supervisor are to:

1. Attend and be certified in AASK blood pressure measurement methods.

2.Use the AASK training materials to be able to train and certify local personnel in the AASK protocol.

3.Inspect and maintain all blood pressure measurement equipment in working order and keep a log of that activity.

4.Measure blood pressure according to study guidelines.

5.Assure that any other person who measures blood pressure for this study is currently certified in the proper technique and follows the guidelines.

6.Train and certify any new observer who enters the center's team as a blood pressure measurer.

7.Participate in the Data Coordinating Center's (DCC) quality assurance methods. This will include:

a.Weekly inspection of the random zero device.

b.Performing a double stethoscope test for all personnel who measure blood pressure at this center and send the results to the DCC (Bi-monthly).

c.Turn in a blood pressure observer technique grading sheet bi-monthly on anyone who measures blood pressure. A blood pressure observer will perform this activity on the Blood Pressure Supervisor.

If additional personnel are needed by a clinical center to perform blood pressure measurements, training and certification are performed by the clinical center's centrally trained blood pressure supervisor.

<u>AASK GFR Technician(s)</u>

AASK technicians must attend the appropriate training session at the Central GFR laboratory or the AASK Centralized Training meeting. Technicians are to be certified in Interviewing, Forms Completion and Conduct of GFR.

Recruitment Coordinators

Recruitment Coordinators must meet study-wide requirements as defined by the Steering Committee and NIH. They are also to meet any center specific requirements and to be certified in Interviewing, Forms Completion and Recruitment.

13.b.2. **Biochemistry Laboratory**

Intentially left blank.

13.b.3. **GFR Procedure**

For quality control of the clinical center GFR procedure:

1)The coefficient of variation (CV) of the GFR for each GFR collection period and the urine flow rates of each GFR measurement are reported to the clinical centers, and these CVs are summarized and analyzed by the Data Coordinating Center.

2)A staff member of the Central GFR Laboratory who is familiar with the AASK protocol is to perform site visits of the clinical centers to observe the GFR technician conducting a GFR, answer questions, and offer suggestions if a problem (i.e., results from a center are erratic or inconsistent) with a center's GFR measurements is identified.

13.b.4. **Blood Pressure Measurements**

Quality control is maintained by centralized training of at least one technician from each clinical center, by certification of all technicians performing blood pressure measurements, by weekly RZ calibrations with results recorded in a log maintained at the clinical center, and by duplicate measurements taken on a bi-monthly basis on quality control individuals (study or non-study individuals). Throughout the study period, the technician performs all blood pressure measurements on quality control individuals concurrently with a second technician performing these measurements on the same individual.

The Quality Control Subcommittee reviews diastolic and systolic blood pressure values for digit preference and differences in duplicate measurements and means by the center and the technician. The Committee reviews the use of non-certified technicians for blood pressure measurements and for any other deviations from protocol.

Quality Control Items to be provided by each clinical center to the DCC:

1.Bi-monthly: Two Y-tube blood pressure readings on all who measure blood pressure.

2.Bimonthly: Complete a Bi-Monthly Checklist for monitoring AASK Blood Pressure Observers on anyone who measures blood pressure. A Blood Pressure Observer will perform this activity on the Blood Pressure Supervisor.

3. Weekly inspections of the random zero device.

4.As needed: Training results on new personnel.

It is hoped that all clinical center personnel will be able to attend the initial training session. However, the DCC will hold training sessions for new or replacement personnel if needed.

Quality Control Items to be provided by the DCC to each study site:

1.Videotape test, and scores from last test.

2. Every three months:

By individual blood pressure observer:

An analysis for terminal digit bias. The digit(s) preferred will not be given.

An analysis of all blood pressures taken by each observer that will calculate the average for each observer and each observer's difference from the mean.

13.b.5. **Data Forms and Data Entry**

In the Full-Scale AASK Study, all data will be entered electronically by each clinical center. A double entry system will be employed and all data will be keyed in no later than 72 hours after each patient visit. Appropriate edit checks will be in place at the key entry (database) level. Original study forms will be entered and kept on file at the Clinical Center. A subset will be requested later for quality control; when a form is selected, the Clinical Center staff will pull that form, copy it, and sent the copy to the DCC for entry a third time.

Any and all paper forms or copies of forms (i.e., copies of ECG strips, questionnaires) that pertain to the AASK study are to be filed in the participant's file in a logical and consistent manner to provide accessibility for the duration of the study. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 3 years after completion of the study.

13.b.6. **Site Visits**

Site visits are to be made to each of the Clinical Centers in years 1 and 2. The primary goals of the site visits are: 1) to observe the clinic under normal operating conditions for adherence to protocol; 2) to increase/improve communication between the study administration, the clinic personnel and the DCC; and 3) to demonstrate the study's concern for the quality of data collection. Site visit teams consist of a DCC staff member familiar with the AASK protocol and the blood pressure requirements, and an NIH representative. A member of the GFR lab staff may be included. A Study Coordinator from another clinical center may be included. All site visits teams will compile a report which is given to the Clinical Center PI and to the DCC. These reports are reviewed by the Quality Control Subcommittee and the Steering Committee.

A special committee will be formed to site visit the DCC on a regular basis. The exact membership of this committee will be determined by NIDDK. It is expected to include a representative from NIDDK, representatives from one or more of the Clinical Centers, a representative from the External Advisory Committee, a biostatistician and a clinical trials expert. The Chairman of the Steering and Planning Committee may be included.

13.c. Quality Control of the Central Biochemistry Laboratory

Data from the Central Biochemistry Laboratory will be handled in the same manner as Clinical Center data; i.e. data will be entered and verified in the database on the Cleveland Clinic Foundation SUN with a subset later selected for additional quality control. Appropriate edit checks will be in place at the key entry (database) level.

The Central Biochemistry Laboratory is to have an internal quality control system established prior to analyzing any AASK samples. This system will be outlined in the Manual of Operations for the Central Biochemistry Laboratory(s) which is prepared and submitted by the Central Laboratory to the DCC prior to initiating of the study.

At a minimum this system must include:

1)The inclusion of at least two known quality control samples; the reported measurements of the quality control samples must fall within specified ranges in order to be certified as acceptable.

2) Calibration at FDA approved manufacturers' recommended schedules.

For an external quality control system, each clinical center will send blind duplicate patient samples semi-annually to the Central Biochemistry Laboratory as specified by the DCC. At the beginning of each month, when the external quality control samples are to be taken, the DCC is to randomly select the participants to be used for quality control and will notify the clinical center. Several alternate participants will be selected as back-ups. One set of samples is labeled with the actual participants IDs and the second set of samples is labeled

with the quality control IDs. The duplicate results from the laboratory will be compared at the DCC.

13.d. Quality Control of the Central GFR Laboratory

Data from the Central GFR Laboratory will be transmitted in batches of data files automatically generated by the counter in the Central GFR Laboratory. Appropriate data integrity checks will be in place in the DCC study database, and batch data entry error reports will be sent back to the GFR Lab for correction.

The Central GFR Laboratory must have an internal quality control system established prior to analyzing any AASK samples. This system is outlined in the Manual of Operations for the Central GFR Laboratory which is prepared and submitted by the Central GFR Laboratory to the Coordinating Center prior to initiating study.

At a minimum this system must include:

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 ensure 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 participant counts are bracketed by matched ^{125}I-sodium iothalamate standards to eliminate instrumental malfunctions during sample counting as an error source.

5)A reproducibility study is performed weekly by selecting a GFR study and remeasuring the specimens the following day.

