Confidential

Polycystic Kidney Disease-Treatment Network (PKD-TN)
Main Study

HALT PKD
(Halt Progression of Polycystic Kidney Disease)

Efficacy of Aggressive
Renin-Angiotensin-Aldosterone Axis Blockade in
Preventing/Slowing Renal Function Decline in ADPKD

Sponsored by
The National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)
The National Institutes of Health (NIH)
U.S. Department of Health and Human Services

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1. INTRODUCTION

We propose to perform a large randomized clinical trial to determine the impact of intensive blockade of the renin-angiotensin-aldosterone system (RAAS) and the level of blood pressure control on progressive renal disease in individuals with early and more advanced stages of autosomal dominant polycystic kidney disease (ADPKD). In Study A, participants with a glomerular filtration rate (GFR) greater than 60 mL/min/1.73 m^2, will be randomized to one of four conditions in a 2-by-2 design: combination angiotensin -converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) therapy at two levels of blood pressure control (standard, systolic 120-130 and diastolic 70-80 mm Hg vs. low, systolic 95-110 and diastolic 60-75 mm Hg) or ACE-I monotherapy at the same two levels of blood pressure control. The primary outcome of Study A is the percent change in total kidney volume, as measured by magnetic resonance imaging (MR). Study B will assess the effects of intensive blockade of the RAAS through combination ACE-I/ARB therapy as compared with ACE-I monotherapy, with both groups treated to a standard level of blood pressure control (systolic 110-130 mm Hg and diastolic 80 mm Hg) . The primary outcome for Study B is a composite endpoint of time to the 50% reduction of baseline eGFR, ESRD or death.

1.1. Motivation for a Clinical Trial to Slow Progression of ADPKD

This randomized clinical trial will test the primary hypothesis that intensive blockade of the RAAS using an ACE-I together with an ARB in hypertensive individuals with ADPKD has a statistically significant advantage over other currently used antihypertensive agents in delaying the renal and possibly cardiac complications associated with this disease, independent of the level of blood pressure control. In addition, a second hypothesis to be tested is that a lower blood pressure target (systolic 95-110 and diastolic 60-75 mm Hg) in the setting of intensive RAAS blockade will delay renal progression early in the course of ADPKD over standard blood pressure control (systolic 120 -130 and diastolic 70-80 mm Hg). These are very important hypotheses to test, not only because of the decreased morbidity and mortality associated with delaying ESRD, but also because of the economic advantage of delaying ESRD. We hope to show that our intervention has the potential to cause a meaningful decrease in the prevalence and cost of ESRD by delaying its onset. For example, the average decline in renal function in all persons with ESRD from any cause is approximately 7.56 mL/min/year. If this rate is slowed by 10% in all individuals with GFRs <60 mL/min; over a 10-year period, the estimated cumulative savings would be approximately 18 billion dollars [Trivedi, 2002]. If the rate of decline in persons with GFRs of <30 mL/min is slowed by 10%, the estimated cumulative savings would be 9 billion dollars [Trivedi, 2002]. The GFR in individuals with ADPKD declines by approximately 4-5 mL/min/year. As 4.7-10% of individuals with ESRD have ADPKD, the potential savings are very significant. Clinical studies of progression in humans with ADPKD are few in number and have not shown consistent outcomes. As discussed below, there is substantial clinical data to implicate the RAAS in the pathogenesis of hypertension in ADPKD, the progression of structural changes such as renal cyst growth and renal interstitial fibrosis, and the development of left ventricular hypertrophy (LVH) as an important cardiovascular manifestation. The question we plan to answer is whether complete interruption of the RAAS impacts the clinical course. To date, this question has not been addressed in a large randomized study.

1.2. Clinical Trials to Slow Progression of ADPKD

Definitive information on the potential role of complete blockade of the RAAS to prevent progression of renal dysfunction in humans with ADPKD is lacking. Maschio et al have been the only

investigators to perform a prospective, randomized, double-blind, placebo -controlled study to assess the benefits of ACE-I on renal progression in nondiabetic kidney diseases that included ADPKD individuals. These investigators found lack of therapeutic efficacy in 64 subjects with ADPKD who were followed for approximately 3 years [Maschio, 1996]. In the ramipril group, a doubling of serum creatinine concentration occurred with equal frequency (27%) as compared to the placebo controlled group (26%) . These individuals had reduced GFR at the onset of intervention (mean Ccr 42 mL/min). In the MDRD study, 200 of 840 subjects had ADPKD [Klahr, 1995]. A 2-by-2 factorial design was employed to compare two levels of dietary protein/phosphorous intake and two levels of blood pressure control. Aggressive blood pressure control was defined as mean arterial pressure (MAP) ≤92 mm Hg and usual as MAP ≤107 mm Hg.

In patients with GFR between 25 and 55 mL/min per 1.73 m^2, there was no significant reduction in GFR decline in those treated with either the low-protein diet or low blood pressure goal. In participants with GFR between 13 and 24 mL/min per 1.73 m^2, assignment to the low MAP group was associated with a more rapid decline in GFR. However, the more rapid decline in GFR did not appear to be due to a detrimental effect of low blood pressure or the antihypertensive agents used to reach the low blood pressure goal. Lower protein intake had a marginal slowing of GFR decline in those with GFR 13 -24 mls/min/1.73m^2 [Klahr, 1995]. The MDRD Study did not assess the effects of ACE-inhibitors on progression.

In a 7-year prospective trial assessing both level of blood pressure control and class of antihypertensive agent used, no advantage of the ACE-I enalapril versus the calcium channel blocker amlodipine was found in reducing the rate of decline of renal function as measured by GFR predicted using the MDRD equation [Ecder, 2000]. Proteinuria and left ventricular hypertrophy (surrogate markers of disease progression in ADPKD [Gabow, 1992]) were significantly reduced in the group treated with enalapril as compared to amlodipine [Ecder, 2000]. Albumin-creatinine ratios (mg/gram) were 148 ± 74 in the amlodipine group and 14 ± 6 in the enalapril group after five years of intervention [Ecder, 2001]. Increased proteinuria was observed with diuretic compared to ACE-I [Ecder, 2001].

A recent meta-analysis from 11 randomized clinical trials in non -diabetic kidney disease reported a 30% relative risk reduction in the composite end-point of ESRD or doubling of serum creatinine in individuals on ACE-I compared with other anti-hypertensive agents [Jafar, 2001]. A separate analysis on 145 of these individuals with ADPKD [Jafar, 2000] showed a 25% relative risk reduction with ACE-I although the result was not statistically significant. These findings were secondary analyses, performed in relatively small numbers of subjects with limited follow-up (2.2 years).

In conclusion, a rigorous clinical trial, adequately powered to assess the effect of ACE-I on renal progression in ADPKD, has not been performed. Past studies may also have been limited by the study of relatively late stages of disease, at which point there may be minimal to no effect of an intervention on slowing the inexorable decline in kidney function and by the use of ACE-I alone, which may incompletely block the RAAS. To date, the impact of intensive blockade of the RAAS through combination ACE-I/ARB therapy on progression of renal insufficiency in individuals with ADPKD has not been assessed. Although the RAAS is implicated in hypertension in ADPKD, associated with progression to renal failure, a large randomized clinical trial is needed to determine if blockade of the RAAS is effective in slowing the progression of ADPKD.

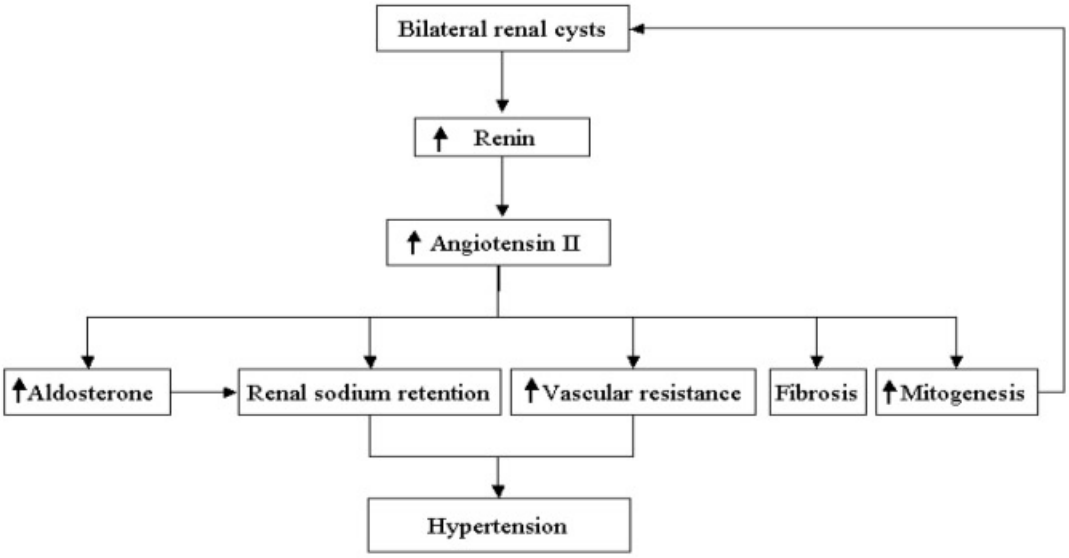
1.3. **Molecular Pathogenesis of ADPKD**

ADPKD is the most common renal genetic disease affecting 1:400 to 1:1000 individuals [Iglesias, 1983]. More Americans have PKD than the combined number of those who have cystic fibrosis, muscular dystrophy, Down's Syndrome, hemophilia, sickle cell anemia, and Huntington's Disease. In ADPKD, as cysts develop and grow over time, they compress the normal renal architecture and vasculature causing an increase in renal size with interstitial fibrosis and tubular atrophy [Zeier, 1992]. The result is progressive kidney dysfunction. Cysts develop from cells in the tubular portion of the nephron and the collecting system. Although all cells carry the ADPKD mutation, very few

actually develop cysts. The current theory is that the wild-type gene develops an inactivating somatic mutation in only a few of the cells leaving expression of the mutated PKD gene unopposed. This leads to monoclonal cyst development [Qian, 2001]. ESRD develops in approximately 50% of affected persons by age 53 years and is rare below age 30 years [Parfrey, 1990; Churchill, 1984]. The decline in renal function is one of the most rapid of all forms of non-diabetic kidney disease [Hunsicker, 1997]. In addition to the development of ESRD, a number of extrarenal complications of ADPKD, such as liver cyst disease, intracranial aneurysms, valvular heart disease, and perhaps diverticular disease, contribute to morbidity and mortality [Perrone, 2001; Perrone, 1997].

1.4. **Activation of the RAAS in ADPKD**

Clinical data support the hypothesis that the RAAS is activated in individuals with ADPKD. Data suggest that as the renal cysts enlarge, they compress the renal vasculature causing intra-renal ischemia, attenuation of the renal vasculature, and activation of the RAAS [Graham, 1988; Chapman, 1990; Torres, 1991; Watson, 1992; Barrett, 1994; Ecder, 2001; Wang, 1991].



Other non-ACE-I dependent mechanisms for the renal activation of the RAAS may also exist. Activation of the RAAS has been found in both normotensive and hypertensive ADPKD subjects and plays a role in the pathophysiology of the hypertension in this disorder. Angiotensin (ANG II) is important in the decreased renal plasma flow and increased renal vascular resistance found in hypertensive ADPKD subjects. Normalization of the renal blood flow in hypertensive ADPKD individuals with ACE-I is not complete. ACE-I block conversion of angiotensin I (ANG I) to ANG II and are used for the treatment of hypertension in the general population and, specifically, in hypertensive ADPKD individuals. However, systemic ANG II levels do not suppress with chronic ACE- I, and both systemic and renal hemodynamic responses to exogenous ANG I and ANG II persist in the presence of ACE-I therapy. Angiotensin receptor antagonism therapy (AT1RA) prevents action of ANG II in systemic and renal circulations by binding with the ANG II 1a receptor. However ANG II levels also increase with chronic AT1RA therapy, exogenous ANG II responses are not totally suppressed in the presence of AT1RA, and tissue penetration of AT1RA may differ across local tissue beds. If ANG II levels and action are important in regulating blood pressure and renal plasma flow and in promoting cyst growth in ADPKD, combination therapy with ACE-I and AT1RA to maximally block ANG II production and action may be warranted.

Clinical studies show higher plasma renin and aldosterone concentrations in the supine and upright positions and in response to ACE-I in subjects with ADPKD compared to matched subjects with

essential hypertension [Chapman, 1990]. Biopsy data from both nephrectomy and autopsy specimens also suggest the RAAS is activated in individuals with ADPKD. These specimens show increased concentrations of renin in the juxta-medullary apparatus, arterioles, small arteries, connective tissue cells around the cysts, and in attenuated vessels within the cyst wall [Torres, 1992; Graham, 1988]. Clearly this activation of the RAAS contributes to the development of hypertension. Hypertension in ADPKD precedes the development of renal failure. ACE-I for six weeks decreased renal vascular resistance in hypertensive ADPKD subjects when compared to subjects with essential hypertension [Chapman, 1990]. Significant numbers of young ADPKD individuals are affected as ambulatory blood pressure monitoring shows that 34% of affected children develop either systolic or diastolic hypertension by the mean age of 12.3 years [Seeman, 1997]. Analysis of unpublished data from the Denver ADPKD database shows that in affected individuals with creatinine clearances above 50 mL/min/1.73 m^2, hypertension occurs in 40% age 18-24 years, 53% age 25-30 years, and 65% greater than age 30 years.

In the first randomized study in this clinical trial, Study A, we hypothesize that intensive blockade of the RAAS with the combination of ACE-I and ARB will delay the progression of cystic disease independent of tight blood pressure control in participants with preserved renal function (GFR > 60mL/min/1.73 m^2) when compared with ACE-I monotherapy. We hypothesize that the RAAS contributes not only to hypertension, but also independently accelerates renal cyst growth disrupting the structural integrity of the kidney in individuals with ADPKD. Renin is synthesized by the tubular epithelium in individuals with ADPKD [Ichikawi, 1991]. Angiotensin II is an important growth factor for renal proximal tubular cells [Ichikawi, 1991; Chatterjee, 1997; Rosenberg, 1993; Wolf, 1990] and renal interstitial fibroblasts [Ruiz- Ortega, 1997]. Tubular epithelial cell proliferation is of fundamental importance in the pathogenesis of polycystic kidney disease [Bernstein, 1987; Ramasubbu, 1998]. With increasing cyst size, blood pressure increases; and a vicious cycle ensues with enhanced cyst growth, hypertension, more cyst growth, and ultimately, ESRD.

In addition, as discussed above, cysts develop in only a few nephrons. Although the compression and atrophy of normal renal tissue, that occurs as the cysts enlarge, contribute to the loss of renal function in individuals with ADPKD, histologic data suggest other mechanisms also contribute. Examination of tissue from both animal [Bachmann, 1995; Cowley, 1993; Schafer, 1994] and human kidneys [Zeier, 1992] shows prominent interstitial inflammatory infiltrates and interstitial fibrosis. Immunocytochemistry studies from human kidneys show an increase in collagen types I and IV, laminin, and fibronectin in individuals with ADPKD [Grantham, 1997; Wilson, 1991; Calvet, 1993]. Examination of an ADPKD animal model (male Han:SPRD rat) shows marked inflammatory infiltrates and interstitial fibrosis developing by 24 weeks of age and coinciding with the development of significant azotemia [Cowley, 1993; Schafer, 1994]. Interstitial fibrosis is an important factor in the progression of ADPKD to ESRD [Grantham, 1997; Torres, 1998]. These observations are particularly interesting as individuals with ADPKD also develop liver cysts but not liver failure. One hypothesis is that the liver does not develop the fibrosis observed in the kidneys of ADPKD individuals. Angiotensin II is not only a potent growth factor, but is also associated with the development of interstitial fibrosis. For example, it has been shown to stimulate renal interstitial fibroblasts to secrete fibronectin and type I collagen via the release of TGF- [Ruiz -Ortega, 1997]. Recent experimental data in rats demonstrated that chronic low-dose angiotensin II infusion stimulated the production of TGF-β_1, the prototype of "fibrosis-cytokines", in both kidney and heart but spared the liver [Rosenberg, 1993]. Interestingly, marked fibrosis developed in the rat kidney and heart, but not in the liver [Rosenberg, 1993]. Both ACE- I and ARB reduce the production of TGF-β_1 and limit interstitial fibrosis in animal models of chronic renal disease [Burdmann, 1995; Zoja, 1997; Shihab, 1997; Otsuka, 1998]. We hope to demonstrate this same effect in humans by showing a delay in renal progression in participants on ACE-I together with ARB when compared to ACE-I monotherapy.

1.5. **Renal Volume as a Marker of Disease Progression in Early Stages of ADPKD**

To measure the impact of aggressive RAAS blockade on cyst growth, we will determine percent change in total kidney size by MR. Three clinical trials involving ADPKD subjects with preserved kidney function (GFR >60 mL/min/1.73 m^2) show a correlation between the rate of kidney growth and renal insufficiency [Fick-Brosnahan, 2002; Sise, 2000; King, 2000]. Although different imaging techniques and measurements of function were employed in each study, kidney volume and renal function were measured at the initial visit and at least once several years later.