For an external quality control system, each clinical center will send blind duplicate patient samples every six months to the Central GFR Laboratory, according to a schedule specified by the DCC. On months when a quality control GFR sample is required, the DCC randomly selects one of the participants on whom a GFR measurement is obtained at that clinical center. The clinical center technician prepares and mails the backup specimens, using the center's quality control IDs. Results from the first and second GFR are compared by the DCC.

13.e. Quality Control of the Data Coordinating Center

Any and all paper forms or copies of forms (i.e., copies of informed consent signature pages) that pertain to the AASK study will be filed in a logical and consistent manner in the

participant's file at the DCC. Participant files will be stored in numerical order and stored in a secure and accessible place and manner.

13.e.1. **Participant Recruitment**

The Data Coordinating Center will produce summary recruitment reports weekly and detailed reports monthly. These reports should be verified by each clinical center and discrepancies reported to the DCC.

13.e.2. **Data Transmission and Editing**

The data entry screens will resemble the paper forms approved by the Steering Committee. Data integrity will be enforced through a variety of mechanisms. Referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks) will be supported. The option to chose a value from a list of valid codes and a description of what each code means will be available where applicable. Checks will be applied at the time of data entry into a specific field and/or before the data is written (committed) to the database. Modifications to data written to the database will be documented through either the data change system or an inquiry system. Data entered into the data base will be retrievable for viewing through the data entry applications. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password.

13.e.3. **Data Queries and Reports to Clinical Centers**

Additional errors will be detected by programs designed to detect missing data or specific errors in the data. These errors will be summarized along with detailed descriptions for each specific problem in Data Query Reports which will be sent to the Clinical Centers via e-mail. Reports regarding the length of time required to resolve queries as well as reports indicating those centers and their specific queries that are still open will be prepared monthly.

The Clinical Center Data Manager will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original (paper) form entering a response to the query. Note that it will be necessary for the Clinical Centers to respond to each query in order to obtain closure on the queried item.

The Clinical Center personnel will be responsible for making appropriate corrections to the original paper forms whenever any data item is changed. No data revisions will be made over the telephone. Written documentation of changes will be available via electronic logs and audit trails.

Feedback to the Clinical Centers will occur at various times depending upon the specific information being disseminated. Most reports will be distributed over electronic mail. Clinical Centers will receive recruitment and retention reports. As required for individual

patients, Baseline Appointment schedules, Eligibility Reports, and Follow-Up Appointment Schedules will be generated as needed.

GFR and biochemistry reports will be sent via e-mail when data are received from the Central Labs. The GFR reports, during follow-up, will include GFR results but only inter-period variability or quality control purposes.

Reports identifying patients who have reached an adverse event condition will also be sent to the Clinical Center. The detection and reporting of such events will be based on data stored in the DCC database.

Queries will be sent when needed due to discrepant data.

Monthly reports summarizing subject recruitment, retention, patient compliance, clinic performance, and progress will be sent to the Clinical Centers, the Central Labs, and the NIH Project Office. Summaries of recruitment will assess the success rates of specific recruiting methods used at each Clinical Center.

Missed Visit Reports will be provided to each Clinical Center monthly specifying patients completing and missing scheduled visits at that Center. This report should enhance the completion of follow-up visits.

Missing Query Response Reports will be provided to each Clinical Center monthly and will consist of queries which have been identified by the DCC and have not yet been responded to by the Clinical Center. These will highlight any query requests which are over 14 days delinquent.

Thorough analyses of quality control will be prepared by the DCC in a quarterly report which will be reviewed by the Quality Control Subcommittee. In brief, adequacy of GFR measurements will be assessed by analyses of inter-period coefficients of variation (CV) of each GFR measurement, percent absolute differences between external split samples, and percent absolute differences of replicate measurements for internal quality control. Similar methods for evaluating internal and external split-sample quality control will be applied for the Central Biochemistry Laboratory. Summaries will be displayed by technician, Clinical Center, or time as appropriate. Adequacy of blood pressure measurements will be assessed by summarizing the distribution of inter-period Cbs of MAP measurements, by analyzing evidence of digit preference, and by summarizing percent absolute differences between duplicate blood pressure measurements by two technicians on individuals selected by the DCC. Certification of at least one technician will be maintained throughout the study. Frequency of missing forms, including forms related to quality control procedures, will be monitored.

13.e.4. **Documentation**

All requests for information from the collaborative database and all statistical analyses will be documented on forms created for that purpose and the information entered into a project tracking database. The DCC will record the time of the request, the lag between the request and its fulfillment, the statistical procedures, graphics and formal reports generated, the level of effort necessary to fulfill the request and the person responsible for producing the results. In addition to providing the DCC with the necessary documentation of statistical analyses and/or reports, this will enable the DCC to project personnel time better for future work and to allocate personnel more efficiently.

13.e.5. **Security and Back-Up of Data**

The need for strict confidentiality of all study records will be emphasized to the staff of the DCC. All forms, diskettes and tapes related to study data will be kept in locked cabinets. Access to the study data will be restricted. In addition, Clinical Centers will only have access to their own center's data. A password system will be utilized to control access to all computer accounts as well as database accounts. These passwords will be changed on a regular basis. All reports prepared by the DCC will be prepared such that no individual subject can be identified.

A complete back-up of the primary DCC database will be performed twice a month. These tapes will be stored off-site in a climate controlled facility and will be retained indefinitely. Incremental data back-ups will be performed on a daily basis. These tapes will be retained for at least one week on-site. Back-ups of periodic data analysis files will also be kept. These tapes will be retained at the off-site location until the Study is completed and the database is on file with NIH. In addition to the system back-ups, additional measures will be taken to back-up and export the database on a regular basis at the database management level. The Oracle database management system provides extensive back-up and documentation.

13.e.6. **Reporting Study Results**

All reports for external distribution (e.g., manuscripts) will be prepared in duplicate and reviewed by the DCC Director or Deputy Director. All files, programs and data sets will be archived. See the Section on Maintenance and Disposition of Study Documents, Data and Materials for more details.

13.e.7. **Description of Hardware at DCC**

A SUN Workstation environment is maintained in the department with a SUN SPARCstation 10 model 41 as the server. All computers within the department are networked via ethernet using the TCP/IP protocol. Clinical Centers and central labs will access the departmental network through the Internet.

Access and predictable utilization of data processing facilities are adequate to service the needs of this study and to ensure the production of periodic reports on the data that are collected. Primary access to the departments computing facilities will be through the Internet, a world-wide cooperative network of computers, modem connection allowing sites to dial into the system directly, will serve as a back-up to the Internet method. These modes of accessibility allow authorized individuals access to the computing resources within the department with relative ease from other workstations within the department, other computers within The Cleveland Clinic Foundation, and from computers at other registered Internet sites at virtually no cost.

Word processing for this study will be accomplished on SUN SPARCstations with laser printers (Hewlett Packard) using Framemaker.

Extensive computer software is available for this project. For maximum programming efficiency, the Oracle database management system and the SAS and BMDP statistical analysis systems will be employed for this study. In this manner, special purpose programming will be kept to a minimum. Specific details regarding software packages to be used in the proposed project are provided as follows:

Oracle is an American National Standards Institute (ANSI) compliant relational data base management system which operates across platforms. It is a premier database product on the Sun workstation environment. The Oracle products in use at the Cleveland Clinic's Department of Biostatistics and Epidemiology include the computer assisted system engineering (CASE) tools, forms and report writer products. All Oracle software is running at the version 7.2 release level.