Sise, et al, retrospectively analyzed 10 subjects with initial creatinine clearances >60 mL/min/1.73 m^2 who had two routine follow-up contrast-enhanced CTs separated by an average of 8.7 years [Sise, 2000]. The mean age at the start of the study was 33.8 years and 80% of the subjects were hypertensive. The annual increase in total kidney volume was a mean (SE) of 53.9 (10) cc/year. The five subjects who developed ESRD had larger kidneys at baseline and more rapid rate of rise in kidney volume compared to those without ESRD. The study likely did not have the statistical power to reach significance.

King, et al, imaged 9 subjects with GFR >60 mL/min/1.73 m^2 by fast electron- beam CT and obtained baseline iothalamate clearances with repeat measurements 8 years later [King, 2000]. The average subject age was 36.6 years and the mean GFR was 91.4 mL/min/1.73 m^2 . At baseline, GFR was negatively correlated with renal volume (r=-0.40; p value 0.28) and cyst volume (r=-0.64; p value 0.06), although neither was statistically significant. Over 8 years, the average increase in total kidney volume was 48.0 (SD 44.5) cc/year and GFR declined an average of 2.79 mL/min/1.73 m^2 per year. Using mean slopes analyses to assess change over time, a more rapid rate of decline in GFR was associated with a greater increase in kidney volume (r=-0.48, p=0.19) and cyst volume over time (r=-0.71; p=0.046). The method for measuring kidney volume was reproducible and confirmed results of two prior cross-sectional studies relating kidney volume with reduced function.

The University of Colorado has completed the largest study to date [Fick-Brosnahan, 2002]. This group followed 229 adult subjects with sequential renal volume measurements by ultrasound performed an average of 7.8 years apart. The mean age at baseline was 37 years and the mean GFR (by the MDRD formula) was 71 ± 22 mL/min/1.73 m^2. Kidney volume increased by a mean of 46 ± 55 cm^3/ year and GFR declined by 2.4 ± 2.8 mL/min/1.73 m^2 / year. Kidney volume was strongly correlated with GFR (r=-0.53, p<0.0001). A faster decline in GFR was associated with younger age (-0.16, p<0.05), increased renal growth rate (-0.20, p<0.005) and larger initial kidney size (-0.25, <0.0001). The investigators also reported males had larger kidneys at baseline, more rapid renal growth rates, more rapid decline in renal function, and more severe hypertension than women of the same age. Although imaging techniques differed, the estimates of the annual growth rate of ADPKD kidneys and the finding of a significant cross -sectional relationship with kidney size were consistent. The significant relationship between the rate of increase in renal volume and decline in GFR in the Colorado study is consistent with King, et al, who noted the same correlation with cyst volume and kidney function in the smaller sample. These data support the use of structural changes as a surrogate outcome for renal progression in early disease as proposed in Study A of the current clinical trial.

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) Study, a NIH-funded prospective observational study, is currently underway and is designed to examine the role of structural changes measured radiologically to represent progressive decline in renal function in early ADPKD and to show the methods they utilize are reproducible in measuring structural change. Cross-sectional data at baseline are supportive of the other studies. Sixty-two percent of the subjects had hypertension and the mean GFR was 98.9 (41-186) mL/min/1.73 m2. The change in kidney volume over the first year was consistent with previous reports (mean (SD) of 44.6 (98) cc/year). Standardization studies using phantoms and subjects demonstrate that MR methods in detecting kidney and renal cyst volumes are stable and reliable. Table 1, below, presents the measurements obtained at each of the different clinical sites for the balloon phantoms, while Table 2 presents information from the standardization subjects at each of the clinical sites. Using a variance components approach to reliability for these data, reliability for the kidney volume is estimated at

.984, and reliability for the cyst volume is estimated at .921.

Table 1: True and Measured Volumes of Balloon Phantoms							
Location	**Size**	**True**	**Volume**	**Measured Mean**	**Volume (SD)**	**Proportion of**	**True**
		Whole	**Balloon**	**Whole**	**Balloon**	**Whole**	**Balloon**
Alabama	Large	621.0	222	607.0(6.3)	230.4(35.0)	0.977	1.038
	Small	255.5	82	252.9(2.7)	86.9(11.7)	0.989	1.060
Mayo	Large	599.0	190	586.4(3.6)	205.9(16.1)	0.979	1.084
	Small	276.5	68	283.0(12.8)	68.8(10.0)	1.024	1.012
Emory	Large	646.0	235	622.3(13.7)	249.4(13.2)	0.963	1.061
	Small	257.0	70	251.0(9.7)	73.8(7.1)	0.977	1.054
Kansas	Large	617.0	220	614.8(5.2)	223.0(13.1)	0.996	1.014
	Small	262.0	69	259.0(4.7)	63.4(8.4)	0.989	0.919

Table 2: Measured Clinical Variables of the Standardization Protocol Subjects		
Variable	**Mean ± S.D.**	**Range**
Height (cm)	175.75 ± 16.51	167-200.5
Weight (kg)	71.20 ± 24.72	56.7-108.1
BMI (m^2)	22.47 ± 3.05	20.33-26.89
BSA (m^2)	1.86 ± .40	1.63-2.49
GFR mL/min/1.73m^2	94.75 ± 30.55	66-137

1.6. **Renal Blood Flow and Progression of ADPKD**

Secondary outcomes to be measured in Study A include the rate of decline in renal function using the four- point MDRD equation estimating GFR from serum creatinine and absolute and rate of decline in renal blood flow by magnetic resonance angiography (MRA). Data recently generated from the CRISP study (as shown in Table 3) suggest that renal blood flow may be the most sensitive measurement that predicts GFR levels in ADPKD individuals, more so than renal volume.

Table 3: Regression Model Predicting GFR: Effect of Age, Sex, Renal Volume and RBF				
	Multiple Regression		**Simple Regression**	
Source	**F Value**	**P Value**	**r Value**	**P Value**
Age	5.84	0.0172	-0.39	0.0001
Sex	2.21	0.1397	0.08	0.3894
Diagnosis of Hypertension	0.17	0.6839	-0.19	0.0347
Total Kidney Volume	0.38	0.5383	-0.30	0.0005
Total Corr Renal Blood Flow	27.54	<0.0001	0.52	0.0001

In the CRISP study, 2 out of the 4 clinical centers have demonstrated reliability and accuracy of measuring renal blood flow with different phantoms and have made renal blood flow measurements using single breathold rapid acquisition MRA technology in over 120 subjects. Significant correlations between renal blood flow and renal structural involvement and renal function were found at both sites.

1.7. **Benefits of RAAS Interruption in Reducing Proteinuria**

In both the ACE-I/ARB group and the control group in Study A, participants will be randomized to tight control of blood pressure (95-110/60-75 mm Hg) or standard control (120-130/70-80 mm Hg).

While multivariate analysis of factors causing renal disease shows hypertension was independently associated with progression of renal failure in ADPKD, controlling blood pressure to the same degree in both RAAS blockade groups will enable us to evaluate whether there is an added advantage of ACE-I/ARB blockade compared to anti-hypertensive therapy.

Another secondary measure that will be studied is the effect of RAAS blockade on albuminuria in the ADPKD group. ACE-I has a renoprotective effect in the progression of diabetic and non-diabetic renal disease independent of any anti-hypertensive effect due to the antiproteinuric effect of ACE-I [Lewis, 1993; Ihle, 1996; Kamper, 1996; Maschio, 1996; GISEN, 1997]. Clinical data suggests that ARBs have similar effects [Plum, 1998; Fernández-Andrade, 1998; Andersen, 2000; Russo, 1999]. Microalbuminuria (30-300 mg/day) and overt proteinuria (>300 mg/day) have been shown to correlate with progression of renal disease in individuals with ADPKD [Chapman, 1994] In fact, ADPKD subjects with overt proteinuria reach a serum creatinine level of 1.5 mg/dl an average of 14 years earlier than subjects without overt proteinuria [Gabow, 1992]. Preferential reduction in proteinuria in ADPKD individuals using ACE-I as compared to dihydropyridine calcium channel blockers has been demonstrated.

1.8. **Cardiovascular Involvement in ADPKD**

As cardiovascular disease is a major cause of mortality in people with ADPKD, any potential modality to decrease this complication would be important to study. Clearly, hypertension is contributing to the development of cardiovascular disease. At the mean age of 44 years, 48% of hypertensive ADPKD adults with normal or mildly decreased renal function have LVH [Ecder, 2001]. Equally concerning, more than 70% of ADPKD subjects initiating dialysis have LVH, a physical finding associated with increased cardiac morbidity and mortality [Levin, 1996]. Therefore, we plan to measure LVH with MR studies at baseline and after 2 and 4 years in Study A. If a statistically significant difference between groups is demonstrated, this will be important for subject care. ACE-I has been shown to exhibit cardioprotective effects in post- myocardial infarction and with left ventricular systolic dysfunction independent of blood pressure [Pfeffer, 1992; SOLVD, 1992]. ACE-I attenuates or reverses the remodeling of myocardial tissue which is modulated by the mitogenic effect of angiotensin II [Pfeffer, 1992].

1.9. **Use of ACE-I as the Control Arm for Early and Late ADPKD**

Although a definitive study to demonstrate efficacy of ACE-I on renal progression in ADPKD has not been performed, a wealth of evidence from several well-designed and rigorous studies shows ACE-I to be of benefit in slowing renal progression in non-diabetic kidney disease, including those without proteinuria, as described above. Clinical practice guidelines from the National Kidney Foundation (NKF) and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) call for ACE-I as the first-line agent for treatment of hypertension in patients with chronic kidney disease [K/DOQI, 2002; JNC VII 2003]. Although many of the participants in Study A will have preserved renal function and thus not meet the chronic kidney disease criteria in these practice guidelines, we estimate that 70% of ADPKD patients with hypertension are taking ACE-I currently. Given the general public awareness of the benefits of ACE-I in kidney disease, recruitment may be limited if a non-ACE-I control arm is used. Consideration is also given to the high prevalence of cardiac disease in ADPKD, with left ventricular hypertrophy present in upwards of 40% at presentation. A recent meta-analysis showed ACE-I, ARB, or CCB to be effective in reducing LV mass while β-Blockers were not. In summary, there is strong justification for the use of ACE- I as the control agent for both early and moderately advanced ADPKD in the HALT-PKD Study.

1.10. **Rationale for Dual Blockade of the RAAS**

ACE-Inhibitors (ACE-I) block conversion of angiotensin I (ANG I) to angiotensin II (ANG II) and are used for the treatment of hypertension in the general population and ADPKD individuals. Systemic ANG II levels do not suppress completely with chronic ACE-I therapy alone, and both systemic and renal hemodynamic responses to exogenous ANG I and ANG II infusions persist in the presence of ACE-I. Angiotensin receptor blockade (AT1 RA) prevents the action of ANG II in systemic and renal circulations by binding with the ANG II 1a receptor. Studies have shown further suppression of ANG II and aldosterone when ARB is added to maximal ACE-I therapy. This may be particularly relevant in ADPKD, where a recent study of tissue extracts demonstrated exuberant interstitial inflammation with mast cells with chymase-like activity. There was significantly greater ANG II production despite ACE-I blockade in PKD tissues as compared with non-PKD controls [McPherson, 2004].

As ANG II levels and action are important in regulating blood pressure and renal plasma flow and in promoting cyst growth in ADPKD, combination therapy with ACE- I and AT1RA to maximally blockade ANG II production and action is warranted. To date there have been a small number of clinical studies to whether intensive blockade of the RAAS through combination therapy (ACE-I and ARB) slows progression more than monotherapy. The largest is the COOPERATE STUDY, a randomized clinical trial conducted in Japan in 366 subjects with non-diabetic kidney disease and a mean GFR ~38 mL/min/1.73 m2, which compared the decline in kidney function in subjects treated with combination tranolapril and losartan versus either agent alone [Nakao, 2003]. At three-year follow-up, the group treated with combination ACE-I/ARB had a 60% reduction in the time to the composite endpoint of doubling serum creatinine, ESRD or death as compared with ACE-I or ARB alone. The effect was more pronounced in subjects with higher levels of proteinuria at baseline. The frequency of hyperkalemia was the same in the combination vs. monotherapy groups (4-8%) and was successfully managed with dietary measures or binders. The impressive results of the COOPERATE Study, the wealth of clinical evidence implicating the RAAS in the structural and functional progression of ADPKD and data showing continued activity of ANG II in the setting of maximal ACE-I or ARB therapy, warrant a well-designed clinical trial to assess the efficacy of combination ACE-I and ARB therapy in ADPKD.

1.11. **Summary**

In summary, demonstration that rigorous treatment with a combination of ACE- I and ARB will attenuate renal disease progression and cardiovascular sequelae in ADPKD will provide a cost-effective, readily available, clinically practical intervention for individuals with ADPKD. Such intervention will potentially prolong the life span and improve quality of life for the ADPKD population, as well as drastically reduce the costs associated with treatment for ADPKD.

2. **METHODS**

2.1. **Overview of Study Design**

The efficacy of interruption of the renin-angiotensin- aldosterone system (RAAS) on the progression of cystic disease and on the decline in renal function in autosomal dominant kidney disease (ADPKD) will be assessed in two multicenter randomized clinical trials targeting different levels of kidney function: (1) early disease defined by GFR >60 mL/min/1.73 m^2 (Study A) and moderately advanced disease defined by GFR 25 -60 mL/min/1.73 m^2 (Study B). Participants will be recruited and enrolled, either to Study A or B, over the first 3½ years. Participants will be recruited and enrolled, either to Study A or B, over the first 3½ years. Participants enrolled in Study A will be followed for a least a total of 5 years, or until July 2014. Participants enrolled in Study B will be followed until the last clinic visit prior to July 2014 resulting in Study B participants being followed for 5-8 years with average length of follow-up being 6 ½ years. The two concurrent randomized clinical trials differ by eligibility criteria, interventions and outcomes to be studied.

In Study A, the efficacy of intensive RAAS blockade using ACE-I/ARB combination as compared with ACE-I monotherapy and of two levels of blood pressure control on structural progression will be assessed using a 2x2 factorial design. Accordingly, participants will be randomized to one of four study arms: 1) combination ACE-I/ARB with standard blood pressure (BP) control (systolic 120-130 and diastolic 70- 80 mm Hg); 2) ACE-I monotherapy with standard BP control; 3) combination ACE-I/ARB treated to a low BP target (systolic 95-110 and diastolic 60-75 mm Hg); and 4) ACE-I treated to the low BP goal. Other antihypertensive agents will be added as needed to meet the BP goals. The primary outcome of Study A is the percent change in total kidney volume measured by magnetic resonance (MR) imaging.

Study B will assess the efficacy of intensive RAAS blockade using ACE-I/ARB combination therapy compared to ACE-I monotherapy on the time to a 50% reduction of baseline eGFR, ESRD or death. All participants will be treated to a standard level of blood pressure control (systolic 110-130 mm Hg and diastolic 80 mm Hg), with addition of other antihypertensive agents as needed.

The titration of medications and addition of open-label antihypertensive agents will be based on home blood pressure readings. Study visits will occur at the PCC at the 4th and 12th months in the first year and every 6 months thereafter. Participants will be followed by telephone visits at least every three months.

2.2. Specific Aims and Main Hypotheses

Activation of the RAAS and hypertension are hypothesized to play important and independent roles in the structural progression of cystic renal disease and in the loss of renal function in ADPKD.

Specific Aims of Study A

To study the efficacy of ACE-I/ARB combination therapy as compared to ACE-I monotherapy and usual vs. low blood pressure targets on the percent change in kidney volume in participants with preserved renal function (GFR >60 mL/min/1.73m^2) and high-normal blood pressure or hypertension (>130/80 mm Hg).

Hypotheses to be tested in Study A

In ADPKD individuals with hypertension or high-normal blood pressure and relatively preserved renal function (GFR >60 mL/min/1.73 m^2), multi-level blockade of the RAAS using combination ACE- I/ARB therapy will delay progression of cystic disease as compared to ACE-I monotherapy, and a low blood pressure goal will delay progression as compared with standard control.

Specific Aim of Study B

To study the effects of ACE-I/ARB combination therapy as compared to ACE-I monotherapy in the setting of standard blood pressure control (systolic 110-130 mm Hg and diastolic 80 mm Hg) on the time to a 50% reduction of baseline eGFR, ESRD, or death, in hypertensive individuals with moderate renal insufficiency (GFR 25-60 mL/min/1.73m^2).

Hypothesis to be tested in Study B

In hypertensive ADPKD individuals with moderate renal insufficiency (GFR 25-60 mL/min/1.73 m^2), intensive blockade of the RAAS using combination ACE-I/ARB therapy will slow the decline in kidney function over ACE-I monotherapy, independent of standard blood pressure control (systolic 110-130 mm Hg and diastolic 80 mm Hg).

3. ORGANIZATION OF THE STUDY TEAM

3.1. The PKD-TN Steering Committee

The participating clinical centers (PCC) and principal investigators (PIs), responsible for recruiting and following 255 study participants each, are the University of Colorado (Dr. R. Schrier), Mayo Clinic Rochester (Dr. V. Torres), Emory University (Dr. A. Chapman), and Tufts Medical Center (Dr. R. Perrone). The Data Coordinating Center, originally managed by Professor J.P. Miller, at Washington University in St. Louis, began the transition of DCC responsibilities to the University of Pittsburgh Center for Research on Health Care (CRHC) Data Center August 1, 2008. The DCC at Washington University remained in charge of enrollment activities and baseline data collection until recruitment ended June 30, 2009. The CRHC Data Coordinating Center assumed full responsibility of HALT-PKD management February 1, 2009. The University of Pittsburgh DCC, led by Dr. James Bost (August 2008-October 31, 2011), transitioned the DCC Principal Investigator responsibilities to Dr. Charity G. Moore on November 1, 2011. Dr. Kaleab Abebe became the University of Pittsburgh DCC lead biostatistician on April 1, 2012. Dr. Schrier is the Chairman of the Steering Committee and each of the other members, as well as Dr. Michael Flessner (NIDDK Program Scientist), has a vote. Principal investigators and co-investigators will attend Steering Committee meetings during the protocol development phase. Study coordinators and other ancillary staff will be invited to attend these meetings once recruitment begins.

3.2. Additional Study Sites

Mayo Clinic and Tufts Medical Center have subcontracted with other clinical centers to aid in recruitment and study visits. Participants will be followed at the same center for all study visits to ensure continuity of care. The additional centers associated with Mayo Clinic are Cleveland Clinic and Kansas University Medical Center. Beth Israel Deaconess Medical Center (BIDMC), also in Boston, will serve as a second study site for Tufts Medical Center.

3.3. External Advisory Committee

An External Advisory Committee (EAC) has been selected by NIH/NIDDK to review the protocol and is made up of nephrologists, who have expertise in PKD and/or have past experience in conducting randomized clinical trials, and statisticians. The protocol requires approval by the EAC before the study can begin. Once recruitment begins, members of the EAC will serve on the Data and Safety Monitoring Board (DSMB).

4. RECRUITMENT

The same recruitment strategies will be used for both studies.

4.1. Recruitment Goals

A total of 548 participants for Study A (GFR >60 mL/min/1.73 m^2) and 470 for Study B (GFR 25-60 mL/min/1.73 m^2) will provide 90% power to detect 25% differences in treatment arms of each study, as discussed further in Section 13. As demonstrated in the Modification of Diet in Renal Disease Study (MDRD) [Klahr, 1995], ADPKD patients tend to be more motivated to participate in clinical trials than other subgroups with chronic kidney disease, and we anticipate that 4 out of every 5 individuals screened will be enrolled. To meet this goal, 165 individuals with GFR >60 mL/min/1.73 m^2 and 142 individuals with GFR 25-60 mL/ min/ 1.73 m^2 will need to be screened at each PCC. The number of potential participants approached, the number enrolled and the reasons for non-participation at each stage of the screening period for each study will be recorded. The means by which participants learned about the study will also be recorded to direct subsequent recruitment efforts to those that have been most effective.

4.1.1. *Source Population*

Recruitment strategies will target participants residing within and outside of the immediate vicinity of the PCC. Participants followed in nephrology clinics or registries, especially if followed for several years, may be biased towards "slow progressors" by virtue of the fact that they are still in the registry or clinic as opposed to on dialysis. Although there has been a push for earlier referral of patients to nephrologists; in reality, much of the targeted population likely still exists outside nephrology practices, as serum creatinine values perceived as "normal" (i.e., <1.5 mg/dl) really reflect substantial reduction of GFR. Recruitment strategies are divided into physician and community sources, as summarized in Table 4, and discussed in detail below.

To ensure that study populations reflect the overall US population with ADPKD, the numbers of women and racial minorities recruited and enrolled to each study will be monitored over time. If minority representation is low, increased efforts will be made to advertise the study in minority- dense regions (e.g. inner city) and to contact clinics and physicians servicing minority populations.

4.2. **Recruitment from the Community**

4.2.1. *Participants and Referring Physicians*

The Steering Committee has developed a pamphlet directed to potential participants, which summarizes the purpose of the study, eligibility criteria, study sites, and general commitments required to participate. A letter directed to physicians has also been developed to inform them of the study and invite them to refer their patients to HALT PKD.

A map of the United States has been divided into four regions, corresponding to the four PCCs, and labeled with a unique toll-free telephone number for each clinic. The map, with its accompanying telephone numbers, will appear on the HALT PKD website and on advertising materials. Potential participants will be instructed to determine the appropriate PCC, according to the above-described map, and then to call that PCC to obtain information regarding the study.

4.2.2. *The Polycystic Kidney Disease Foundation*

The PKD Foundation has agreed to send the pamphlet for participants (described above) to its national mailing list. Fundraising and educational events (e.g. newsletters, "Walk for the Cure", patient education sessions, members meetings) are arranged by local chapters of the PKD Foundation and offer additional opportunities for advertising the study. Nationwide publicity generated by the initiation of the study should lead to additional interest and involvement on the part of the ADPKD community. The PKD Foundation will post information on its website to inform their membership about the study and will also provide a link to the public HALT PKD website.

4.2.3. *Web-Based Advertising Strategies*

A **new** public HALT PKD website: www.haltpkd.org has been developed by the University of Pittsburgh DCC. The study has met its recruitment goal, therefore, the website is not being used as a recruitment tool. The website provides a summary of the study and its purpose. Study participants will have the option to enter the site with login information and a password provided by the study coordinator. After logging in, the participant will have access to study updates, coordinator contact information and study forms that can be downloaded.

4.2.4. *Mass Media/Public Advertisements*

Principal investigators at each PCC will advertise the study within local newspapers and radio stations or on local and/or national television networks. Posters will be displayed on public transportation (subway/public bus) and community bulletin boards (e.g. supermarket, YMCA, church, community centers). All posters, information pamphlets and web-based materials have been approved by the Steering Committee, but also require approval by the Institutional Review Board at each clinical center.

4.3. Referral from Physician Clinics

A personalized letter and study pamphlet will be mailed to local pediatric and adult nephrologists, primary care physicians, transplant surgeons and urologists, inviting referrals to the study. The same materials will be sent to members on the national mailing list of the American Society of Nephrology. Posters and pamphlets for participants will be distributed among outpatient nephrology, urology, general medical clinics and dialysis units (the latter for recruitment of family members).

Table 4: Specific Recruitment Strategies for Physicians Clinics and in the Community

Referring Physicians	Community
1. Pamphlet and letter to pediatric and adult nephrologists/ PCPs/ urologists 2. Posters in outpatient clinics (nephrology/general internal medicine/urology/ dialysis units/transplant) 3. Pamphlet and letter sent to national mailing list of the American Society of Nephrology	1. PKD Foundation – mailings to members (invitation letter and pamphlet) 2. Website advertisement linked to PKD Foundation/ keyword search for PKD 3. Educational talks through PKD Foundation / newsletters / fundraising events 4. Television: public service announcements and interviews on local news stations 5. Advertisements in local newspapers/ public transport

4.4. Source Populations for Each PCC

The PIs at each PCC are well known by both the patient and nephrologist communities for their research into and care of patients with ADPKD. Estimates of numbers of participants from existing clinical and study databases at each PCC who may be eligible to participate in HALT PKD are as follows:

4.4.1. *The University of Colorado*

Since 1985, 1,474 members of 463 ADPKD families have participated in clinical studies at the University of Colorado. Within these families, 969 participants are known to be affected with ADPKD and 645 are between the ages of 15-65. Specific information is available for 561 of these participants, of whom 80% have a serum creatinine <1.4 mg/dl, the mean age is 41 years and 61% are female. Since announcement of the PKD-CTN last summer (2002), the University of Colorado has been contacted by an additional 644 families (unrelated to the 463 families above) that have expressed interest in participating in future clinical studies.

4.4.2. *The Mayo Clinic*

The Mayo ADPKD database consists of 2,250 active ADPKD patients, 19% of which are within the immediate counties, and 31% within Minnesota and surrounding states. Forty one percent of patients within the database have a normal serum creatinine, 58% are female and 92% are non-Hispanic Caucasian. The Mayo Clinic Dialysis Services encompasses 13 dialysis units and 6% of these patients have ADPKD and are likely to have eligible and interested family members. The Mayo Nephrology Collaborative Group consists of 83

nephrologists at 31 study sites throughout the US, which provides an additional source of study participants who could be referred to the nearest regional PCC. Mayo has subcontracted with two other study sites, Kansas University Medical Center (KUMC) and the Cleveland Clinic, both of which follow large numbers of ADPKD patients. Two hundred eighty-five ADPKD patients are actively followed at KUMC, and an additional 293 have been referred from the PKD Foundation and 85 from area physicians. There is an estimated 1679 ADPKD patients within in the surrounding KUMC area. Approximately 100 patients are currently followed by the nephrology group at the Cleveland Clinic. This center also has 11 affiliated hospitals and 12 satellite clinics in close proximity, which provide additional patients.

4.4.3. *Emory University*

Two recent studies conducted at Emory are expected to be completed within the first year of recruitment to HALT-PKD and have involved a large number of ADPKD participants, many of whom would be eligible for the present study. The Cohort Study is an observational cohort study funded by the PKD Foundation that began in 1998 and will be completed in 2004, the purpose of which is to determine factors associated with a more aggressive course of disease. Over 272 families are enrolled and many affected family members have been identified. Two hundred eighty-four individuals are currently eligible for Study A and 220 for Study B. Emory is also a PCC for the CRISP Study, described earlier, and there are 51 participants currently eligible for Study A and 6 for Study B. Both the Mayo Clinic and Emory were study sites for the CRISP Study and were easily able to meet their recruitment goals, and in fact, had to turn away interested individuals. The Emory University Renal Clinic has 16 practicing nephrologists, who actively follow 40 families. Within these families multiple affected individuals have been identified. Dr. Chapman has contacted Atlanta-based private nephrologists and has identified an additional 50 affected families within the immediate vicinity. Finally, referrals from physician members of the Georgia Society of Nephrology and the NKF of Georgia will provide access to an additional 3-400 families with ADPKD, each likely to have 1-2 affected family members who may be eligible for the study.

4.4.4. *Tufts University*

Tufts Medical Center has subcontracted with Beth Israel Deaconess Medical Center (BIDMC), also in Boston, to recruit, enroll and follow participants in the study. A review of administrative databases at Tufts Medical Center and three Rhode Island Hospitals within 45 minutes driving distance of Tufts, identified 400 ADPKD patients older than 18 years of age. After excluding patients with ESRD, those greater than 64 years of age, and those with serum creatinine >3.0 mg/dl, approximately 59 individuals would be eligible for this study. Dr. T. Steinman, of BIDMC (Co-PI for this PCC and who has established a large practice of ADPKD patients over the years) has identified an additional 48 patients, from his practice alone who would be eligible for the study. Although an extensive a database of active ADPKD patients does not exist at this PCC, as compared with the others, the high density of population in the Northeastern US and the relatively short driving distances between major medical centers will be advantageous in recruiting additional participants to the study. In the Metro Boston area there are estimated to be 689-1,380 individuals with ADPKD, as well as 6,300-12,000 individuals with ADPKD in the state of Massachusetts. Nephrologists at all of the major medical centers in the Boston area and their affiliated community hospitals and other major medical centers in the Northeastern states have been contacted and have agreed to refer patients to this study. The PKD Foundation has provided an estimate of members on its mailing list within the New England States and New York, which totals over 24,000, 70% of whom are affected with ADPKD. Dialysis Clinic Inc., the dialysis provider at Tufts Medical Center, has agreed to advertise the study in its 43 dialysis units within the Northeastern states, which will serve as an additional means to recruit potential participants to the study. Other

dialysis providers in the area will also be contacted. Since Tufts Medical Center/BIDMC's involvement in PKD-TN was announced in August 2002, more than 40 affected families have contacted the PCC expressing interest in the study.

5. Eligibility

5.1. Inclusion Criteria for Study A

1. In participants with a family history, the diagnosis of ADPKD will be based on Ravine's Criteria [Ravine, 1994], which requires the presence of at least 2 renal cysts {unilateral or bilateral} in a participant younger than 30 years; at least two cysts in each kidney among those 30-59 years; and at least 4 cysts in each kidney among those aged 60 years or older. In the absence of a family history, the diagnosis will be based on the presence of renal cysts bilaterally, totaling at least 20, in the absence of findings suggestive of other cystic renal diseases.
2. Age 15 - 49 years.
3. Glomerular Filtration Rate (GFR) >60 mL/min/1.73 m^2, estimated from serum creatinine using the 4-variable MDRD equation [Levey, 2000].
4. Hypertension or high-normal blood pressure, defined as a systolic blood pressure of $\geq$130 mm Hg and/or a diastolic blood pressure of $\geq$80 mm Hg [JNC VII, 2003] on three separate readings within the past year, or by current use of antihypertensive agents or diuretics for blood pressure control.
5. Informed consent.

5.2. Exclusion Criteria for Study A

1. Currently pregnant or intention of becoming pregnant in the subsequent 4 years. Women who have had a pregnancy of more than 12 weeks duration (past the first trimester) must wait a minimum of 6 months post partum, miscarriage or abortion before screening and must not be lactating at the time of screening. For a pregnancy of 12 or fewer weeks' duration, a minimum of 2 months post miscarriage or abortion is required before the screening visit.
2. Documented renal vascular disease.
3. Spot urine albumin-to-creatinine ratio of $\geq$0.5 and/or findings suggestive of kidney disease other than ADPKD.
4. Diabetes requiring insulin or oral hypoglycemic agents or a fasting serum glucose of $\geq$126 mg/dl or a random non-fasting glucose of $\geq$200 mg/dl (in accordance with ADA recommendations for diagnosis of diabetes [Report of the Expert Committee, 2003]).
5. Serum potassium >5.5 mEq/L for participants currently on ACE-I or ARB therapy; >5.0 mEq/L for participants *not* currently on ACE-I or ARB therapy.
6. History of angioneurotic edema or other absolute contraindication for ACE-I or ARB. An intolerable cough, associated with ACE-I, is defined as a cough developing within six months of initiation of ACE-I in the absence of other causes and resolving upon discontinuation of the ACE-I.
7. Indication (other than hypertension) for β-blocker or calcium channel blocker therapy (e.g. angina, past myocardial infarction, arrhythmia), unless approved by the site principal investigator.
8. Systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications.
9. Systemic illness with renal involvement.
10. Hospitalization for an acute illness in past 2 months (not including elective admissions).
11. Any serious comorbid condition for which life expectancy is <2 years.
12. History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance that would preclude successful completion of the study.
13. Known presence of unclipped cerebral aneurysm $\geq$7 mm in diameter
14. Treatment within the past 30 days (prior to starting HALT PKD study medication at baseline) on an interventional study that would, in the PI's opinion, interfere with HALT PKD, or creatine supplements within three months prior to the screening visit.

15. Congenital absence of a kidney.
16. Known allergy to sorbitol or sodium polystyrene sulfonate.

Exclusions specific to MR imaging acquisition and measurement:

17. Partial or total nephrectomy or renal cyst reduction (including aspiration) done <1 year ago, performed percutaneously, laparoscopically, or by open surgical procedure.
18. Cardiac pacemaker.
19. Presence of MR incompatible metallic clips (e.g. clipped cerebral aneurysm). This exclusion may be center-specific as some institutions permit MR compatible metallic clips.
20. Body weight >159 kg (350 lbs) or untreatable claustrophobia.

5.3. Inclusion Criteria for Study B

Participants with moderate renal insufficiency (GFR 25-60 mL/min/1.73 m^2), who demonstrate a rapid GFR decline of at least 4 mL/min/1.73 m^2/year, are targeted for Study B. The most consistent indicators of progressive decline at this rate or higher are the presence of hypertension and reduced renal function at baseline. The following criteria will be used to establish eligibility for Study B:

1. A diagnosis of ADPKD as described in item 1 of Inclusion Criteria for Study A (5.1, #1).
2. Age 18 - 64 Years.
3. GFR 25-60 mL/min/1.73 m^2, equated from serum creatinine using the 4-variable MDRD equation.
4. Hypertension or high-normal blood pressure, defined as systolic blood pressure $\geq$130 mm Hg and/or diastolic blood pressure 80 mm Hg [JNC VII, 2003] on three separate readings within the past year, or by current use of antihypertensive agents or diuretics for blood pressure control.
5. Informed Consent.