Oracle, coupled with the hardware available within the department, is well suited for the development of large databases with sophisticated data integrity checks. The connectivity of the computer system allows data entry to occur from workstations within the department or from a "remote" site. Oracle supports a graphical user interface mode (GUI) as well as a character based environment. Thus, access to the Oracle data base is possible from many different types of terminals ranging from character based to a graphical based terminal and, therefore, is not restricted to a particular type of hardware or software interface.

Oracle facilitates sophisticated integrity checks through a variety of mechanisms including stored procedures, stored triggers, and declarative database integrity--for between table verifications. Oracle allows data checks to be programmed once in the database rather than repeating the same checks among many applications. Oracle provides multi-user support,

ANSI standard SQL, journaling for database recovery and database transaction rollback. Security is enforced through passwords and may be assigned at different levels to groups and individuals. A query optimizer automatically selects the most efficient way for performing all database transactions. Oracle provides a utility that allows for bulk loading data into the database while enforcing any integrity checks previously defined in the database. This feature will be useful in loading the central lab data which will be electronically output from the labs computerized analyzers. The CASE tools allows the generation of more reliable applications in less time. An established CASE tools methodology for developing applications within the department provides a consistent and methodical approach to building data entry systems. Additionally, Oracle is compatible (via SAS access) with the SAS system which will be the primary statistical analysis tool.

SAS is the predominant analysis tool and has a very solid reputation within the field of statistical analysis. In addition to the base SAS product several add-on features are available including: SAS/STAT, SAS/GRAPH, SAS/IML. All are necessary to run currently developed analyses and for the development of future analyses. Means for importing/exporting SAS data from/to other platforms are provided.

SAS/ACCESS software provides an interface between the SAS System and the ORACLE database management system by directly accessing data in ORACLE tables from within a SAS program.

S-Plus is available within the department and is used primarily for sophisticated data modelling. Its interactive graphics capabilities make it a superior product and allow it to contribute significantly to the types of analyses that are able to be conducted. It is an excellent tool for the purpose of and programming new statistical methods because of its extensive selection of mathematical and array manipulation routines.

The Biomedical Computer Program P-Series (BMDP) package is accessible to the Department via the Medical Information Services Division's DEC VAX. BMDP provides specialized programs for categorical data analyses, logistic regression, proportional hazards modelling, and analysis of longitudinal and incomplete repeated measures data.

14. ADMINISTRATIVE STRUCTURE

14.a. Administrative Structure: National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)

14.a.1. **Director of the NIDDK**

The Director of NIDDK is responsible for the major program decisions of NIDDK. This includes allocation and management of Institute funds as well as other resources.

14.a.2. **Director of the DKUHD**

The Director of DKUHD represents the NIDDK Director to the Steering and Planning Committee and to the EAC. It is his responsibility to ensure that the scientific and technical goals of the study are consistent with the Institute's (and NIH's) mission and responsibilities. The Chairman and Vice-Chairman of the Steering and Planning Committee and the members and Chairman of the External Advisory Committee are chosen and appointed by the Director of DKUHD.

14.a.3. **The End-Stage Renal Disease and Office of Minority Affairs Director**

The Director of the End-Stage Renal Disease Program and the Minority Health Program is the Program Officer for the AASK Study. He is a member of the Steering and Planning Committee, the Executive Committee and has either full or ex officio membership on the study's working committees. He has primary responsibility for the administrative management of the study. With the Director of the Clinical Trials Program, he represents the Institute with regard to scientific and technical matters and to the meetings of the External Advisory Committee. He is responsible for NIDDK's negotiations with the pharmaceutical industry with regard to the acquisition of study drugs.

14.a.4. **The Clinical Trial Program Director**

The Director of the Clinical Trials Program is a member of the Steering and Planning Committee, the Executive Committee and has full or ex officio membership on the study's working committees. In addition, he serves as the Executive Secretary of the External Advisory Committee. With the Director of the End-Stage Renal Disease Program and the Minority Health Program, he takes an active role in the scientific and technical direction of the clinical trial.

14.b. Administrative Committees

14.b.1. The External Advisory Committee (EAC)

The External Advisory Committee (EAC) is composed of individuals with expertise in nephrology, hypertension, clinical trials, biostatistics, ethics and nursing, who are independent of the study. The members of the EAC are appointed by the Director of the Division of Kidney, Urologic and Hematologic Diseases (DKUHD) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The EAC will meet twice annually as deemed necessary by the Chairman of the EAC or the Director of DKUHD. The Chairman and Vice Chair of the Steering and Planning Committee and the Director of the Data Coordinating Center are ex-officio members of the Committee. The Clinical Trials Program Director, DKUHD, serves as the Executive Secretary. The EAC is advisory to DKUHD/NIDDK.

The responsibilities of the EAC are as follows:

1.Review the study protocol prior to initiation of the study and make recommendations to the DKUHD.

2.Review ethical aspects of the study protocol and communicate any concerns relative to the protection of participants from research risks.

3.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.

4.To ensure participant safety, the EAC will routinely monitor study data to which the investigators are blinded. Specific participant safety problems may also be referred to the EAC by the Chairman of the Steering and Planning Committee for immediate consideration.

5.The EAC will monitor study data to ensure the quality of the data and procedures for analysis.

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

7.Review interim and final results and provide advice to the Director of DKUHD regarding interpretation and implications for the treatment of chronic renal disease associated with hypertension among African Americans.

8.Provide advice to DKUHD regarding the primary (final) results paper for the full-scale clinical

trial which will be prepared by a Committee established by the Steering and Planning Committee.

14.b.2. **The Steering Committee**

The Steering Committee is composed of the NIDDK project officer, the Director of the NIDDK Clinical Trial Program, the chairman, the Principal Investigator from each of twenty clinical centers, the Principal Investigator of the data coordinating center, a panel of medical advisors for protocol development, and representatives from the pharmaceutical industry.

Administration. The Chair of the AASK has been appointed by NIDDK. A Vice-Chair from the clinical centers was likewise appointed, who serves as the acting Chair in the absence of the Chairman. In addition to conducting meetings, the Chair is responsible for the creation of new subcommittees as the issues before the Steering Committee evolve through the different phases of the study.

An Executive Committee has been formed to coordinate and facilitate the overall management of the project. Its members are the NIDDK project officer, the NIDDK Clinical Trials Program Director, the Chair and Vice- Chair of the Steering Committee, and the principal investigator of the data coordinating center.

Governance. The Steering Committee is subdivided into subcommittees which focus their efforts on selected areas. Between meetings of the Steering Committee, every subcommittee Chair distributes assignments among the members of his subcommittee and leads a meeting via telephone conference call. At the subsequent meeting of the Steering Committee, the subcommittee Chair presents a verbal progress report on the activities of their respective subcommittee. The Steering Committee discusses the recommendations of the various subcommittees. Votes of the Steering Committee is carried by a simple majority. The voting members are: The NIDDK project officer, the Chair of Steering Committee, the principal investigators of the clinical centers, and the principal investigator of the Data Coordinating Center.

Role of the Pharmaceutical Company Representatives. Representatives from a number of leading pharmaceutical manufacturing firms are included as non-voting advisors to the Steering Committee.

14.c. <u>Other Committees</u>

14.c.1.**The Executive Committee** will monitor the progress of the study and will be the liaison between the External Advisory Committee and the full Steering Committee. It will be composed of the Chairman and the Vice-Chairman of the Steering Committee, the Principal Investigator of the Data Coordinating Center, the Director of the End-Stage Renal Disease and Minority Programs at NIDDK and the Director of the Clinical Trials

Program at NIDDK.