5.4. Exclusion Criteria for Study B

1. Currently pregnant or intention of becoming pregnant in the subsequent 4-7 years. Women who have had a pregnancy of more than 12 weeks duration (past the first trimester), must wait a minimum of 6 months post partum, miscarriage or abortion before screening and must not be lactating at the time of screening. For a pregnancy of 12 or fewer weeks' duration, a minimum of 2 months post miscarriage or abortion is required before the screening visit.
2. Congenital absence of a kidney or history of a total nephrectomy. A history of cyst reduction or aspiration or partial nephrectomy will not preclude participation in Study B.
3. Documented renal vascular disease.
4. Spot urine albumin-to-creatinine ratio $\geq$1.0 and/or findings suggestive of kidney disease other than ADPKD.
5. Diabetes requiring insulin or oral hypoglycemic agents or a fasting serum glucose of $\geq$126 mg/dl or a random non-fasting glucose of >200 mg/dl (in accordance with ADA recommendations for diagnosis of diabetes [Report of the Expert Committee, 2003]).
6. Serum potassium >5.5 mEq/Lfor participants currently on ACE-I or ARB therapy; >5.0 mEq/L for participants *not* currently on ACE-I or ARB.
7. History of angioneurotic edema or other absolute contraindication for ACE-I or ARB. An intolerable cough associated with ACE-I as defined above (see 5.2, #6).
8. Systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications.
9. Systemic illness with renal involvement.
10. Hospitalization for an acute illness in past 2 months (not including elective admissions).
11. Any serious comorbid condition for which life expectancy is <2 years.
12. History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance that would preclude successful completion of the study.
13. Known presence of unclipped cerebral aneurysm >7 mm in diameter.

14. Indication (other than hypertension) for β-blocker or calcium channel blocker therapy (e.g. angina, past myocardial infarction, arrhythmia), unless approved by the site principal investigator.
15. Treatment within the past 30 days (prior to starting HALT PKD study medication at baseline) on an interventional study that would, in the PI's opinion, interfere with the HALT-PKD study, or creatinine supplements within three months prior to the screening visit.
16. Known allergy to sorbitol or sodium polystyrene sulfonate.

6. STUDY TIMELINE

Tables 5A and 5B summarize the study visits that will take place between screening and the end of the study, with shaded columns representing in-person visits at the PCC. At the first visit, S (Screening), participants will be consented for Screening and Drug Washout (B0) and trained to monitor blood pressure at home. Screening laboratory measurements will also be drawn at the S visit. After review of the labs drawn at S, the study coordinator will contact participants via telephone to initiate a 2-4 week drug washout period for those participants currently on antihypertensive pharmaceutical therapy. If no washout is required, S and B1 visits may be combined (SB1).

At the B1 visit, participants will be consented for baseline and beyond (Study A or Study B), baseline lab measurements will be obtained, participants will be randomized and study medications will be dispensed. The participant will be instructed to begin the treatment regimen (at the B2 visit) once two central serum creatinine results have been checked and found to be consistent with one another. The study drug will be incremented over three subsequent visits (F1-F3) two weeks apart to be conducted over the telephone. Serum potassium, creatinine and BUN will be checked between dose increments at the PCC or a local lab.

Once study drugs have been maximized and blood pressure stabilized, home blood pressure records will be reviewed every three months (by phone or in clinic). Study visits at the PCC will occur at the 4^{th} (F5) and 12^{th} (F12) months in the first year and every 6 months thereafter. The study drug and open label antihypertensive medications will be adjusted to maintain BP goals over the duration of the study. Serum creatinine will be measured centrally every 6 months in participants of both studies after the first year. Study A participants will have MR/MRA/cardiac MR at baseline, 24, 48 and **60** months.

The last HALT-PKD participant was recruited in June of 2009. Both Study A and Study B will be extended until July of 2014, rather than the closing date at the end of January 2013.All participants will continue on study until this date even if they reach their 60 month visit at an earlier date.

Participants will be triaged out of the study at their last clinic visit prior to July 2014. This extension allows all participants to reach their 60 month visit prior to the end of the study.

The site PI will taper/discontinue blinded study medications as follows:

If on 80 mg. once daily, change to 40 mg. once daily and monitor blood pressure daily for 1-2 weeks. If no change in blood pressure after 1-2 weeks, discontinue medication and continue monitoring blood pressure as below.

If on 40 mg. once daily, discontinue and monitor blood pressure daily for 1-2 weeks.

If blood pressure is controlled (max 130/80) upon reducing dose or discontinuing study medication, no further intervention.

If blood pressure is not controlled upon reducing dose or discontinuing study medication, the PI will prescribe an increased dose of existing open label therapy and/or add other antihypertensive medications as appropriate.

The PI at each site will send a letter to the participant's primary physician notifying him/her of their patients status in the study and informing him/her of the need to transition care of the participant for ongoing hypertension management and requesting them to monitor the participants as they stop study medication.

Table 5A: Schedule of Assessments - PS-F5

Visit Code	PS	S[@]	B0	B1	B2	L1	F1	L2	F2	L3	F3	L4[^]	F4	F5
Time Point		K	K		0 wk	1 wk	2 wk	3 wk	4 wk	5 wk	6 wk	8 wk	9 wk	16 wk
Demographics	x	x												
Informed Consent		x		x*										
Renal Disease History		x												
Family History		x												
Comorbid Conditions		x												
Hypertension History		x												
PCC Seated/Standing BP		x		x										x
Complete Physical Exam		x												
Symptom-directed Exam				x										x
Background Questionnaire		x												
QOL + Pain Questionnaires				x										
MR/MRA (Study A Only)				x										
Interval History				x			x		x		x		x	x
Home BP Review				x			x		x		x		x	x
Review of Medications		x		x			x		x		x		x	x
Adverse Event History		x		x			x		x		x		x	x
Titrate Medication					start		x		x		x		stable	
Serum Creatinine[D]		x		x[E]										X[E]
Total Electrolyte Panel: Na, K, Cl, CO[2], BUN		x												x
Partial Electrolyte Panel: K, BUN, Creatinine[C]				x[A]		x[B]		x		x[B]		x		
Transaminases, Bilirubin, Alkaline Phosphatase		x												
Albumin, Calcium, Phosphorus		x												
Glucose[M]		x												
CBC with PLT		x												x
PCC Random/Spot Urine: Microalbumin + Creatinine		x												
β-HCG urine pregnancy[F]		x												
Digoxin				x[L]		X[B,L]		x[L]		X[B,L]		x[L]		
24-hr Urine Collection[H, #]		#		x[#]										x[#]
Genetic Sample[G]														x
Specimen Banking[I]				x										x[J]

A=At the B1 visit, K and BUN must be done at the PCC lab, but creatinine will be done centrally (see D and E).
B=Safety samples must be drawn for all participants at L2 and L4, and at L1 and L3 for Study B participants. (See Section 9.1.4)
C=May use outside lab during titration (L1-L4), if drawn at PI discretion, and after GFR <30 (potassium and serum creatinine required). D=PCC lab must be used at S visit, Cleveland Clinic (Quest, if necessary) for all other visits. Confirm baseline results before starting randomized drugs.
E=TWO samples drawn at B1 & F5 (>1 hour apart). At B1 ship same day to CCF. Repeat ASAP at CCF or Quest if results are >20% different.
F=All women of child-bearing potential at S visit, then only if a period is missed or pregnancy is suspected.
G=Optional blood sample. Participant must sign separate informed consent at the F5 visit agreeing to cell immortalization.
H= Urinary Aldosterone + Urine Chemistry samples (Na, K, creatinine, microalbumin) are batch-shipped to DLF at Harvard.
I = Archival blood (serum and plasma), shipped on cold packs on the day of collection, and archival urine (freshly voided and 24-hour collection, with and without boric acid), batch-shipped to the NIDDK Biosample Repository at Fisher BioServices.

^=Note that L4 is drawn TWO weeks after the final dose increment, instead of one week.
@=Results from labs (blood) drawn at PCC lab up to EIGHT weeks prior to the S/SB1 visit may be used as the S/SB1 lab results.

Table 5B: Schedule of Assessments - (following F5 Visit)

Visit Code	F7	F10	F12	F15	F18	F21	F24~	F36~	F48~[%]	F60~[&]	F72~[&]	F84[&]	F96[&]
Time Point	7 mo	10 mo	12 mo	15 mo	18 mo	21mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo	96 mo
Demographics													
Informed Consent													
Renal Disease History													
Family History													
Comorbid Conditions													
Hypertension History													
PCC Seated/Standing BP			x		x		x	x	x	x	x	x	x
Complete Physical Exam													
Symptom-directed Exam			x		x		x	x	x	x	x	x	x
Background Questionnaire													
QOL + Pain Questionnaires			x				x	x	x	x	x	x	x
MR/MRA (Study A Only)							x		x	X			
Interval History	x	x	x	x	x	x	x	x	x	x	x	x	x
Home BP Review	x	x	x	x	x	x	x	x	x	x	x	x	x
Review of Medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event History	x	x	x	x	x	x	x	x	x	x	x	x	x
Titrate Medication													
Serum Creatinine[D]			x		x		x	x	x	x	x	x	x
Total Electrolyte Panel: Na, K, Cl, CO[∠], BUN			x		x		x	x	x	x	x	x	x
Partial Electrolyte Panel: K, BUN, Creatinine[C]													
Transaminases, Bilirubin, Alkaline Phosphatase													
Albumin, Calcium, Phosphorus			x				x	x	x	x	x	x	x
Glucose[M]			x				x	x	x	x	x	x	x
CBC with PLT			x		x		x	x	x	x	x	x	x
PCC Random/Spot Urine: Microalbumin + Creatinine													
β-HCG urine pregnancy[F]													
Digoxin[L]			x		x		x	x	x	x	x	x	x
24-hr Urine Collection[H, #]			x		#		x	x	x	x	x	x	x
Genetic Sample[G]													
Specimen Banking[I]			x				x	x	x	x	x	x	x

C=May use outside lab if drawn at PI discretion and after GFR <30 (potassium and serum creatinine required).
D=CCF (or Quest, if necessary) must be used for all visits ≥B1. If doubling occurs, repeat within two weeks to confirm/deny increase.
F=Required for all women of child-bearing potential only if a period is missed or pregnancy is suspected.
H= Urinary Aldosterone + Urine Chemistry (Na, K, creatinine, microalbumin) are batch-shipped to UPCI at the University of Pittsburgh as of July 31, 2009.
I = Archival blood (serum and plasma), shipped on cold packs the day of collection, and archival urine (freshly voided and 24-hour collection, with and without boric acid), batch-shipped to the NIDDK Biosample Repository.
L=Participants on Digoxin must have levels tested every 6 months, and 1 week after changes in ARB/placebo. M=Glucose is random at all annual visits.
#=Containers and instructions for 24-hr urine collection may be sent home with participant for the next visit. ~After F24, continue 3 month phone calls, 6 month PCC visits as during the second year until the end of study.
Study A participants that extend beyond F48, obtain F60 MRI and continue follow up to F96 or until July 2014 as noted in section 10.1. Continue following all Study B participants through F96.
[&]Study B participants end with F96 visit or when the last participant enrolled has been followed for 60 months.

7. SCREENING

7.1. Pre-Screening Interview by Telephone and Registration

Participants referred by physicians or self-identified within the community will contact the nearest regional PCC via a toll-free telephone number. The Recruitment and Retention Study Coordinator at each PCC will conduct a brief ten-minute pre-screening interview over the phone, the purpose of which is to gather basic demographic information and to determine whether a potential participant should be excluded at this time (5.1 -5.4). Individuals currently on a BP drug for a non-hypertensive indication will be allowed to enroll in the study. If, after going over the inclusion/exclusion criteria, a potential participant appears to be eligible, the participant will be asked to contact the primary physician's office and request that required records be sent to the PCC – a copy of the most recent serum creatinine result, if available, *and* an ultrasound report or other diagnostic imaging report* confirming ADPKD, *and* documentation of high-normal blood pressure or hypertension (current use of blood pressure medication or readings $\geq$130/80 mm Hg on three separate occasions in the past year). Once these records have been received and reviewed by the study coordinator, all potential participants not excluded by major exclusion criteria from the list below will be scheduled for a screening visit, registered to the study, and assigned a HALT-ID. Total numbers of men and women completing pre-screening interviews will be reported to the DCC monthly.

**Imaging reports must be reviewed for all individuals. In addition, the original films must be reviewed if an imaging report shows <20 cysts present in an individual without a family history of ADPKD. The PI may also wish to review films for any individual if there is a question as to the diagnosis of PDK.*

Participants will be EXCLUDED if ANY of the following items apply:

1. <15 or >64 years of age
2. Absence of ADPKD documented by ultrasound, CT, or MR
3. GFR, predicted from the participant's most recent serum creatinine (if available) using the 4-variable MDRD equation, is out of range for a given age.*

   For participants 15-64 years of age, GFR <25 mL / min/ 1.73 m^2
   OR
   For participants >49 years of age, GFR >60 mL/min/1.73 m^2

   **Participants without a prior serum creatinine measurement will be invited to a Screening Visit as long as no other exclusion criteria apply. Participants may be screened even if most recent serum creatinine would predict borderline ineligibility, based on the discretion of the PI or co-investigator. In such cases, individuals may be screened without repeating outside lab work, but should be warned of potential ineligibility. If an outside or PCC creatinine is elevated due to some acute event, illness, or medication, a repeat value should be obtained after 2-4 weeks.*

4. Normotensive (<130/80 mm Hg and not currently taking blood pressure medication)
5. Diabetic requiring insulin or oral hyperglycemic agents
6. Currently on dialysis or functional kidney transplant or ESRD is anticipated within 6 months

Individuals who are ineligible will have the reason for their ineligibility explained to them and will be instructed to follow-up with their regular physician. Relatives of individuals with ADPKD who have never been diagnosed are also likely to phone the PCC for information. Such individuals will be directed to their primary care physician for further evaluation and discussion of the risks (insurability, preexisting conditions) and benefits of making a new diagnosis of ADPKD.

7.1.1. **Standardization of Conditions under which Serum Creatinine are Measured**

Study participants will be instructed to avoid medications that may alter renal hemodynamics or with potential nephrotoxicity (NSAIDS, antibiotics), or that alter serum creatinine independent of GFR (trimethoprim [Bactrim], cimetidine) for 1 week prior to all PCC visits. However, participants taking low dose aspirin (81 or 325 mg once daily) will be allowed to continue on this dose throughout the study as effects on renal hemodynamics are minimal. During the 24-hour period prior to each visit, participants will be instructed to refrain from eating large protein meals (i.e., >1.3 g/kg/d) and/or vigorous exercise. With regard to intake of water and other fluids, participants will be instructed to drink to thirst.

7.1.2. **Additional Instructions Given to Participants Prior to Screening Visits**

Participants will be asked to contact the study coordinator or PI immediately if any serious new medical event (i.e. hospitalization, infection requiring antibiotic use, new diagnosis of chronic disease, e.g. cancer) occurs between the screening phone interview and the Screening Visit in order that the visit may be rescheduled or cancelled. In addition, individuals will be instructed to bring their current medications *and* any medical records and/or imaging reports/films with them to the S visit if they were not forwarded to the PCC previously.

7.2. **The Screening Visit (S)**

A standard protocol will be followed for the screening visit. On the morning of admission to the GCRC (or other clinical facility at which study visits will occur) participants will meet with the PI, or his/her representative, who will summarize the purpose of the study, go over the commitments required of participants accepted to the study, and answer questions. The appropriate informed consent will be obtained before the Screening Visit begins. (Each PCC will obtain, according to its institutional policies, either one informed consent pertinent to the entire study, or two informed consents, one covering the Screening Visit and Drug Washout and one covering the Baseline Visit through the end of the study). Each participant is required to name a primary care physician (PCP), other than a study investigator, as indicated on the appropriate consent document. Any participant who does not have a PCP will be referred to one. Participants will also indicate on the consent document whether he/she authorizes HALT PKD to communicate with the named PCP. Such communication will consist of an initial letter informing the PCP of his/her patient's participation in the study and reports regarding any abnormalities or other concerns.

Past records, including laboratory results and imaging report(s), will be reviewed. A medical history and complete physical examination will follow, with blood pressure measured according to JNC VII guidelines [JNC VII, 2003]. Individuals currently on a BP drug for a non-hypertensive indication will be allowed to enroll in the study. However, individuals on a β-blocker or calcium channel blocker for a non-hypertensive indication must be on a small dose of the medication and must be approved by the principal investigator prior to being enrolled in the study. A background questionnaire will be completed. A complete blood count, serum electrolytes (sodium, potassium, chloride, total carbon dioxide), liver function tests, serum BUN, albumin, calcium, phosphorus and creatinine, fasting glucose and spot urine albumin-to-creatinine ratio will be sent to the PCC laboratory. Serum creatinine will be sent to the PCC laboratory for analysis at the screening visit, but for the baseline and subsequent PCC visits serum creatinine will be measured centrally at the Cleveland Clinic Foundation Reference Laboratory. Women of childbearing potential will be screened for pregnancy with a qualitative urine β-HCG test.

If results for required blood tests, run at the PCC lab, are available at the time of screening (S or SB1 visit) and are no more than eight (8) weeks old at that time, it is unnecessary to redraw

the samples. The following blood tests are required at screening: serum creatinine, complete blood count with platelets, serum electrolyte panel (sodium, potassium, chloride, total carbon dioxide), serum BUN, liver function tests (transaminases, bilirubin, alkaline phosphatase), albumin, calcium, phosphorus and fasting glucose.

*If a test result required for the S or SB1 visit was **not** obtained with the samples previously drawn at the PCC lab, it is necessary to draw blood at the S or SB1 visit for only those test(s) for which results are still needed. Samples will be collected for the S or SB1 visit only if results are not available, are >8 weeks old, or were not run at the PCC lab.*

If additional information is still required by the end of the screening visit or the participant wishes to discuss participation with friends and family, the study coordinator will follow up with the participant over the telephone to confirm eligibility. If the participant is eligible, drug washout may begin, with study medications being shipped to the participant as necessary. Consent for drug washout will have been obtained in person as part of the Screening Consent Form, and participants will have received an electronic blood pressure measuring device, as well as training for its use, at the screening visit. If there is a delay in obtaining the necessary information from which to establish eligibility (>8 weeks after the S visit for drug washout, >10 weeks after the S visit for randomization), the potential participant will be required to repeat the screening visit.

Participants excluded after the S Visit will have the reason(s) for exclusion explained to them, and will be informed of any concerning lab results. Participants will be encouraged to follow up with their primary care physician and/or nephrologist. If authorized, PCCs may inform physicians directly.

7.2.1. Study Arm Assignment based on Screening Serum Creatinine

Serum creatinine will be measured at the PCC laboratory during the Screening Visit and equated to GFR using the 4-variable MDRD prediction equation, with the result being used to determine study assignment (Study A vs. B). Participants treated with ACE-I or ARB will still be taking their respective therapies at the time the screening measurement is drawn; thus the true estimated GFR by MDRD will be, if anything, higher than that measured.

The recalibration of the serum creatinine method to the IDMS traceable standard gives lower serum creatinine values, and using the original MDRD formula with these values gives falsely higher eGFRs. Using the revised IDMS MDRD formula with IDMS values gives the correct eGFR, so use of the new GFR calculator will be required for all PCC and local lab serum creatinine values obtained at an institution that uses the IDMS traceable methodology.

In addition, PCC laboratories, though of high-quality, will not be calibrated to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) or to each other. It is recognized that this will lead to differences in study assignment at one PCC vs. another for participants with a GFR close to the cutoff (GFR 60 mL/min/1.73 m^2). However, the cutoff for study assignment is arbitrary; and a center-specific difference in study assignment for the few individuals with GFRs close to 60 mL/min/1.73 m^2 will not affect the internal validity of the study. The expense and time required to avoid this misclassification in study assignment for a small number of patients, which would require central measurements or calibration of PCC laboratories, is not felt to be justified.

If the screening GFR value is lower than 25 ml/min/1.73 m^2, the participant will be contacted immediately, informed of ineligibility status and instructed to resume the antihypertensive agents used prior to drug washout.

7.2.2. **Rescreening for Failure to Meet Eligibility Criteria at Screening Visit**

If, in the judgment of the study investigator, resolution of a reversible event is likely, then rescreening may occur within 4 months after screening. In all other cases, rescreening may occur only *after* an interval of 4 months.

1. Participants may be rescreened no more than two times (total of 3 attempts including initial failed screening), at a 4-month or longer interval, for the following reasons.

   a. PCC serum creatinine value (calculated GFR) out of range:
      Study A: ≤60 Study B: <25 or >60
   b. Albumin-creatinine ratio ≥0.5 for Study A, or ≥1.0 for Study B
   c. Fasting serum glucose ≥126 mg/dl or random non-fasting serum glucose ≥200 mg/dl

2. Women of child-bearing potential who test positive by qualitative β-HCG urine pregnancy test may be rescreened per protocol exclusion criteria, ≥6 months postpartum and not currently lactating or ≥2 months post miscarriage or abortion for pregnancies of <12 weeks duration.

3. Major abnormalities in parameters for routine (safety) labs (Na, K, Cl, CO2, BUN, transaminases, alkaline phosphatase, albumin, calcium, phosphorus, CBC w/ PLT) should be adjudicated, based on the rubric of "serious comorbid conditions," no more than 2 times (total of 3 attempts including initial failed screening).

   a. In cases of hyperkalemia *prior* to the use of study drugs (off ACE-I and/or ARB), participants may be rescreened, for potassium levels >5.0, at ≥4 month intervals.

   b. In cases of hyperkalemia while on ACE-I and/or ARB therapy, participants may be rescreened, for potassium levels >5.5, at ≥4 month intervals.

7.3. **Standardized Blood Pressure Measurements**

7.3.1. **Selection of Home BP Monitor and Cuff**

At the Screening Visit, each participant will be provided with an autoinflation, electronic blood pressure monitoring device (e.g., LifeSource UA767P) and instruction on how to use it. The appropriate cuff will be selected based on arm circumference. The width of the bladder should be 40% and the length 80% of arm circumference. The bladder of the Lifesource BP device is calibrated and indicates whether it is of appropriate size. A marker on the cuff also indicates where the brachial artery should be when placing the cuff. An instruction sheet on the proper placement of BP devices will be distributed to study participants. Participants who are determined to be ineligible to participate in the study prior to the B1 visit will be contacted by telephone and given instructions for mailing the machine back to the PCC.

7.3.2. **Arm for BP Measurements**

The non-dominant arm (in terms of handedness) will be used to obtain BP readings unless there is a reproducible (on at least three consecutive measurements) difference in systolic BP of 20 mm Hg or more between arms. If there is a reproducible difference in systolic blood pressure of 20 mm Hg or more between both arms, the arm with *the higher* blood pressure will be used. In all other cases, the non-dominant arm will be used. Both office and home BPs should be measured in the same arm.

7.3.3. **Procedure for Taking BP Measurements**

Due to the importance of obtaining accurate measurements for calibration of home BP monitors, a temporary method will be employed during the first several months of HALT PKD in order to establish a study threshold for acceptable variability. Once adequate data has been obtained to establish a threshold for acceptable variability, the temporary method of obtaining 6 sequential BP readings per visit will be replaced by a standardized procedure for measuring blood pressure at study visits. Participants will be trained to use the same standardized procedure at home.

7.3.3.1. Temporary Method for Measuring BP

Data will be gathered from 6 sequential BP readings, obtained at each visit, each alternating between the home BP device and a mercury sphygmomanometer. The readings obtained with the mercury sphygmomanometer must be recorded to within the nearest 2 mm Hg in order to reduce the effects of digit preference. If a mercury device is not available, the PCC may use a non-automated, aneroid device. The same monitor used to measure sitting blood pressure should be used to measure standing blood pressure.

7.3.3.2. Standardized Procedure for Measuring BP

After sitting quietly for at least 5 minutes with the arm resting at heart level, three readings will be obtained at least 30 seconds apart. If there is a difference of more than 10 mm Hg (systolic or diastolic) between the second and third readings in one sitting, a fourth and fifth reading will be recorded for that sitting. BP is not to be taken immediately after the participant awakens in the morning, due to BP surge, but is to be measured at least 30 minutes after awakening but before eating breakfast. Participants will also be instructed to abstain from smoking and consuming caffeine for 30 minutes prior to taking their BP measurements.

7.4. **Enrollment and Drug Washout (B0 visit)**

The purpose of the drug washout is to provide a baseline serum creatinine and urine albumin-to-creatinine ratio measured in the absence of ACE-I or ARB or other antihypertensive agents (e.g., vasodilators such as hydralazine, minoxidil and dihydropyridines) that may influence these values independently of renal function. In theory, the acute hemodynamic effects should have no bearing on the long-term outcome of Study B, but an estimate of baseline renal function devoid of significant hemodynamic-mediated effects of medications is desired, if possible.

If, prior to the conclusion of the Screening Visit, all required laboratory results from the PCC lab have been received and the potential participant is determined to be eligible for the study, the drug washout may follow directly from the Screening Visit. The participant will be enrolled to the study prior to the start of drug washout (visit B0). If a drug washout is not required, the participant may be enrolled and randomized to the treatment regimen as soon as eligibility is confirmed and the baseline visit has been completed.

At the B0 visit, the study coordinator will inform participants of their eligibility for Study A or B after review of the data from the Screening Visit (at the end of the visit or over the telephone within a few days of the visit). Individuals currently on a BP drug for a non -hypertensive indication will be allowed to enroll in the study. However, individuals on a β-blocker or calcium channel blocker for a non-hypertensive indication must be on a small dose of the medication and must be approved by the principal investigator prior to being enrolled in the study. Participants will be enrolled and instructed to stop taking existing antihypertensive medication and begin taking labetalol 100 mg po BID for

two-to-four weeks or, for participants with a contraindication to β-blocker therapy, clonidine at a starting dose of 0.1 mg po BID. Participants taking labetalol as their sole BP therapy will not require a drug washout. Participants taking a beta- blocker other than labetalol as their sole BP therapy will switch to labetalol for the washout period. Participants taking clonidine as their sole BP therapy will not require a drug washout. Those taking clonidine in combination with other BP therapies will discontinue other BP medications and continue taking clonidine alone and may have labetalol or other therapies added during washout, if necessary. For participants whose BP is very well controlled with relatively little medication, the PI will have the discretion to taper off existing medication during drug washout without using labetalol or clonidine. Those participants who taper off their BP medications during washout, but who are not on labetalol or clonidine, will be closely monitored.

Participants taking more than one medication prior to washout should have their medications discontinued gradually, according to standard clinical practice and the investigator's best clinical judgment. Clonidine will be tapered slowly over the course of several days to weeks (depending on the starting dose) due to the risk of rebound hypertension associated with its taper.

A higher dose of labetalol or the addition of clonidine may be needed for those participants who were on more than one antihypertensive medication or who had uncontrolled BP prior to washout, to be decided on a case -by-case basis by the PI. In addition, participants whose blood pressure cannot be controlled during the drug washout period with labetalol alone may have clonidine added subsequently. The two-to-four week drug washout period will be followed by the baseline visit to the PCC for randomization (see Section 8).

Participants will be instructed to measure blood pressure at a minimum frequency of every other day during the drug washout period. If blood pressure is >140/90 mm Hg, or symptoms of hypertension (e.g., headache, blurred vision) or hypotension (e.g., lightheadedness, fatigue) develop, or if there are intolerable side-effects of the washout medications, participants will be instructed to contact the study coordinator or PI and an immediate visit to the PCC for randomization will be arranged. Participants will also be provided with written guidelines instructing them to contact the PCC if their blood pressure is >140/90 mm Hg. If the participant is unable to be assessed at the PCC within 24 hours, blood pressure will be managed with increased labetalol and/or clonidine and/or other therapies (other than ACE-I or ARB), to be directed by the PI with close follow-up over the telephone until the next study visit. If, for some reason, the drug washout period is interrupted (i.e., the subject starts ACE-I or ARB), the drug washout may be restarted so long as the participant is able to be randomized within 8 weeks of the Screening Visit. After the Baseline Visit, labetalol/clonidine and/or other medications will be tapered off and discontinued, as study drugs are initiated and increased according to a stepped protocol (Section 9).

7.5. Dietary Instruction: Salt and Potassium Intake

All participants will be instructed to reduce their salt intake to <2.4 g (100mmol) per day or less. All participants will be instructed on a moderate potassium restriction (60-80 mmol per day). Protein and phosphate restrictions will be recommended as clinically indicated.

8. RANDOMIZATION AND BASELINE VISIT (B1)

8.1. Randomization

On completion of the drug washout period, participants will return to the study center for randomization, based on lab values and assessments obtained during the screening visit, and a Baseline visit (B1). If no drug washout is required, randomization may take place the same day as the screening visit. Study coordinators and investigators will provide information and answer questions relating to the process of informed consent, randomization, interventions, subsequent study visits and risks/benefits of participation in the study. After informed consent has been obtained (if applicable), an interval history and symptom directed physical examination will be performed and

participants will complete baseline questionnaires. Health status will be assessed at baseline using the Medical Outcomes Study Short-Form 36 Questionnaire (SF-36v2), a self-questionnaire that assesses physical, mental and social aspects of health-related quality of life. The HALT-PKD Pain Questionnaire will be used to measure pain and its impact on daily life. Blood will be drawn for potassium, BUN and creatinine and a 24-hour urine sample will be collected for aldosterone, creatinine, sodium, potassium, and albumin. Participants enrolled in Study A will undergo imaging exams at baseline: 1) MR to measure renal volume and liver cysts; 2) MRA to measure renal blood flow; and 3) cardiac MR to measure left ventricular mass.

At Baseline and throughout the study, PCCs will inform participants of any concerning lab values (per Table 9) or abnormalities found on MR scans and encourage them to follow up with the physician identified at the Screening visit as their primary care physician (PCP). When a participant is randomized, the HALT PKD investigator will send an initial letter to the named PCP to inform him/her of the patient's participation in HALT PKD. The participant will have indicated in the consent document, signed at the Screening visit, whether HALT PKD is authorized to communicate with the PCP. If participants have granted authorization, PCCs may directly inform PCPs of any abnormalities or concerns.

Study B participants, whose GFR is <30 mL/min/1.73 m^2 at the time of randomization, will be immediately referred to their primary nephrologist for more frequent follow-up than every 6 months (the HALT study visit frequency). Participants who start the study with GFR <30 mL/min/1.73 m^2 will also be required to obtain additional safety tests (serum creatinine and potassium) at 3-month intervals.

Participants failing to meet eligibility criteria at or before randomization, or who are deemed by the investigator to be unfit for randomization, are considered screening failures. The DCC is to be notified of such failures within three business days of site personnel becoming aware of them.

8.1.1. *Home Blood Pressure below Limit for Eligibility*

Participants who meet eligibility criteria for BP at the Screening visit, but whose subsequent self-taken, home BP measurements fall below the limit required for eligibility (<130 mm Hg), will be randomized and will start study medication at the lowest dose, with follow-up as outlined in the protocol.

8.2. Baseline Serum Creatinine Measurement

At the B1 visit two serum creatinine measurements, drawn a minimum of one hour apart, will be sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for analysis. Cleveland Clinic is standardized to the IDMS-Traceable calibration standard, and its core labs use the Roche Modular Analytics (Basel, Switzerland) instrumentation and reagent platform. Quality control is performed at a frequency that meets all regulatory requirements.

The average of the two serum creatinine measurements will be used to establish the baseline measurement. Participants will remain fasting (other than clear liquids) between venipunctures. The average of the two measurements drawn under the same conditions should reduce the variability due to laboratory error. We anticipate all participants will be in steady state after a two-week drug washout period, but the second laboratory measurement will confirm this.

A difference of 20% or less will be considered an acceptable level of agreement. If the two measurements differ by >20%, arrangements will be made for a second set of measurements to be drawn. For those individuals who live far from the PCC, the repeated blood samples will be drawn at a local laboratory and shipped by overnight mail to the central laboratory, or will be drawn and

analyzed at a Quest lab calibrated to the same standard as that of the central laboratory. Participants will remain on labetalol/clonidine and will not begin masked study medications until baseline creatinine has been remeasured according to the above procedure.

If there is still a difference of >20% in the results from the second set of samples, washout therapy will be discontinued and all medications will be returned to the PCC. The participant will not receive the treatment regimen, but will continue to be followed under intent to treat. At each visit after baseline, only one sample will be drawn for serum creatinine measurement. Back-up samples will be stored at the site until results are available. Blinded quality control samples will be collected on a random 3% of all samples. This same procedure for collecting two serum creatinine measurements will be repeated at F5 to provide a baseline measure after maximizing the ACE-I and telmisartan or placebo.

8.2.1. **Start of ACE + ARB (Visit B2)**

Participants will not begin masked study medications until the results of the two baseline serum creatinine measurements, confirming a difference of 20% or less, are received from the central laboratory. Once serum creatinine results have been received at the PCC, the study coordinator will contact participants by phone to instruct them to begin taking study medications (B2 visit). At this time labetalol (or clonidine) will be tapered off and discontinued.

8.3. **Urinary Aldosterone and Other Urinary Chemistry Levels**

To gauge the intensity of blockade of the RAAS, urinary aldosterone levels will be measured at baseline (B1), after maximization of study drug at 16 weeks (F5), at one year (F12) and annually thereafter. A standardized procedure for collecting 24-hour urine samples will be used. The 24-hour urine samples will be collected at GCRCs whenever possible. However, participants who are unable to collect their 24-hour urines at a GCRC may be given collection jugs at the preceding PCC visit (e.g., S for the B visit). The 24-hour collection will begin the day before the study visit date. All voids over the course of the next 24 hours, including the first void on the morning of the PCC visit, will be collected in the jug.

Twenty-four-hour urine samples will be sent for analysis only if collections meet the criteria for acceptability based on the mechanics of collection (MOP). If the 24-hour urine sample falls within the 75-125% range of predicted creatinine excretion, based on Walser formulas using actual body weight, it will be considered an adequate collection [Walser, 1987] for determination of aldosterone excretion rate. If a sample falls within the 50 -150% range of predicted, based on Walser formulas using actual body weight, it will be considered adequate to be used for determination of aldosterone to creatinine ratios.

One aliquot of urine, to be used for analysis of urinary aldosterone, will be transferred to a tube containing boric acid. A second aliquot will be used for central analysis of urinary sodium, potassium, creatinine, and microalbumin. Both samples will be frozen and batch -shipped on dry ice to a central laboratory (Diagnostic Laboratory Facility at Brigham and Women's Hospital, Boston, MA). Back- up samples will be stored at the site until results are available. Blinded quality control samples will be collected on a random 5% of all samples. Additional urine samples will be archived at the NIDDK Biosample Repository for future analysis.