14.c.2.**Design and Intervention Subcommittee** will formulate the study design and will address the choice of drugs, the clinical time table for participants visits, and the detail of the data to be collected at particular clinic visits. It will define the flow of participants through the study, that is, the sequence of scheduled participant procedures visits. It will participate in form development for the baseline and subsequent clinical data. It will formulate the medical guidelines for participant care including, in particular, the rules for medication titration and adjustment both in the Baseline and in the post-randomization periods. It will have primary responsibility for the generation and monitoring of the corresponding sections in the Protocol Document and the Manual of Operations.

14.c.3.**Recruitment Subcommittee** will solicit and monitor possible effective recruitment strategies for the full scale study. Data from the Pilot Study may be used, as needed, to guide the development of effective strategies. It will help develop study brochures and other contact materials. It will be responsible for the primary screening forms: for use in review of participant charts in a clinical or hospital setting, and a second for use if the initial contact is by telephone, health fair interview, etc. It will be responsible for reviewing and revising the corresponding section in the Manual of Operations.

14.c.4.**Inclusion/Exclusion Subcommittee** will review the inclusion and exclusion criteria for: (1) entering a participant into the baseline period, and (2) participant randomization and make recommendations to the Steering and Planning Committee for suggested revisions. It will also review the study action items and stop points. It will address the documentation and handling of adverse events. The committee will have special input into the data collection forms documenting study eligibility, those documenting adverse events, those listing new clinical events or symptoms, and those documenting the occurrence of participant stop points. Members of this sub-committee will be included into the Clinical Management Subcommittee at the end of randomization.

14.c.5.**Ancillary Studies and Publications Subcommittee** will review the policy for the consideration and approval of ancillary studies and the form for submission of proposal for ancillary studies. The subcommittee will also review the established policies and procedures for editorial review of all releases of study related information. This will include preparation of manuscript, abstracts, presentations and formal interviews.

14.c.6.**Compliance Subcommittee** will consider ways to facilitate participant compliance for participants who are enrolled in the baseline phase. It will explore ways to monitor participant compliance with study procedures, medication schedules

and visit schedules.

14.c.7.**Clinical Management Subcommittee** will evaluate the adherence by clinical centers to the clinical management procedures outlined in the Protocol and the Manual of Operations.

It will review and monitor all serious adverse events that occur during the study, with special attention to episodes of acute renal failure that occur post-randomization. In addition, it will advise the Steering Committee on management of renal failure as deemed appropriate by the committee. It will review and monitor all records for participants reaching study stop points.

It will assist the clinical centers in the interpretation and implementation of these procedures in a uniform manner in order to ensure that treatment regimens are administered in a comparable manner across the centers. It will review and monitor all action items and end points, as well as attrition rates and their causes. It may refer particular cases to the external Advisory Committee, as deemed appropriate. This subcommittee must approve all treatment (including drugs) or devices used by the clinical centers in the implementation of the protocol.

14.c.8.**Quality of Care and Data Monitoring Subcommittee** will monitor and oversee the validity of all data collected, including measurement of renal function including GFR, creatinine clearance and urinary excretion rates of albumin, electrolytes and urea. Issues concerning the validity of test results from the GFR measurements will be addressed in conjunction with the central laboratory. Issues related to the technical aspects of the GFR measurements will be brought to the attention of this committee from the central laboratory via the DCC.

This committee will assist the DCC in the development of both internal and external quality control procedures for the central laboratories. Will monitor the quality of performance of both the central laboratories and the local laboratories. If problem are found with technical aspects of the procedures, it will make recommendations for improved procedures or techniques. It is also responsible for monitoring the operations of the DCC with respect to accuracy of data entry and timeliness and quality of reporting.

14.c.9.**Publications and Ancillary Studies Subcommittee** will review the policy for the consideration and approval of ancillary studies and the form for submission or proposal for ancillary studies. The subcommittee will also review the established policies and procedures for editorial review of all releases of study related information. This will include preparation of manuscript, abstracts, presentations and formal interviews.

14.c.10.**Renal Function Subcommittee** will review the currently employed method for glomerular filtration rate determination and will make recommendation to the full Steering Committee for any suggested change. It will make recommendations concerning the following: number and timing of the study GFR determinations, whether other renal studies should be done at the time of the GFR and, if so, what these should be; the scheduling of the 24 hour urine and the list of tests to be run on these by the central laboratory, as well as the tests to be collected on urine processed in the clinical center laboratories (locally). It may also make recommendations to the Steering Committee on the appropriate renal function monitoring.

14.c.11.**Study Coordinators Subcommittee** will consider ways to best implement the study protocol at the Clinical Centers. The Committee will have special input into the conduct of the trial and make recommendations to the full Steering Committee for any suggested change. The Committee will explore ways to enroll participants and to maintain compliant study participants for the duration of the trial.

14.d. The Clinical Centers

The Clinical Centers, under the directions of their respective Principal Investigators, will collaborate with the other Steering Committee members, the data coordinating center, the central laboratories and the NIDDK staff in the generation and implementation of the study protocol document, the manual of operations and the data collection forms. They will be required to meet their recruitment goals. They will work with the central laboratories and the DCC for the acquisition and transmission of high quality data. It is the duty of the principal investigators to assure that an appropriate administrative structure and clinical environment with adequate institutional support exist so that the study may be conducted properly, without impediment. It is also their responsibility to provide appropriate leadership for and supervision of the research teams at their individual centers in order to assure adherence to the protocol and the procedures outlined in the manual of operations.

14.e. The Data Coordinating Center (DCC)

The Data Coordinating Center is responsible for taking the lead in the design and development of the protocol, the manual of operations and the study data collection forms and for coordinating the development process. This will include close collaboration with the

members of the Steering Committee and NIDDK staff. The DCC provides the general administrative support for the cooperative group as a whole. This includes the planning of meetings and meeting arrangements, setting up of training sessions and certification procedures, setting agendas and the preparation of minutes from the Steering Committee Meetings and Executive Committee Meetings. It arranges for consultant services, when necessary. It provides collation and distribution of study materials to the group. It is the repository for all study related materials and central files, including the data files, and will maintain appropriate confidentiality and security of these files. It has the responsibility of the design and implementation or review of quality control procedures for the clinical centers and their local laboratories, for the central laboratories and for data collection, transmission and entry. It will provide appropriate statistical analyses and report generation for administrative and operational data such as arise from recruitment activities, compliance evaluations and clinic performance, and for the main study goals. It will prepare and submit reports to the Steering Committee, appropriate subcommittees and to NIDDK as required.

14.f The Drug Distribution Center

Under the direction of Ed Jones, Pharm. D., R.Ph., will be located at the Cleveland Clinic. It will work with the AASK Program Office in the acquisition of drugs required for participants in the AASK Study and will serve as the official liaison with the pharmaceutical suppliers of the drugs, the encapsulators, and the packagers of blinded medications. It will assure the drugs are distributed to each of the clinical centers on a timely basis. It will assist the clinical center pharmacies (or designated persons) in establishing and following procedures required by the Food and Drug Administration for the control of investigational drugs as described in the drug distribution center's section of the Manual of Operations. Quarterly reports will be submitted to the Quality Control Subcommittee.

14.g The Central GFR Laboratory

The GFR determinations will be done by the ^{125}I-iothalamate method. The samples will be centrally processed by the Renal Function Laboratory of the Cleveland Clinic Foundation. The director of this laboratory is Phillip M. Hall, M.D., and his chief technologist for this study is Ms. Diane Pexa. This group is experienced in handling these determinations for multi-center clinical trials. They will provide centralized training and certification for the clinical center GFR technicians at the Cleveland Clinic at the start of Phase II. They will maintain adequate local quality control and will provide appropriate quality control data to the Coordinating Center, when requested. They will also review the GFR data collection forms for adequacy and suggest revisions, if needed They will report the results of the GFRs to the clinical centers and the DCC on a timely basis.