8.4. Archived Samples/Specimen Banking

8.4.1. Genetic Sample (whole blood)

At the F5 visit, participants enrolled in HALT-PKD will be asked to provide a blood specimen for EBV transformation to be sent to the NIDDK Genetic Repository at Rutgers University for use in future studies related to kidney disease. Participants will have the option to refuse to provide genetic samples. For participants who agree to provide blood specimens for genetic analysis, it is suggested that a separate, written, informed consent be obtained. If a *separate* informed consent is not used, the participant's consent to provide this specimen must have been obtained previously as part of the overall study consent form. Genetic samples will **not** be obtained from participants who refuse cell immortalization. Briefly, three 8.5-mL Vacutainer tubes (ACD yellow-top) will be obtained from donors at the F5 visit. These will be coded and only the clinical center will have access to the names of participants. Whole blood samples will be sent to the Genetic Repository on the day of collection and, on receipt, will be stripped of identification codes and processed for future identification.

The Repository will initially cryopreserve cells from participants and will be making DNA when samples are received at the Repository. With the cryopreservation of cells, the Repository will not be making immortalized cell lines immediately, but will have the option of doing so in the future. Samples will be stored in such a way as to allow retrieval of aliquots upon the desire of the HALT-PKD Steering Committee and subsequently that of NIDDK.

8.4.2. Biological Samples (Serum and Plasma)

On the morning of the visit (B1, then annually), a maximum of 38 ml of whole blood will be collected and processed for the NIDDK Biosample Repository at Fisher BioServices. Twenty (20) ml will be collected in two SST tubes (tiger-top, 10 ml each) and 16 ml in two PST tubes (green/grey-top, 8 ml each). Samples will be centrifuged and shipped on cold packs to the NIDDK Biosample Repository at Fisher on the day of collection, where they will be aliquoted into 1 ml tubes and archived. Samples will be coded and only the clinical center will have access to the names of participants. If the serum/plasma samples are hemolized or otherwise lost or destroyed, they will be redrawn if the participant lives locally to the PCC.

8.4.3. 24-Hour Urine Archived Sample

Two aliquots from each participant’s 24-hour urine collection will be used for central analysis of urinary sodium, potassium, creatinine, microalbumin, and aldosterone (Section 8.3). Additional urine samples will be archived at the NIDDK Biosample Repository at Fisher BioServices for future analysis. Twenty ml of urine containing boric acid, and 20 ml of urine without boric acid will be aliquoted (into four 5ml tubes each), coded and batch-shipped to the repository. Only the clinical center will have access to the names of participants.

8.4.4. Fresh Urine Sample

On the morning of the B1, F5, F12, and subsequent annual visits, participants will be instructed to collect their second morning void (the first morning void having been collected as part of the 24-hour collection sample). Twenty (20) ml of urine will be collected (over a 2-3 hour period if necessary) and poured off into four 5ml tubes. These samples will be frozen and batch-shipped to the NIDDK Biosample Repository at Fisher BioServices to be archived for future analysis. Samples will be coded and only the clinical center will have access to the names of participants.

9. INTERVENTIONS

9.1. ACE-I/ARB Combination vs. Active Controls (Studies A and B)

9.1.1. Supply of Study Drugs

HALT PKD will procure open-label antihypertensive agents for study use, with the exception of lisinopril, which will be provided by the pharmaceutical company Merck. Masked study medications (telmisartan [ARB] and placebo) will be provided by the pharmaceutical company Boehringer-Ingelheim. HALT PKD will be responsible for packaging and distribution of the telmisartan/placebo. Each PCC will receive a supply of packaged, masked study medications (telmisartan and placebo) every six months, which will be stored on-site and distributed to participants, as needed. Each PCC will be supplied with bottles of lisinopril from Merck on an annual basis. No personnel from Boehringer-Ingelheim, Merck, or any other participating pharmaceutical company, had influence into the development of the HALT PKD protocol, nor do any pharmaceutical personnel sit on the HALT PKD Steering Committee.

9.1.2. Masking Study Drugs

While all participants will receive open-label ACE-I, investigators, study coordinators and participants will be blinded to the identity of the ARB/Placebo in both Studies A and B. The dispensing pharmacy will also be blinded to the identity of the ARB/placebo in both studies.

9.1.3. Dispensing Drugs

Once masked study medications have been manufactured by Boehringer-Ingelheim, they will be sent directly to Aptuit, Inc. (formerly Quintiles Clinical Supplies), for packaging. The study medications will be packaged in 32-count, double-foil, blistered drug cards containing either 40 mg tablets or 80 mg tablets. Each drug card will come with a double label, one to remain affixed to the card and one to be torn off and placed in the participant's research chart. Each label will include the dose strength, a unique ID number, and a dedicated space in which to write the participant's HALT-ID number and the date the card is dispensed. Once masked study medications have been packaged, they will be stored at Aptuit under controlled conditions, with the DCC informing Aptuit of the specific drug card ID numbers to be shipped to a specific PCC. Masked study medications will be shipped to the PCCs approximately every six months, and PCCs will remain blinded to the code.

Adequate supplies of study medications for the titration period will be dispensed to participants at the Baseline visit (B1), factoring in dose increments, to last until the next study visit (F5) at 4 months. Only 40 mg drug cards of telmisartan and placebo will be dispensed for the titration period. Those participants titrating to the 80 mg strength will be instructed to take two 40 mg tablets. Participants will be instructed not to take ACE-I or masked study medication until the results of the two serum creatinines drawn at baseline are available from the central lab. Once these results have been received and it is verified they are within the acceptable level of agreement (<20% difference), the study coordinator will contact the participant by telephone to instruct him/her to begin taking study medications (B2 visit).

Lower doses of study medications will be available at each PCC for participants who are intolerant of the starting dose (see 9.2.5). Pediatric participants weighing 40 kg will receive adult doses of study medications. For pediatric participants weighing <40 kg, the only agent that will need to be reduced is hydrochlorothiazide, which is an open-label therapy.

9.1.4. **Titration of Study Drug**

Study medications will be initiated at the B2 visit and dose incremented every two weeks until the maximal dose is achieved, unless the participant is symptomatic of hypotension (Studies A and B) OR blood pressure is below the accepted, targeted range – standard BP group: 120-130/70-80 mm Hg; low BP group: 95-110/60-75 mm Hg (Study A). At two-week intervals, the study coordinator will contact participants by telephone (F1-F4 visits) and, after reviewing lab results and home blood pressure records from the prior two-week interval, will instruct them to increase study drugs. As only 40 mg tablets of telmisartan or placebo are being dispensed for the titration period, the study coordinator will instruct participants titrating to 80 mg of telmisartan or placebo to take 2, 40 mg tablets. At all visits, coordinators must confirm the start date of the previous dose increment, especially the start of ACE-I/ARB at B2. Assuming dose increments at 2-week intervals, the study drug is expected to be at maximum dose 8 weeks after randomization.

Participants will be instructed to take study medications in the morning and monitor blood pressure at least every four days during the study drug titration period, with study medications being incremented ahead of schedule, per the stepped protocol, for participants whose blood pressure is out of range or who experience symptoms of hypertension. Participants will be asked to bring all packages of study medications with them to the PCC for subsequent visits.

Serum potassium, creatinine, and BUN must be measured, at the PCC or a local lab, one week after the specified dose increments, with results from outside laboratories being faxed or communicated electronically to the PCC. Safety labs are not required if the dose is not increased. For participants enrolled in Study B, safety samples will be drawn after *every* dose increment, expected to occur at weeks 1, 3, 5, and 8 (L1-L4). For participants enrolled in Study A, safety samples will be drawn after every *second* dose increment, expected to occur at weeks 3 and 8 (L2 and L4). Safety samples must be collected no later than 14 days after the dose increment and the PI must review results prior to the next dose increase. Safety samples must be collected, at *minimum*, as specified above. However, depending on the participant's baseline potassium and kidney function and on how quickly the dose is escalated, safety samples may be collected more frequently than the minimum required, per the discretion of the investigator.

9.1.4.1. **Shortened Titration of Study Medications for Participants with Difficult-to-Control Blood Pressure**

For individuals with difficult-to-control blood pressure, study medications (ACE plus ARB/placebo) may be started at a dose step higher than the first, at the discretion of the PI. It is clearly preferable to use more than one dose step to achieve the targeted BP goal, as opposed to starting with too high a dose step, as the latter may precipitate hypotension or hyperkalemia. The schedule of safety labs will be different for those participants who start at a dose higher than Step 1 if enrolled to Study A, but will not change if enrolled to Study B. Labs are to be drawn one week after each dose increment whenever a step is skipped, regardless of enrollment to Study A or Study B. This is felt to be sufficient for the full therapeutic effect of the drugs to be apparent.

9.1.5. **Protocols for Study Drug Titration and Addition of Open-Label Therapies**

Study drugs and additional antihypertensive agents will be added in a stepped fashion according to the protocols shown in Table 6A (Study A) and Table 6B (Study B). The gray areas indicate masked study drugs, with all other medications being open-label. Study drugs will be maximized as tolerated while ensuring blood pressure does not fall below the lower limit of the targeted range. Home blood pressure records from the prior two week

period will be reviewed at each telephone visit to guide subsequent therapy. If blood pressure remains above the target after the study drug is maximized (8 weeks), open-label therapies will be added according to the protocol. For participants in whom any of the open-label medications (Steps 5-10) are contraindicated, the contraindicated medication may be skipped (e.g., metoprolol [generic] if contraindication to beta-blocker).

Table 6A: Protocol for Addition of Antihypertensive Agents in Study A

Step	Treatment		Control	
1-4	Combination ACE-I/ARB *ACE-I/* Lisinopril 5mg/ Lisinopril 10mg/ Lisinopril 20mg/ Lisinopril 40mg/	Combination ACE-I/ARB *ARB* Telmisartan (Micardis®) 40mg Telmisartan (Micardis®) 40mg Telmisartan (Micardis®) 80mg Telmisartan (Micardis®) 80mg	*ACE-I/* Lisinopril 5mg Lisinopril 10mg Lisinopril 20mg Lisinopril 40mg	*Placebo*
5	Hydrochlorothiazide 12.5 mg qd*		Hydrochlorothiazide 12.5 mg qd*	
6-8	Metoprolol (generic) 50 BID Metoprolol (generic) 100 mg BID Metoprolol (generic) 200 mg BID		Metoprolol (generic) 50 mg BID Metoprolol (generic) 100 mg BID Metoprolol (generic) 200 mg BID	
9 onwards	Non-dihydropyridine and dihydropyridine calcium channel blockers (diltiazem), clonidine, minoxidil, hydralazine at discretion of investigator		Non-dihydropyridine and dihydropyridine calcium channel blockers(diltiazem), minoxidil, clonidine, hydralazine at discretion of investigator	

Gray indicates masked study drugs. *For pediatric participants weighing <40 kg, hydrochlorothiazide needs to be reduced.

Table 6B: Protocol for Addition of Antihypertensive Agents in Study B

Step	Treatment		Control	
1-4	Combination ACE-I/ARB *ACE-I/* Lisinopril 5mg/ Lisinopril 10mg/ Lisinopril 20mg/ Lisinopril 40mg/	Combination ACE-I/ARB *ARB* Telmisartan (Micardis®) 40mg Telmisartan (Micardis®) 40mg Telmisartan (Micardis®) 80mg Telmisartan (Micardis®) 80mg	*ACE-I/* Lisinopril 5mg Lisinopril 10mg Lisinopril 20mg Lisinopril 40mg	*Placebo*
5-6	Furosemide 20 mg - 40 mg BID		Furosemide 20 mg - 40 mg BID	
7-9	Metoprolol (generic) 50 mg BID Metoprolol (generic) 100 mg BID Metoprolol (generic) 200 mg BID		Metoprolol (generic) 50 mg BID Metoprolol (generic) 100 mg BID Metoprolol (generic) 200 mg BID	
10 onwards	Non-dihydropyridine and dihydropyridine calcium channel blockers, clonidine, minoxidil, hydralazine at discretion of investigator		Non-dihydropyridine and dihydropyridine calcium channel blockers, clonidine, minoxidil, hydralazine at discretion of investigator	

Gray indicates masked study drugs.

9.2. Controlling Blood Pressure

9.2.1. Achieving Targeted Level of Blood Pressure Control with Home Blood Pressure Monitoring

Maintaining separation between the standard and low blood pressure groups is critical for studying the effects of BP control on cystic progression (Study A). Thus, blood pressures will be monitored at home and at the PCC throughout the study. Home readings will be used to guide medication increments/additions because PCC blood pressure readings are likely to be systematically higher, and it will be difficult to obtain more frequent PCC readings for participants living long distances from the PCC. Precedence exists for using home blood

pressure readings to achieve separation between blood pressure targets, similar to those in the present study, in ADPKD patients. The University of Colorado conducted an RCT to assess the effects of two different levels of blood pressure control on left ventricular hypertrophy and renal progression. Good separation between the blood pressure targets was achieved and maintained over a 7-year period through home BP monitoring [Schrier, 2002]. Participants were initially contacted weekly until control was achieved, after which contact was made monthly during the first year and every 2 months thereafter to the end of the 7-year study.

9.2.1.1. Frequency of Home Monitoring

The frequency of BP measurements, however, will differ at different stages of the study. Blood pressure measurements to titrate antihypertensive medications will be obtained during the washout period (at least every other day), titration period (at least every four days) and through the duration of the study (at least monthly), as described subsequently. Participants will be given a log in which to record BP readings and dates and times of measurements.

9.2.2. Frequency of Home Blood Pressure Monitoring and Schedule of Dose Adjustments

Table 7 summarizes targeted blood pressures at different time points in the study, frequency of home monitoring, and measures to be taken if blood pressure falls outside the targeted goals. In general, if BP is below the accepted range, the prior step in the ordered protocol for titration and addition of antihypertensive agents is followed. If BP is too high, the subsequent step of the ordered protocol will be followed.

Table 7: Blood Pressure Control over the Course of the Study

Time (visit #)	*Phase of Study*	*Minimum Frequency of Home BP Readings*	*Minimum Follow-up with Study Personnel*	*Targeted BP (mm Hg)*	*BP at which Participant Calls Study Coordinator (mm Hg)*	***Urgent Intervention Required***
-2 to 0 weeks (B0- B1)	*Drug Washout*	*Every other day*	*At the B1 Visit.*	*≤140 / 90*	*>140 / 90 OR symptoms of hypertension or hypotension#*	***If Blood Pressure is Elevated:*** *a. Increase dose or add medications b. BP monitoring daily c. Immediate visit and randomization d. If c not possible, restart therapy (other than ACE-I, ARB, CCB) e. Retry washout if possible* ***If Symptomatic Hypotension:*** *Reduce/discontinue per PI discretion*
0 to 9 weeks (B2-F4 or stable BP)	*Study Drug Titration*	*Every four days*	*Every 2 weeks, or weekly if necessary*	*≤140 / 90; closer to target by F4 visit*	*>140 / 90, OR symptoms of hypertension or hypotension#*	***If Blood Pressure is Elevated:*** *a. Increment study drug ahead of schedule b. If study drug(s) maximized, proceed to next step of protocol (open-label agents)* ***If Symptomatic Hypotension or BP Below Targeted Range:*** *Return to prior step*
> 9 weeks (F4 to the end of the study)	*Follow up*	*Weekly until at target, then Monthly*	*Every 3 months, or more often per PI discretion*	*See 9.2.4 for targeted standard or low BP ranges*	*Average of the last 2 out of 3 home BP readings in a single sitting outside accepted range (9.2.4)*	***If Blood Pressure is Elevated:*** *a. Add /increment agent(s), per next step of protocol, until target reached b. Close follow-up by PCC c. If BP does not respond to added agents, urgent visit to PCC may be necessary per discretion of PI*

						If Symptomatic Hypotension or BP Below Targeted Range: Return to prior step

[#]Symptoms of hypotension: lightheadedness, fatigue, malaise; Symptoms of hypertension: headache, blurred vision, malaise, fatigue.

9.2.3. **Definition of Uncontrolled BP Used for Dose Adjustment**

During the drug washout period and titration period, if a *single* BP reading exceeds 140/90 mm Hg, blood pressure is considered to be out of control. For out of control BP during the drug washout period, participants will be instructed to increase the dose of labetolol (or clonidine) or add other medications, monitor BP daily, and arrange an immediate visit to the PCC for randomization. Participants will be provided with written guidelines instructing them to contact the PCC if their blood pressure is >140/90 mm Hg. During the titration period, participants will be instructed to call the PCC, at which time medication will be increased ahead of the next scheduled titration. During the titration phase (B2 to F4), if BP remains above the targeted *goal* but $\leq$140/90 mm Hg, doses will be titrated at two-week intervals until the BP target is reached or the study drugs are maximized.