14.h<u>The Central Laboratory for Biochemistries and 24-Hour Urines</u>

The 24-hour urines and a panel of blood biochemistries will be obtained on a regularly scheduled basis. These will be processed centrally by the laboratory of the Biochemistry Section of the Division of Pathology of the Cleveland Clinic Foundation. The director of that laboratory is Frederick Van Lente, Ph.D. Dr. Van Lente's laboratory has previously served as the central laboratory for multi-center clinical trials. They will advise the clinical centers in required sample collection, handling and shipping procedures. They will maintain local quality control procedures and will provide appropriate quality control information to the Coordinating Center, when required. They will ensure that results of the tests are reported to the clinical centers and the DCC on a timely basis.

15. PROTOCOL CHANGES

15.a. General Principles of Protocol Change

During the conduct of the study, protocol changes are not desirable and should not be made unless the safety of the participants is compromised or new information becomes available and strongly suggests that such changes would strengthen the scientific validity of the study. In the event that alterations are necessary, the following procedures will be followed:

15.b. Protocol Change Procedures

Recommendations for protocol changes may originate from the External Monitoring Committee, the Data Coordinating Center, or one of the Working Committees. All proposed changes will be submitted to the Steering Committee for consideration. The Steering Committee will decide whether the proposed modifications merit consideration and will determine the method of incorporating the proposed changes in the Protocol. Approval by the Steering Committee must have support from two-thirds of the voting members. For major changes, the recommendations of the Steering Committee will be presented to the External Monitoring Committee who will advise the NIDDK as to whether the Protocol changes are advisable. The NIDDK may seek further advise from the external Advisory Committee or other experts outside of the AASK Study before making the final decision as to whether the recommended Protocol changes are approved.

16. ANCILLARY STUDIES

16.a. Ancillary Studies Definition

Ancillary studies are defined as research studies employing participants, biological specimens or the data base from the main study which have relevance to the overall objectives of the main study, but are not part of the mainstream protocol for all centers.

16.b. Funding of Ancillary Studies

Ancillary studies will not be funded by the main study, but will require an independent source of funding.

16.c. Approval Procedures for Ancillary Studies

a.Proposals may be generated by a participating clinical center or by other interested investigators providing at least one center is included as a co-investigator. These applications are submitted to the Data Coordinating Center for review by the Publications and Ancillary Studies Subcommittee.

b.There will be a two-step review by the Publications and Ancillary Studies Subcommittee. The first step is to have the proposal reviewed for its concept and general acceptability. This will be done in 2-4 weeks. A short description of the study including the following information should be submitted.

i. Hypothesis to be tested.
Specific outcome variables that will be assessed.
Need for data from the DCC.

ii. Significance of the proposed ancillary study.

iii.How will performance of this ancillary study affect the main AASK Study? Specifically:

a.Will there be any deviations from the main AASK Study protocol? If so, what will they be?

b.How much additional participant, staff and DCC time will be required to complete this ancillary study?

c.Will additional funds be requested for the study and what will their source be?

If this proposal is acceptable in concept to the Publications and Ancillary Studies Subcommittee, a more detailed proposal should be written and submitted for review. This proposal should include detailed information on:

i.Hypothesis to be tested.

ii.Significance of the study.

iii.Conduct and performance of the study including specifying the study population and the data to be collected.

iv.Sample size justification.

v.Quality control of the data.

vi.Data analysis methods.

c.The Publications and Ancillary Studies Subcommittee will make its recommendation within 2-4 weeks and submit it to the Steering Committee. The proposal will be discussed and voted upon at the next Steering Committee meeting. At that time, the applicant has the option to discuss his or her proposal before the Steering Committee.

16.d. Guidelines for Genetic Ancillary Studies

1.An annual schedule for grant proposals. It was agreed upon that all grants dealing with genetic studies be submitted by July 1st of any given year for the duration of the study. These will then be considered as a group similar to an NIH study section and judged based on priority and quality of science and ancillary funding. This year (1995) we will have an additional deadline for submission (October 1, 1995).

2.Internal Priority to Investigators. All submissions for genetic grants must have either the principal or a co-investigator of a respective AASK center intimately involved with the study. Letters of support by either the PI or CO-PIs are not acceptable for evaluation of the protocol.

16.e. Publication of Ancillary Study Results

The policies regarding publications and presentations of the result of ancillary studies are the same as those governing the publications and presentations of results of the main study. These policies are designed to:

1.Assure timely publication of the results to the appropriate professional audiences.

2.Avoid premature publications of results that might compromise the performance of the main study or that might compromise the ability to publish the results in high quality peer reviewed journals.

3. Maintain high standards of the published material.

4. To guard against duplicate publication of results.

5.Assure equitable attribution of credit to all of the professionals participating in the ancillary study and the AASK Study.

17.MAINTENANCE AND DISPOSITION OF STUDY DOCUMENTS DATA AND MATERIALS

17.a. Introduction

This chapter contains the procedures that will be used for the handling, filing and disposition of documents connected with the AASK Study, the related data collection forms, computer diskettes and/or tapes containing study data, reports of data analyses and any other materials generated by the study.

17.b. Internal Distribution of Study Documents

The DCC for the AASK Full-Scale Study is responsible for the maintenance of files containing all of the minutes of the Steering Committee meetings, the subcommittee meetings and the meetings of the External Advisory Committee, all study documents and all reports. The DCC is also responsible for the appropriate distribution of the relevant reports, the Protocol Document and the Manual of Operations. Upon completion of the study, the DCC will develop an archive of these documents and forward them to the National Technical Information Service. At the end of the, study the minutes will be placed on microfiche and sent to NIDDK for their files. Copies of all executed informed consent documents will be maintained on file at the DCC.

17.c. External Distribution of Study Documents

All requests for external distribution of study documents and manuscripts (to persons not associated with the AASK study) should be addressed to the NIDDK, which will be responsible for their distribution.

17.d. Data Collection Forms

The DCC will maintain a complete set of all submitted data forms including those assessing the quality of the central laboratories. These forms will be placed on microfiche and forwarded to NIDDK at study end. Any personal identifiers will be suppressed. Individual participant files will be maintained both at the DCC and at the clinical centers. The clinical center files will be attached to the participants medical records at the close of the study.

17.e. Data Tapes and Analysis of Results

At the end of the study the DCC will create a summary tape including the raw data, compiled results and the study analyses. The tape will be completely documented. This will include details of all formulae and statistical analyses actually used or referenced in the study documents. Two copies will be made, one for NIDDK and the other for the National Technical Information Service (NTIS). The study information will be made available to the scientific community through NTIS for a small charge.

17.f. Laboratory Specimens and Materials

Some pre-specified and after-thought specimens will be kept at the appropriate central laboratories and stored until needed by an ancillary study or until the end of the main study. It will be the responsibility of the Steering Committee to decide the ultimate disposition of these specimens. Other participants information received at the DCC and not at the individual centers will be stored at the DCC until the end of the study. At that time they will be offered to the appropriate clinical centers for inclusion in the participants medical records. If any materials or specimens remain unallocated by the Steering Committee and/or unclaimed by the clinical centers, these will be destroyed following the study completion.

18. SCHEDULE OF PARTICIPANT EVENTS

18.a. Screening Period (Visits SV-1,SV-2) Schedule

Screening visits SV-1 and SV-2 will be used to determine initial interest and eligibility of the potential participant for the study. During these visits, the participant's interest and written informed consent will be obtained. A complete medical history, physical examination, and screening laboratories will be performed. If desired, these may be combined into a single visit (SV-2).

18.b. Baseline Period Schedule

The participant will enter Baseline if evaluations meet inclusion/exclusion criteria. Baseline will be divided into four phases or visits. Details are shown in Table 18.1.

1)The Back Titration Phase (Visits BT-1 ... BT-99) is the first phase of the Baseline Period, and will be done if necessary. During this phase, antihypertensive medications will be withdrawn if necessary, until blood pressure increases into the qualifying range. If the participant is taking medications belonging to the classes which include the randomized drugs, these agents will be the first ones down-titrated or replaced (if possible) by other classes of drugs (Section 8.i). Participants will be seen at weekly or more frequent intervals during the Back Titration (BT) phase. At each BT visit, the participant's vital signs, weight, compliance (by questioning and pill count), the presence of adverse drug reactions or intercurrent illness will be assessed, and a limited history/physical exam (H/P) will be performed. As soon as the participant's blood pressure increases into the qualifying range, the first GFR determination will be scheduled.

2)GFR 1 will be done.

3)If the G-1 GFR was within the qualifying range, the second GFR visit (G-2) will be scheduled.

18.c. Consent (Visit CV)

The patient may consent for randomization at a special consent visit held after the G2 GFR. Alternatively, this may be done at the G2 visit.

18.d. Randomization

Once all baseline period studies have been completed, the forms corresponding to these studies have been received by the Data Coordinating Center, the participant has signed the consent forms, and it has been determined that the participant meets all eligibility requirements (including an acceptable level of compliance with study procedures), the Data Coordinating Center will verify that the participant is ready to be randomized using Report 54. The Clinical Center will do secondary screening with Form 53. The Clinical Center will

receive a blood pressure goal and a blinded randomized treatment assignment for that participant using Form 52.

18.e. Follow-up (Visits FV-0 ... FV-n)

The patient will receive his medications at FV0-0, which will occur as soon as possible after randomization. Serum potassium and creatinine tests will be measured 5-7 days after FV0-0, at an FV0-1 visit, in order to detect critical deviations in these laboratory tests. Then, participants will be seen monthly or more frequently in order to achieve or maintain blood pressure control. At all FV visits, the participant's vital signs, weight, compliance (by pill count), the presence of new symptoms, adverse drug reactions, or intercurrent illness will be assessed, and a limited H/P will be performed. See Table 18.2.

18.1 Table: Frequency and Visit for Study Procedures and Laboratory Tests during the Screening and Baseline Periods.

Procedure	**SV1***	**SV2***	**BT1**	**BT2**	**G1**	**G2***	**CV***
Consent for Baseline	L						
Follow-Up Consent or Sincere Discussion							L
Complete H/P (Form 4 or 12)		L					
Limited H/P (Form 11)	L	L	L	L	L	L	L+
Symptom Questionnaire		L	L	L	L	L	L+
Quality of Life (Form 80)		L					
SMA 18	C+	C			C		
CBC (Form 13)		L			L		
Urinalysis (Form 13)		L					
Lipid Profile (fasting)					C		
Buffy Coat					C		
24-Hr Urine** (Form 23)					C		
GFR (and HCG if necessary) (Form 24)					C	C	
ECG (Form 14)		L					
Blood Pressure (Form 10)	L	L	L	L	L	L	L

+Optional; C-Central Lab; L=Local Lab/Procedure; SV=Screening Visit; G=GFR; CV=Consent; BT=Back Titration.
*The Screening SV1 and SV2 can be combined. The G2 and Consent Visit CV can be combined.

18.2 Table: Frequency and Visit for Study Procedures and Laboratory Tests during the Post-Randomization Period

Procedure	FV0	FV0-1	FV1	FV2	FV3	FV4	FV5	FV6 and Every 6 Months	FV 12 and Annually	FV 16 and Every 4 Months
Complete H/P (Form 4 or 12)									L	
Limited H/P (Form 11) (every visit)	L	L	L	L	L	L	L	L	L	L
Assess Drug Compliance	*		L	L	L	L	L	L		
Symptom Questionnaire	L		L	L	L	L	L	L	L	
Quality of Life (Form 80)									L	
SMA 18									C	
Serum Potassium**		C			C			C	C	
Serum Creatinine**		C			C			C	C	
CBC (Form 13)		L							L	
Lipid Profile (fasting)									C	
24-Hour Urine (Form 23)								C		
Urinalysis (Form 13)									L	
GFR (and HCG if necessary) (Form 24)					C			C	C	
ECG (Form 14)									L (Every two years)	
Blood Pressure (Form 10) (every visit)	L	L+	L	L	L	L	L (Every visit thereafter)	L	L	L

*Give the patient his or her medications.
FV=Follow-Up Visit; C=Central Lab; L=Local Lab/Procedure; +Optional
**Potassium and Creatinine are done at FV3, FV6, FV12, and every 6 months thereafter.

19. PUBLICATION POLICY

19.a. Introduction

The policy of the AASK Study concerning publications and presentations is designed to achieve five objectives:

i. To assure timely publication of the results of the AASK Study to the appropriate professional audiences,

ii. To avoid premature publication of results that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically convincing) or that might compromise the ability to publish the results in high quality peer reviewed journals (as by premature release to the lay press),

iii. To maintain high standards of quality of all material published by the AASK Study,

iv. To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees, and

v. To assure equitable attribution of credit to all of the professionals participating in the AASK Study.

To accomplish these ends, it is the policy of the AASK Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Study Chairman after consultation with Chairman of the Publications and Ancillary Studies (PAS) Subcommittee to specifically appointed writing committees, and that all such materials must be reviewed and approved by the PAS Subcommittee and/or the Steering and Planning (S&P) Committee before publication.

19.b. Scope of Policy, and Exception for Local Publicity Materials

All material to be presented orally or submitted for publication or dissemination by individuals associated with the AASK Study and dealing with any aspect of the AASK Study must receive prior review and approval by the PAS Subcommittee/S&P Committee with the following exception:

Material prepared for publicity purposes either nationally or within the recruitment region of an AASK Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the AASK Study and its objectives, need not be reviewed by the PAS Subcommittee. Such material must be limited to a background discussion of the issue of blood pressure control as a treatment for progressive renal disease and a description of the AASK Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously unpresented and unpublished AASK Study outcomes or other citable professional reference.

19.c. Source of Suggestions for Publications of the AASK Study

Suggestions for topics appropriate for preparation of abstracts, peer reviewed papers or chapters and reviews are made by the PAS Subcommittee, in addition, all participants in the AASK Study are invited to suggest topics appropriate for preparation as abstracts, peer reviewed papers, or chapters and reviews from the AASK Study. Such suggestions should be made to the DCC and the Chair of the PAS Subcommittee, who shall review the request to be certain that there is no overlap with materials previously assigned to other writing committees. Where such overlap exists, the Chair of the PAS Subcommittee may make recommendations to the Study Chair that the suggestion be referred to an existing writing committee, that additional study participants be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter will be made by the Study Chair after consultation with the Chair of the PAS Subcommittee.

It is the policy of the AASK Study to encourage non-physician professionals to prepare scientific presentations to their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may well overlap with material being prepared by writing committees for medical journals, it is the policy of the AASK Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in section 1.6.

In addition, the PAS Subcommittee will formulate and maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the AASK Study are reported to the scientific community in a timely fashion.