After the titration period (F4 to the end of the study), if the mean of the last 2 out of 3 readings in a single sitting is above the targeted range for either the systolic and diastolic readings of the respective study group, blood pressure is considered to be out of control. Excluding the first reading, if there is an unacceptable level of variability between the last two readings (>10 mm Hg difference in systolic or diastolic), the measurements of that sitting will not be counted. At PCC visits, the last two readings will be repeated. Participants measuring their blood pressure at home will record a fourth and fifth reading for that sitting and the average of the last four readings (2- 5) will then be the official reading for that sitting. Participants whose BP is out of control will be instructed to call the PCC, and open-label therapies will be added in a stepped fashion. For very out -of-control BP that does not respond to additional antihypertensives, an urgent visit to the PCC may be required, to be decided on a case-by-case basis by the PI.

9.2.4. **Frequency of Home BP Monitoring and Dose Adjustments after Masked Drug Maximized**

Frequency of Home Monitoring: After the blood pressure target has been reached, anticipated by F4, participants are to check BPs at home twice daily for 7 consecutive days (i.e., 14 readings) during the month prior to every PCC visit. BP is to be measured before breakfast, but 30 minutes after waking, and before the evening meal. Ten is the minimum number of readings considered acceptable. If a participant does not meet the minimum number of readings prior to the PCC visit, he/she will be asked to obtain readings over one week within the month immediately after the PCC visit, with dose adjustments then being made based on the average of these home BP measurements. The participant will be considered non-compliant if, in the month after the PCC visit, he/she does not obtain the minimum number of readings over the course of one week. The official blood pressure reading used for dosing at the PCC visit will be defined as the average of the readings for the week (last 2 out of 3, or last 4 out of 5) and will be computed for that individual at the specified visit.

All BP readings taken by the participant each month between the F5 and F10 visits will be collected, averaged, and data-entered by study coordinators at the F7 and F10 telephone visits. This will allow investigators to monitor BP during the eight-month interval between the F5 and F12 clinic visits.

Dose Adjustments: The range of BP readings that will be accepted as the standard and low BP targets for Study A follow below. The BP targets for Study B also follow below.

	Target	Accepted Range (mm Hg) Systolic	Diastolic
Standard BP Study Arm (1/2 Study A)	≤130/80	120-130	70-80
Low BP Study Arm (1/2 Study A)	≤110/75	95-110	60-75

	Target	Accepted Range (mm Hg) Systolic	Diastolic
Standard BP (all Study B)	≤130/80	110-130	80

In general, if either the systolic, diastolic or both readings are out of range for the average of the last two out of three readings (or four out of five) within a single sitting (at home), a dose adjustment will be made. A wider range of diastolic blood pressures may need to be accepted in order to keep the systolic blood pressure in the desired range, to be decided at the discretion of the PI on a case-by-case basis.

Dose adjustments are ***not*** to be made if BP measurements at a PCC visit show elevated readings. Rather, the participant should be instructed to take BP readings at home, after the PCC visit to confirm or deny the need for dose adjustment.

In some cases, BP levels in Study A participants may be above the desired range at one step and below the range on the next higher step. In other cases, systolic BP may be within or below the range but diastolic BP may be above the range. Tables 8A and 8B below include suggested guidelines for dosing in such instances:

Table 8A – Suggested Guidelines for Dosing Study A – Standard BP Range (120-130 mm Hg systolic and 70-80 mm Hg diastolic)		
Systolic	**Diastolic**	**Action**
125-130 mm Hg	>80 mm Hg	Increase dose
120-124 mm Hg	>80 mm Hg	Maintain same dose
114-119 mm Hg*	>80 mm Hg	Maintain same dose*
114-119 mm Hg*	70-80 mm Hg	Reduce dose*
<114 mm Hg*	Any	Reduce dose*

Table 8B – Suggested Guidelines for Dosing Study A – Low BP Range (95-110 mm Hg systolic and 60-75 mm Hg diastolic)		
Systolic	**Diastolic**	**Action**
100-110 mm Hg	>70 mm Hg and participant has no symptoms of hypotension	Increase dose
95-100 mm Hg	≥60 mm Hg	Maintain same dose

***Note:** When a reduction of medications is needed for a Study A participant because BP is below range, the PI can use his or her discretion to decide whether to decrease the open -label medication (lisinopril) by a full step or by only a half step. This will be necessary in some cases to ensure that BP is within the desired range.

Half-Step Dose Reduction – If a scheduled dose increase for a Study A participant results in a level of BP significantly below the lower limit of the targeted range, investigators will have the discretion to *reduce* the dose of open-label medication by a half step, as appropriate, to achieve a level of BP that is either within the targeted range or much closer to the lower limit

of the targeted range than the previous dose increment allowed. As the goal for the low BP group in Study A is not only to get BP within target, but also to optimize blockade of the renin angiotensin system (RAAS); the investigator may increase study medication a step further once a participant in the low BP group reaches the targeted range (95-110/60 -75 mm Hg), as long as BP stays within the targeted, or acceptable, range, study medications are well tolerated and symptoms of hypotension are not present.

Half- Step Dose Increase – In a case in which a participant's BP is not perfectly within range (e.g., systolic in range, diastolic a bit above target), but may almost be there, investigators will have the flexibility to *increase* open-label study medication by a half-step in order to achieve the goal of getting participants within the correct BP range. The investigator will also have the discretion to use a half-dose as the first step for participants who, prior to enrolling in the study, were on only one anti-hypertensive medication at a low dose. In such a case the participant will start with a half-dose of lisinopril (2.5 mg); and if the participant's BP is then not in range, lisinopril will be increased to the full dose for Step 1.

In Study B, more steps of the ordered protocol will be needed to achieve the targeted BP of 130/80 mm Hg. Blood pressure medications will be titrated up for Study B participants, per the stepped protocol for study medications, until BP is at target. Investigators will try to achieve the target for both systolic and diastolic BP, but the preference will be given to systolic. Once BP is at target (130/80 mm Hg) study medications will be stopped and not pushed further. A lower limit of 110 mm Hg for systolic BP will be in effect, so the acceptable range for BP in Study B will be 110-130 mm Hg systolic. For those with systolic BP below 110 mm Hg and diastolic BP in range (at or below 80 mm Hg), the investigator will cut study medications back so systolic stays above 110 mm Hg. If a participant has systolic BP at 110 mm Hg or above and diastolic BP above 80 mm Hg, the investigator may choose to push study medication further. These types of cases would likely be rare. In anticipation of greater difficulty and increased length of time to achieve the targeted level of blood pressure control, the frequency of home monitoring and study visits will be the same as in Study A.

Contact with PCC for Review of Home BP: Blood pressure logs will be reviewed with the coordinator every three months by telephone or will be reviewed at the PCC if the three-month period coincides with a study visit. Participants will visit the PCC at the fourth month in the first year, at which point BP is anticipated to be in the targeted range for the majority of participants. Subsequent PCC visits will occur 12 months after baseline and every 6 months thereafter. Contact may be required weekly for participants with difficult-to -control BP. For patients with BP elevated above the target, additional antihypertensives will be added, according to the stepped protocol, with close follow-up by the PCC, until the targeted BP is achieved. For very out-of-control BP that does not respond to additional antihypertensives, an urgent visit to the PCC may be required, to be decided on a case-by-case basis by the PI.

9.2.5. **Management of Hypotension**

Low blood pressure will be defined by symptoms (e.g., lightheadedness) deemed intolerable by the participant or by blood pressure below the accepted range for the targeted goal. The following changes in study drugs will be made if hypotension persists:

i) lisinopril will be reduced by half (from 5 mg to 2.5 mg). If hypotension persists,
ii) lisinopril will be stopped. If hypotension persists,
iii) masked study medication (telmisartan or placebo) will be stopped.

For Step 1, the participant will be instructed to cut the lisinopril tablet in half; or if the participant is unable to do such, 2.5 mg tablets will be sent by overnight mail.

9.2.6. **Procedure for Measuring Office BP**

The same procedure as that used for home BP monitoring will be used to measure BP at the PCC. For the purpose of safety, a standing BP will be obtained at every PCC visit and compared with the sitting BP. If BP drops >20 mm Hg from sitting to standing, consideration will be given to reducing study drugs, irrespective of symptoms.

9.2.7. **Calibration of Home BP Monitors**

Participant BP technique is to be reviewed and home BP monitors are to be recalibrated, using the method described below, each time the participant visits the PCC.

1) Ascertainment of BP using A&D calibration test meter (CTM) connected to home monitor – The long end of the black hose from the CTM will be plugged into the Home BP unit, while the cuff from the Home BP monitor will be plugged into the short end of the black hose. The blood pressure cuff will then be placed onto the participant's arm, and the start buttons of the CTM and Home BP unit will be pressed. Both devices will perform the BP measurement automatically, presenting the results on the LCD display of each device. The results will be compared; and if the difference between the two exceeds 2 mm Hg (systolic or diastolic), measurements will be taken again after a wait of at least 30 seconds. If the subsequent measurements differ by 4 mm Hg or greater, the investigator may choose to replace the Home BP device and repeat the process.

2) Optional Pressure reading – Y-tubing connects the cuff and Digimano 1000 monitor (AME Corporation, Corona, California). The cuff is inflated to 220 mm Hg on a dummy arm (Styrofoam cylinder) and the decline across instruments is observed. No greater than 3 mm Hg difference between the device and electronic BP will be deemed acceptable. If a difference of >3 mm Hg is found, the home BP device will be returned to the vendor, BV Medical, for recalibration and replaced with a new monitor. The Digimano will be sent to AME once per year to ensure its calibration. Calibration information for the Digimano must be maintained locally at each PCC and will be audited during site visits.

9.2.8. **Calibration of Office BP Monitor (Dinamap*)***

Each PCC will use an auto-inflation electronic device (e.g., Dinamap) to obtain BP measurements from participants at their office visits. During each clinic visit, BP measurements will also be obtained using the participant's home BP monitor, which will itself be calibrated using a calibrated test monitor (CTM), as described above in Section 9.2.7. The home BP monitor may also be calibrated with a Digimano device, as described above; although such calibration with the Digimano is considered optional. Although home BP is not actually calibrated to the Dinamap, these measurements, taken at nearly the same time, should be quite adequate to allow for quality control of the correlation between the two devices. Clinical sites are to calibrate the Dinamap device per each institution’s policy. It is recommended that this be done at least annually, or more frequently for heavy use or if the unit is dropped. If the Dinamap measurements are systematically different than those obtained with the home BP device, the Dinamap should be calibrated. Measurements taken with the home BP monitor and calibration devices will not be submitted to the DCC, but should be recorded locally and made available for audit.

9.2.9. **Discrepancy between Home and Office BP Readings**

Participants will be observed taking their own BP measurements at the clinic. These measurements, obtained by participants, will then be compared with BP measurements taken by the nurse in the clinic. Four situations may arise:

Improper technique – Improper technique is implied when there is disagreement in the measurement between participant and nurse in the clinic using the same device. The participant is retrained and the coordinator will follow-up with readings taken over the subsequent four weeks.

Home BP monitor is not in calibration **–**The participant is provided with a new device and the coordinator will follow-up with readings taken over the subsequent four weeks.

White-coat hypertension – If BP is controlled at home but higher than home readings and the targeted range when taken by the nurse in clinic, calibration of the home monitor will be checked. If this is not the explanation for discrepancies in readings, the participant's technique in taking BP with the home monitor will be reviewed. If self-measured BP in the clinic, using the participant's home monitor, is higher than the home readings, this is suggestive of white-coat hypertension; and 24-hour ambulatory blood pressure (ABP) monitoring may be arranged, at the discretion of the PI. Results from 24-hour ABP monitoring will be retained in the participant's research chart. White-coat hypertension is confirmed if the 24-hour ABP monitoring shows blood pressure readings similar to those reported by the participant, using the home monitor, and systematically lower than those taken in clinic. Again, the home monitor readings are considered the official BP readings in such participants, and titration of antihypertensives should be made on the basis of these readings, *not* the office readings. Alternatively, the PI may ask the participant to obtain further readings at home over the course of the following week.

Non-compliance – If BP is controlled at home but high when taken by the nurse or self-measured in the clinic, non-compliance is implied. The investigator may choose to verify implied non-compliance via 24-hour ABP monitoring. Results from 24-hour ABP monitoring will be retained in the participant's research chart. If it is determined that a participant is non-compliant, such non-compliance will be documented as a protocol violation. A non-compliant participant is to continue taking home BP readings; but the official BP readings used to gauge adequacy of control and titration of medications will be based on BP readings obtained at the PCC from this point onwards.

Table 9: Summary of Procedures for Blood Pressure Measurements at Home and at the PCC

	BP Device	**Training**	**Calibration**	**Procedure**
Home	Auto-inflation electronic device (LifeSource)	Study coordinator at screening visit	Machine recalibrated at each study visit	Seated position after 5 min rest. 3 readings, at least 30 seconds apart.
PCC	Auto-inflation electronic device (Dinamap)	Training certification annually	Machines calibrated per individual PCC policies	Seated position after 5 min rest. 3 readings, at least 30 seconds apart.

10. **FOLLOW-UP VISITS**

10.1. **Follow-up Study Visits**

After the first year, study visits at the PCC will occur every six months until the end of the study, the purpose being to monitor/manage blood pressure, record outcomes, and maintain interest in the study. At each study visit, an interval history will include review of unscheduled medical encounters, hospitalizations, start of dialysis, or transplantation. Adverse drug events will be ascertained using a standardized questionnaire. Health status will be assessed annually using the SF-36v2. The HALT- PKD Pain Questionnaire will be used to measure pain and its impact on daily life. Blood pressure measurements and an interval physical examination will follow.

Study A participants will be asked to continue beyond follow up visit 48 for an additional year (F60). All participants will continue on study until July of 2014, even if they reach their 60 month visit at an earlier date. An extended follow up period is being added to allow for a longer timeframe to study changes in TKV, eGFR and other endpoints. Participants will be asked to continue in the study and sign the addendum to the consent form. Study visits, treatment and medications will remain the same and an MRI will be performed at 60 months.

Study B participants will be asked to continue until the last clinic visit prior to the July of 2014 time point (F60-F96 expected visit ranges). An extended follow up period is being added to allow for the prospective evaluation of participants for a minimum of 60 months. Participants will be asked to continue in the study and sign the addendum to the consent form. Study visits, treatment and medications will remain the same.

The following laboratory measurements will be obtained at study visits:

Semi-Annual Visits (6-month): CBC with platelets, serum electrolytes, BUN (PCC lab). Serum creatinine (central lab) is to be repeated within two weeks of initial doubling to confirm/deny increase. Two central serum creatinine samples, drawn 1 hour apart from each other, will be collected at the F5 visit at month 4 and shipped to CCF within two weeks. If the two measurements differ by >20%, arrangements will be made for a second set of measurements to be drawn.

Annual Visits (12 -month): As above plus random glucose, albumin, calcium and phosphorus. Twenty -four-hour urine collection for sodium, potassium, creatinine, albumin and aldosterone (central lab). Biological samples, including serum and plasma, aliquots of fresh urine and 24-hour urine as described in Section 8.4.

Pregnancy testing will be carried out in women of child-bearing potential only if there is a missed menstrual cycle. MR, MRA and cardiac MR studies will be obtained for Study A participants at the 24 month visit, the 48 month visit and at the **60 month visit.**

10.2. **Quest Visits in Lieu of PCC Visits, as Necessary**

After the first year of the study, if a participant *cannot* return to the PCC for a 6-month or 12-month visit, a Quest visit, conducted by phone within $\pm$3 months of the target visit date, can be accepted in lieu of the PCC visit. All possible required data will be collected from the participant, with all required labs being collected at a local Quest laboratory. For Study A participants, imaging scans should occur as near as possible to Months 24 and 48 and 60, $\pm$ 6 months of the target visit date. For Study B participants it is important to obtain centrally processed serum creatinine labs.

Quest visits in lieu of PCC visits will be used as a *last resort*, reserved for those cases in which a routine clinic visit would be an *undue burden* for a participant. Participants will be allowed no more than one Quest visit within a 12 month period. If a Quest visit is necessary, the preference will be to obtain such in lieu of a 6-month visit (e.g., Q18), rather than a 12-month visit (e.g., F24).

Calibration of the home BP monitor will be waived for Quest visits, as this omission introduces minimal added risk of collecting inaccurate blood pressure readings from participants.

10.3. Blood Pressure Control

10.3.1. Lifestyle Measures for Improving Blood Pressure Control

Coordinators will regularly counsel participants regarding lifestyle measures to improve blood pressure control, as per guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [JNC VII, 2003].

Participants will be instructed to reduce salt intake to less than 100 mmol/day and participants with a BMI >27 kg/m^2 will be provided with dietary instructions to promote weight loss. Participants will be encouraged to participate in some form of exercise for at least 30 minutes for most days of the week.