19.d. Assignment of Writing Committees

Topics suggested for presentation or publication that do not overlap with an existing committee will be circulated to the Principal Investigators of all clinical centers, DCC, central laboratories and the NIH. These groups are requested to suggest and justify names for lead authors (Chair of writing committees) and co-authors. These names will be collated and reviewed by the PAS Subcommittee. A recommendation for a writing committee will then be made to the Study Chair who will decide on the final composition of the writing committee after consultation with the Chair of the PAS Subcommittee. If a topic is suggested by a participant of the AASK Study, the writing committee will be formed as just described except that the person making the suggestion will be considered as the potential lead author. The Principal Investigator of an ancillary study should be considered for lead author of material derived from this study. If only a subset of clinical centers participate in an ancillary study, only investigators from these centers should be considered to be on writing committees relating to this study. Appointments of writing committee

chairmanships will be made in an equitable fashion to all professionals -- physicians, study coordinators, nurses, statisticians, and others -- in a fashion that recognizes the special contributions of each member of the AASK Study to its performance. Any dispute about lead author or co-author will be settled by the Study Chair after consultation with the Chair of the PAS Subcommittee. In all cases, writing committees dealing with an issue that requires analysis of data by the Data Coordinating Center will have a member of the DCC assigned to it.

From time to time it may be expedient for the chairmanship of a writing committee to be reassigned to another member of that committee, or for members to be dropped from or added to a writing committee. The Chair of the PAS Subcommittee and Study Chair are authorized to make such changes with the consensus of the members of the writing committee, or on their own authority where there is clear cause.

19.e. Reports of the AASK Study: Classes of Reports

There are four classes of reports of the AASK Study:

A. Reports of the major outcomes of the Study. It is assumed that there will generally be only one or two such reports derived from each Phase of the Study.

B. Reports addressing in detail one aspect of the AASK Study, but in which the data are derived from the entire study.

C. Reports of data derived from a subset of centers by members of the AASK Study, (e.g., substudies or ancillary studies), or originally conceived analyses of data from the entire AASK Study (original analyses).

D. Reports of investigations initiated outside of the AASK Study, but using data or samples collected by the AASK Study. The investigators may be AASK or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the AASK Study itself. Writing committees for this type are formed and presentations and publications made in accordance with the general policy rules for AASK publications. However, the Principal Investigator of an ancillary study should take primary responsibility in publishing the results of the study.

19.f. Authorship Policy

The authorship policy of the AASK Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire AASK professional staff. Thus, all reports, of whatever Type, must give recognition to all the participants of the AASK Study, and reports of Types A and B must give primary recognition to the entire study professional staff. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and

timely publication of the results of the AASK Study. The AASK authorship policy attempts to recognize each of these goals. The authors of AASK publications will be listed as detailed below for each type of publication.

Type A publications:
abstracts: from the African American Studies of Kidney Disease[1], presented by XXXX.
papers: from the African American Studies of Kidney Disease[1], prepared by XXXX.
[1]The AASK participant box, detailed below, must be included in these papers. If a journal's publication policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:
abstracts and papers: Authors' names, from the African American Studies of Kidney Disease[1]
[1]The AASK participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

Type C and Type D publications:
abstracts and papers: authors' names and the AASK Study
[1]The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. In Type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

19.g. <u>Authorship: Professional Participants Listing in the AASK Participant Box</u>

The AASK participant box will list all professionals that have participated in the AASK Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center staff listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not by the specific position which he/she held in the study. The centers will be listed in the following order:

NIH
Study Chair
Clinical Centers (in alphabetical order)
DCC
Central Laboratories (in alphabetical order)

Prior to the publication of any papers from the AASK Study, each center will be asked to confirm and approve the listing of the personnel from that center in the AASK Participant Box.

19.h. Acknowledgement of Support and Reprint Addresses

Acknowledgement of grant support to be used in all papers reporting results of the AASK Study. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The AASK Study is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH. Additional support is provided by the (list of any industrial or other support).

The following information regarding reprint requests should be included in all papers prepared for the AASK Study. The DCC will maintain an inventory of all AASK Study publications and will mail out the reprints.

Requests for reprints should be addressed to:

AASK Data Coordinating Center
Department of Biostatistics and Epidemiology, Desk P88
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

19.i.Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time that a writing committee is constituted, the PAS Subcommittee will establish a timetable for the completion of the writing assignment that takes into account deadlines for the publication, the amount of time that will be required for data analysis, the other commitments of the DCC, and the priority of the publication. The Chair of the Writing Committee should provide the Chair of the PAS Subcommittee a general outline of the proposed publication within a month of receiving its assignment, to permit the PAS Subcommittee to identify any overlap with the assignments of other writing committees, and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the PAS Subcommittee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Study Chair. The Chair of the PAS Subcommittee will report at each meeting of the S&P Committee on the progress of the various writing committees.

19.j.Review of Abstracts and Presentations by the PAS Subcommittee

To expedite review of abstracts, oral presentations, and any other material for which there is an explicit deadline for submission, the following procedure will be used:

i.The writing committee wanting to submit an abstract, give a talk, or submit other material for

which there is an explicit submission deadline shall contact the Chair of the PAS Subcommittee. In the event that the Chair is unavailable, the Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of three members of the PAS Subcommittee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be mailed by the submitter directly to these three reviewers so as to reach them no fewer than seven (7) days prior to the deadline for submission.

ii. The members of the subcommittee shall review the material and notify the Chair solely of their approval or disapproval. If there is unanimous approval, the PAS Subcommittee Chair (or Alternate Chair) shall inform the submitter that he/she has AASK Study approval for the submission. In the event of a split vote for approval, the issue will be reviewed by the PAS Subcommittee Chair (or Alternate Chair) with the Chair of the AASK Steering & Planning (S&P) Committee (or in his unavailability with the Vice-Chair of the S&P Committee) whose decision will be binding.

iii. All materials submitted for approval in this fashion will be distributed by mail, together with notice of the disposition, to all members of the PAS Subcommittee and to the Chair of the S&P Committee. All approved materials will also be forwarded to the NIH Project Coordinator, and for record purposes to the Principal Investigator of the Data Coordinating Center, and will be distributed to the entire membership of the S&P Committee at the next meeting of that Committee.

Approval for submission of an abstract or oral presentation does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation. Normally this review will be done by the same subcommittee of the P&As Committee that reviewed the initial abstract.

i. In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.

ii. In case of a poster presentation, the content of the poster material must be submitted for review.

19.k. <u>Review of Papers by the PAS Subcommittee</u>

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Subcommittee for formal review by the entire Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair, PAS Subcommittee, at least 30 days prior to the deadline, to permit such review. This review will be conducted as follows:

i. The Chair, PAS Subcommittee, shall appoint a panel of three primary reviewers, two of whom must be PAS Subcommittee members, and one of whom may be any professional member of the AASK Study Group with appropriate expertise. The Chair shall distribute the material to all members of the PAS Subcommittee and to the Principal Investigator of each center participating in the AASK Study. The three members of the review panel shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PAS Subcommittee. The P.I.s of the various clinical centers will be given a deadline by which any comments or critiques that study personnel at their center may wish to make must be received by the Chair, PAS Subcommittee. This mechanism will assure that each professional participating in the AASK Study will have an opportunity to review any materials that will be submitted for publication bearing his/her name as a participant and co-author.

ii. The Chair, PAS Subcommittee shall schedule a meeting of the Committee (generally by conference call), including review of papers and other non-time critical materials as Agenda items. The reviews of the panel members and any comments received from the center P.I.s will be distributed to the committee with the agenda.

iii. While discussion of the submitted papers and other materials will be led by the three appointed reviewers, all members of the Committee will be invited to participate and all shall vote on final disposition.

iv. In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.

v. The Chair, PAS Subcommittee shall be responsible for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non-acceptance of the material as submitted but with suggestions for revision and resubmission, he and the writing committee may agree not to proceed with a report to the Executive or S&P Committees at that time, pending revision and resubmission.

vi. If there is a recommendation for approval or final approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the Chair, PAS Subcommittee shall report this outcome in writing to the Executive Committee for final action. In the case of a dispute between the PAS Subcommittee and the author(s), the Chair, PAS Subcommittee shall provide a copy of the submitted material and a summary critique to Executive Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.

vii. The authority to grant final approval for a formal scientific paper of the AASK Study rests with the S&P Committee, or the Executive Committee in the interim between meetings of the S&P Committee.

viii. All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the S&P Committee. All materials receiving final approval by the Executive or S&P Committee will also be forwarded to the NIH Project Coordinator, and for record purposes to the Principal Investigator of the

DCC.

ix. In the event that editors of a scientific journal to which an approved AASK scientific manuscript is submitted suggest or require revisions of the manuscript, the revised manuscript must be reviewed again by the PAS Subcommittee prior to resubmission in the same manner as described above. Generally, the Chair will appoint the same reviewers that first read the paper to review the revision, and every effort will be made to expedite such repeat reviews.

19.l. Criteria for Review of Materials by the PAS Subcommittee

All materials submitted to the PAS Subcommittee will be reviewed for acceptability on two grounds:

i. Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved AASK materials reflect well on the AASK Study.

ii. Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the AASK Study or compromise the eventual publication of AASK findings in high quality peer reviewed journals. In this later regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer reviewed journal.

19.m. Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all official publications and presentations of the AASK, separated into the following categories:

i. Peer reviewed papers accepted and published in professional journals
ii. Invited editorials, reviews, chapters, and books
iii. Abstracts published in citable journals
iv. Other presentations at regional or national meetings which do not result in a citable abstract.

This listing will be updated at least every six months and will be distributed to the P.I. of each center participating in the AASK Study, together with reprints or copies of any papers, chapters, or abstracts accepted for publication since the last update. This is intended to facilitate the updating of curricula vitae and the timely submission of reports to CRCs and other such organizations within the participating centers.

19.n.<u>Acknowledgement and Acceptance of AASK Policies on Publications and Presentations by the Professional Participants in the AASK Study</u>

To assure that all professionals involved with the AASK Study know and understand the policies of the AASK Study, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of this Chapter and will be asked to sign a Statement of Understanding Form (see next pages) listing the major provisions of the Chapter and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding Form should be returned to the DCC for record purposes. The copies of the Chapter and the signed Statement of Understanding Form should be kept by the AASK professional participant for reference.

AASK STUDY

Statement of Understanding of Policy
Concerning Publications and Presentations

To assure that all professionals involved with the AASK Study know and understand the policies of the AASK Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of protocol section 19 detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized below.

I. Material Covered by These Policies

All material to be presented orally or submitted for publication or dissemination by individuals associated with the AASK Study and dealing with any aspect of the AASK Study must receive prior review and approval by the Publications and Ancillary Studies (PAS) Subcommittee with the following exception:

Material prepared for publicity purposes either nationally or within the recruitment region of an AASK Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the AASK Study and its objectives, need not be reviewed by the PAS Subcommittee. Such material must be limited to a background discussion of the issue of blood pressure control as a treatment for progressive renal disease and a description of the AASK Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must <u>not</u> include discussion of any previously unpresented or unpublished AASK Study outcomes or results, and must <u>not</u> itself result in publication of an abstract or other citable professional reference.

II.Assignment of Writing Committees for Publications

The PAS Subcommittee will solicit volunteers for each writing committee for abstracts and publications and make a recommendation on the writing committee and the topic to the AASK Steering Committee Chair. The AASK Steering Committee Chair will decide on the final composition and topic of the committee after consultation with the Chair of the PAS Subcommittee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be by the Chair of the Steering Committee.

III.Authorship

The AASK policies specify the authorship for each of the four different classes of publication or abstract (See Section 19.e-h of the protocol). These policies are binding and must be followed in all publications derived from the AASK Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by members of the PAS Subommittee before being submitted (See Section 19.j of the protocol). These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the AASK Study.

V.Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PAS Subcommittee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Subcommittee for formal review by the entire Subcommittee (see Section 19.k in the protocol). If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair of the PAS Subcommittee at least 30 days prior to the deadline, to permit such review.

VII.Certification by AASK Study Participant

This is to certify that I have read the above statement of policies of the AASK Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the AASK Study.

_____ _____

(Signature) *(Date)*

_____

(Print or Type Name and Institution)

March 8, 1995

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21. GLOSSARY OF ABBREVIATIONS

α	alpha
AASK	African American Study of Kidney Disease
ASCII	American Standard Code for Information Interchange
AST	aspartate transaminase
β	beta
BB	beta blockers
BID	twice a day
BMI	body mass index
BP	blood pressure
BT	back titration
BUN	blood urea nitrogen
BV	biopsy visit
Ca	calcium
CAP	College of American Physicians
CAT	computerized axial tomography
CBC	complete blood count
CCB	calcium channel blocker(s)
CEI	converting enzyme inhibitor(s)
CHF	congestive heart failure
cm	centimeter
CV	coefficient of variation or consent visit
DBP	diastolic blood pressure
DCC	Data Coordinating Center
DKUHD	Division of Kidney, Urologic, and Hematologic Diseases
e.g.	for example
ECG	electrocardiogram
ESRD	end-stage renal disease
etc.	et cetera
FV	follow-up visit

Glossary of Abbreviations (Cont'd)

G1, G2	GFR visit (1, 2)
GFR	glomerular filtration rate
H/P	history/physical
H_2	hydrogen
HCG	human chorionic gonadotropin
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	HTLV (human T-cell leukemia virus; human T-lymphotropic virus)
HMO(s)	Health Maintenance Organization(s)
HPF	high power field
HTN	hypertension, hypertensive(s)
I	iodide, iodine (as in ^{125}I)
i.e.	that is
ID(s)	identification
IRB(s)	Institutional Review Board(s)
JNC	Joint National Committee
K	potassium
kg	kilogram
LDL	low density lipoprotein
LPF	low power field
m	meter
MAP	mean arterial pressure
Mb	megabytes
MDRD	Modification of Diet & Renal Disease
mEq/L	milliequivalents per liter
Mg	magnesium
mg	milligram(s)
mg/dl	milligrams per deciliter
MHz	megahurtz
mm	millimeters

Glossary of Abbreviations (Cont'd)

mmHg	millimeters of mercury
Na	sodium
NaCl	sodium chloride
NCEP	National Cholesterol Education Program
NCR	No Carbon Required
NIDDK	National Institute of Diabetes and Digestive and Kidney Disease
NIH	National Institutes of health
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NTIS	National Technical Information Service
P-wave	an ECG wave
PGE_2	prostaglandin E_2
PGI_2	prostaglandin I_2
PT	prothrombin time
PTT	partial thromboplastin time
Q day	once a day
QRS	an ECG wave
RBC	red blood cell
RDA	Recommended Dietary Allowance
RV	randomization visit
s	sigma
SCr	serum creatinine
SMA	
SV	screening visit
T-wave	an ECG wave
U.	urine
U.S.	United States
WBC	white blood cell

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