10.3.2. Long-term Blood Pressure Management

Participants will be instructed to continue monitoring BP readings at least once a month after targeted control has been achieved and to continue reviewing BP records with the study coordinator by telephone every three months for the duration of the study. All BP readings taken by the participant each month between the F5 and F10 visits will be collected, averaged, and data-entered by study coordinators. At F7 (telephone visit) study coordinators will collect, average, and data-enter all BPs taken during the two months prior to that visit. At F10 (telephone visit) all BPs taken over the three months preceding that visit will be collected, averaged, and data-entered. This will allow investigators to monitor BP during the eight-month interval between the F5 and F12 clinic visits. Additional antihypertensive agents will be added from the stepped protocols, as needed. The frequency of home blood pressure monitoring and of study visits may be increased, at the physician's discretion, for individuals whose blood pressure is 'out of control' at any point in the study.

10.4. Management of Other Risk Factors for Progression of Renal Disease

Smokers will be identified at the screening visit via self-reported questionnaire. Participants will be referred to their primary care physician for smoking cessation counseling and therapy. Study personnel will provide support and encouragement to participants at each visit to help motivate them to stop smoking. Lipid management will be left to the primary care physician or nephrologist. Per the National Kidney Foundation's K/DOQI Guidelines [K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002], management will be recommended specifically to target an LDL cholesterol of <100 mg/dl using HMG-CoA reductase inhibitors after dietary interventions.

11. MEASUREMENT OF PRIMARY AND SECONDARY OUTCOMES

11.1. Primary Outcome Study A: Percent Change in Kidney Volume by MR Over Time

The primary outcome of Study A is the percent change in total kidney volume as assessed by MR at baseline, 24 and 48 and 60 months follow -up. MR images will be obtained at each PCC using the procedures described below. After the acquisition, MR images will be reviewed locally at each PCC site and securely transferred via secure internet connection to the Image Analysis Center (IAC). The procedures for MR scanning of the heart (HALT study only), kidneys and liver are as follows:

Before each study, the MR scanner will be adjusted for proper shimming.

1. Breath-holding instruction will be provided, and the subject will be coached prior to MR

scanning. Administration of oxygen via nasal cannula may help improve the breath-hold capacity, particularly for subjects with limited breath-hold capacity.

2. EKG pads will be placed over the chest. If EKG gating is not available or functioning, it may be replaced with a peripheral pulse gating.

3. Subject will be placed supine on the MR table with his or her arms to the side.

4. (HALT only) A phased-array surface coil will be positioned with its center over the heart. For a MR scanner with a moving table technology, a second surface coil will be positioned with its center over the inferior costal margin, i.e. over the expected location of the kidneys.

5. (HALT only) Cardiac-gated, breath-hold 2D true-FISP (FIESTA) short-axis cine images will be obtained to cover the left ventricle from the AV ring to the apex (10 mm slice thickness, no gap, FOV 250-320 mm; typically 10-15 breath-holds to cover the whole left ventricle). The subject will be moved out for the abdomen imaging. Or, for a MR scanner with a moving table technology, the MR table will be moved to center over the second coil to image the abdomen.

6. A phased-array surface coil will be positioned with its center over the inferior costal margin, i.e. over the expected location of the kidneys.

7. Scout scan to locate the scan range of the entire kidneys. A stack of axial images to cover the most anterocaudal and posterocranial aspects of the kidneys is highly recommended.

8. The field-of-view (FOV) should be kept as small as possible (30-35 cm) without producing wrap- around artifacts.

9. Breath-hold, coronal T2 scan (SSFSE/HASTE **with** fat sat) with 9mm fixed slice thickness, usually achievable in a single breath-hold. Please make sure both kidneys are imaged completely without missing any anterior or posterior portions. **This coverage assurance is critical for the following T1 imaging**.

   ****This is the most important sequence.** Coronal T1 scan (3D VIBE/FMPSPGR/LAVA **without** fat sat) with 3mm fixed slice thickness (acquisition will be performed at 6mm thickness and then the slice will be interpolated at 3mm, i.e., in GE, ZIP =2 in the slice direction). Keep the flip angle 15^{o}. To improve SNR, keep the Bandwidth low (62 kHz or 42 kHz) and/or increase the number of phase-encoding steps (be aware, the acquisition time will increase). In GE LAVA sequence, turning off "optimize flip for CNR" will allow to change the flip angle or bandwidth. Do NOT use parallel imaging (no SENSE, ASSET, iPAT or GRAPPA). Please see Consideration #2 above.

10. Breath-hold coronal T2 scan (SSFSE/HASTE **with** fat sat) with 3mm fixed slice thickness, which would require 1-4 breath-holds depending on the kidney size. Use as few breath-holds as possible. The first scan should cover the posterior aspect of the kidney. Neighboring image groups should be overlapped by a single 3mm slice. To determine correct table position choose the "shift-mean (starting point in GE)" of the second scan for example: the first shift-mean = - 60mm, the number of slices in the first set =23, (23-1)x3=66mm, new shift mean =-60+66=6mm.

11. Breath-hold coronal T2 scan (SSFSE/HASTE **without** fat sat) of the kidneys with adjusted slice thickness, 3-6 mm, i.e. the slice thickness best attainable with a single breath-hold (The adjusted slice thickness may not remain the same in a follow-up MR scan if there is a change in the subject's breath-hold capacity or kidney size.) Repeat the scan over the liver with the same slice thickness. This scan and the scan for the kidney should share one overlapping liver slice (i.e., the most posterior slice

of the liver scan should be identical to the most anterior slice imaging the liver in the kidney scan. If more than two scans are required to cover the anterior liver, again the neighboring scans should be overlapped by one slice.

12. **Breath-hold coronal 2D true-FISP (FIESTA) **without** fat sat with 3mm fixed slice thickness, which would require 1-2 breath-holds depending on the kidney size. Use as few breath-holds as possible. The first scan should cover the posterior aspect of the kidney. Neighboring image groups should be overlapped by a single 3mm slice. To determine correct table position choose the "shift-mean (starting point in GE)" of the second scan for example: the first shift-mean = - 60mm, the number of slices in the first set =23, (23-1)x3=66mm, new shift mean =-60+66=6mm.

13. **(For renal blood flow measurement) Breath-hold, oblique-coronal 2D true-FISP (FIESTA) **with** fat sat with 4mm fixed slice thickness at 2mm spacing (i.e., overlap 50%) over the aorta and renal arteries. See the figure below for the orientation of the image plane. Typical parameters: 192x256 matrix, 75^{o} flip angle, 125 kHz BW, 15-sec scan.

15. (For renal blood flow measurement) Breath-hold, phase-contrast technique of renal blood flow measurement. From the FIESTA images, the renal arteries will be identified. To accurately measure velocity, it is important to choose the imaging slice perpendicular to a vessel. Velocity encoding (VENC) value of 100 or 50 cm/sec will be used. Small FOV (14-16 cm) and large matrix (256x192 or 512x512) are important for an accurate measurement of the vessel size. segmented, prospectively cardiac-triggered phase contrast flow measurements will be obtained to compute the mean and peak velocities, as well as the total mean flow, during the cardiac cycle.

Please, see the renal artery figures below (Courtesy of James Glockner from Mayo).

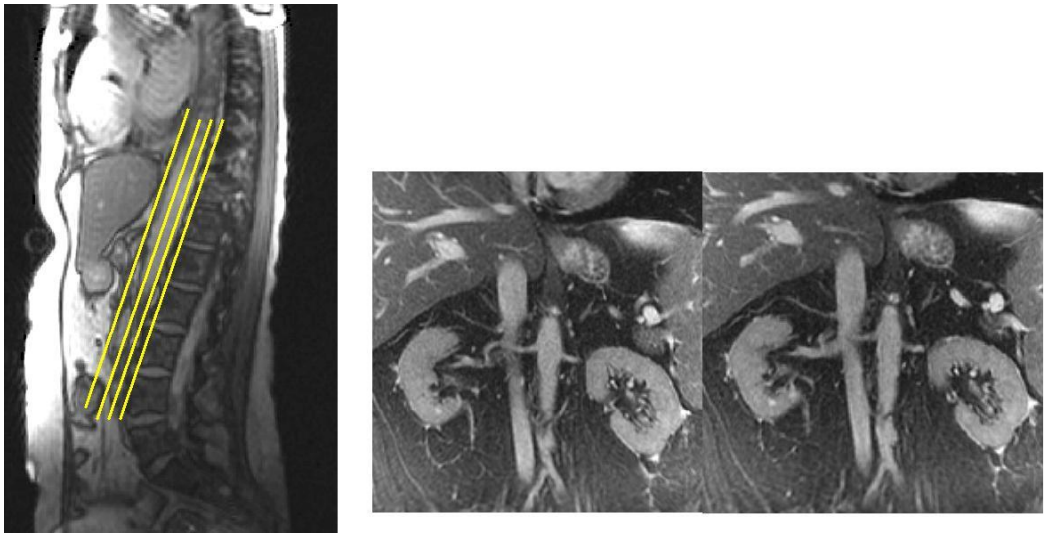


Figure: 2D Fat-Saturated FIESTA Renal Artery Localization. The image plane was selected from the sagittal scout image.

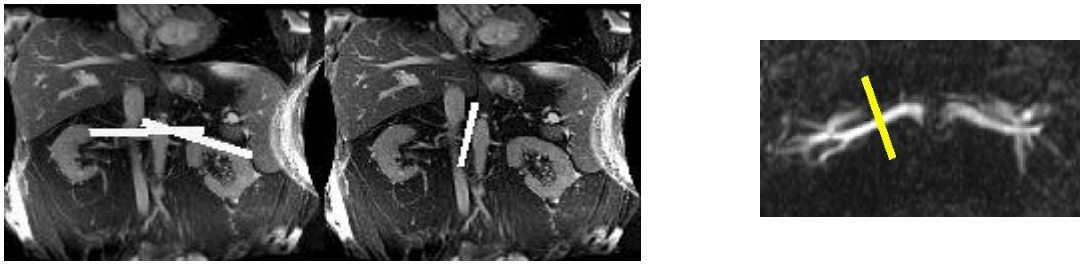


Figure: Cine PC scout image for renal artery localization, and the phase and magnitude images.

A radiologist at each PCC will establish the MR imaging protocol according to the above specifications. MR scans will be performed by a certified MR technologist(s) who is familiar with the protocol and objectives of the MR study. Prior to scanning participants, the MR technologist will be trained or will have experience in scanning PKD participants according to the MR study protocol. The radiologist will oversee all MR scans.

For image transfers, the IAC will provide PC workstations, installed with custom DICOM software, to PCC sites that are not part of the CRISP study. Images will be pushed from the local PCC MR scanner to the PC workstation. For participant confidentiality, participant names and identifiers will be removed and replaced with HALT- ID numbers and accession numbers prior to image transmission to the IAC. A virtual private network (VPN) client will be installed on the PC workstation to encrypt the data for secure transmission via the Internet.

The IAC will review the images and generate quality control reports for PCCs. Images determined to be inadequate for measurement must be reacquired. For non-CRISP PCCs, after the installation of the PC workstation, the IAC will construct PKD phantoms using water- filled balloons and agarose and dispatch them to the PCCs. The phantoms will be scanned and their MR images will be transferred to the IAC. The phantom images will be reviewed and analyzed to evaluate proper implementation of the imaging protocol and to verify good image quality control.

A well-designed infrastructure at the University of Pittsburgh for processing and measuring kidneys is already in place. Radiologists (including Dr. Bae) and image analysts involved in the CRISP Study will perform measurements for HALT PKD. Individual whole kidney volumes will be measured from T1 images by means of stereology methods, while T2 images are reviewed simultaneously. In the T1 images, the parenchyma and cysts are dark, as compared to renal fat and other surrounding tissues, making the outline of the kidney relatively easy to observe for measurement with stereology methods. The renal cysts are very bright on T2 images, and background tissues are relatively easy to separate from renal cysts and kidney parenchyma.

The stereology method, a quantitative morphology by statistical analysis of the structures of random sections, is widely used in cytopathology and medical imaging analysis. A point- counting stereologic technique involves a simple, fast method of segmenting an object by counting the number of intersections of a randomly oriented and positioned grid over the object. This method does not require border tracing or threshold determination, but relies on the operator's decision of selecting each point that intersects the object. The areas of the whole kidney in each image can be calculated from the collection of points, and volume measurements can be made from a set of contiguous images. This method will be applied to T1-weighted MR images. Analysis software, written by the Mayo Foundation, will be utilized for making stereology measurements. Each volumetric measurement will be made by a trained analyst at the DCC, and will be reviewed by a radiologist for quality control. Agreement between the radiologist and technician in the CRISP Study was very high (97%). The result from the radiologist's review of stereology measurements will be used to calculate the whole kidney volume.

11.2. **Secondary Outcomes for Study A**

The two interventions, ACE-I/ARB combination vs. ACE-I monotherapy and low vs. standard blood pressure control are hypothesized to impact on the following secondary outcomes i) the rate of change of GFR over time; ii) the rate of change in renal blood flow by MRA over time; iii) the rate of change in left ventricular mass; iv) the rate of change in albuminuria; v) rate of change in 24-hour excretion of aldosterone; vi) all-cause hospitalizations; vii) hospitalizations due to cardiovascular cause; viii) quality of life and pain ; and ix) the frequency of PKD-related symptoms or medical conditions (e.g. ruptured renal cyst) as collected on the Symptoms Checklist (Form 5); ix) adverse effects of study medications.

11.2.1. **Rate of Change of GFR**

The secondary endpoint of primary importance for the HALT-PKD Study A is eGFR. This

will be calculated using the CKD-EPI formula (13-16) rather than the MDRD equation. The former calculation of eGFR is more accurate, namely at higher levels of GFR (>60 ml/min). Serum creatinine measurements will be obtained at the baseline, F5, and F12 visits, and at every subsequent 6-month visit, and sent to the Cleveland Clinic Foundation Reference Laboratory for analysis.

11.2.2. **Measuring Renal Blood Flow**

The procedures for measuring renal blood flow can be found above in Section 11.1, Numbers 14 and 15.

11.2.3. **Measuring Left Ventricular (LV) Mass by MR**

LV mass will be measured by cardiac MR at baseline, 24 and 48 months in Study A participants. Cardiac MRs to measure LV mass will be obtained at the same sitting as the MRs for measuring kidney volume and the MRAs for measuring renal blood flow as described above in Section 11.1.

11.2.4. **Rate of Change in Albuminuria**

As described in Section 8.3, an aliquot of 24-hour urine will be analyzed for albumin and creatinine at baseline, 4 months, 12 months and yearly thereafter. The change in albumin to creatinine ratio over time will be compared among intervention arms.

11.2.5. **Rate of Change in 24-Hour Excretion of Aldosterone**

An aliquot of 24-hour urine will be analyzed for the 24-hour aldosterone excretion rate (AER) at baseline, 4 months, 12 months and yearly thereafter, as described in Section 8.3. The rate of change in 24-hour AER over time will be compared between intervention arms.

11.2.6. **Hospitalizations**

At each 3-month study visit (over the telephone or at the PCC), participants will be asked if they have been hospitalized since the last study visit. If hospitalized, participants will be asked to sign a consent form authorizing pertinent medical records to be released and forwarded to the PCC. The study coordinator will enter the date(s) and the primary reason(s) for admission on the Hospitalization Form (Form 30) . The primary reason for admission will be classified according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) of the National Cancer Institute (Appendix B). The PI is required to review the hospital encounter information entered on Form 30 prior to submission to the DCC.

Hospital discharge summaries will be collected by the PCC. The study coordinator will de-identify the report and fax it to the DCC. The DCC will distribute the report to the Endpoints Committee. A formal adjudication of coding for the primary cause of hospitalization and designation of relatedness to PKD/CKD will be performed by the Endpoints Committee.

11.2.7. **Adverse Event Reporting**

Differences in the frequency of adverse events will be compared across study arms. The definitions of adverse events, as well as the methods for collecting them, are detailed in Section 12.3.

11.2.8. **Quality of Life and Pain**

The HALT PKD study provides a unique opportunity to describe HRQOL and pain/symptom experience in a large cohort of PKD subjects at varying stages of chronic kidney disease, as defined by structural and functional measures. Quality of life and pain are also important secondary outcomes

of the HALT PKD study.

It is possible that targeting the low vs. usual BP goal and/or the combination of ACE-I/ARB vs. ACE-I monotherapy may impact on participants' perceived quality of life. For example, the low BP goal may limit activity. The dietary restrictions imposed on participants with hyperkalemia, anticipated to be more common in the ACE- I/ARB group, may negatively impact quality of life. The Medical Outcomes Short-Form Questionnaire (SF-36v2) will be employed to measure QOL in this study. It is the most widely-accepted instrument for measuring HRQOL and has been validated in many populations, including those with CKD.

Pain or symptoms due to the mass effect of an enlarged liver or kidney(s) are relatively common and unique aspects of PKD [Bajwa, 2004]. If the interventions under study affect cyst growth, this is likely to translate into differences in the pain experienced by participants. The SF-36v2 contains only two questions addressing pain, and a pain questionnaire specifically validated for PKD patients does not exist. Thus, an instrument used in the largest prior study of pain in individuals with PKD has been adapted [Bajwa, 2004] for use in HALT PKD and is entitled "The HALT PKD Pain Questionnaire" (Form 39) . It is a modified version of the Wisconsin Brief Pain Questionnaire, an instrument validated in various populations with chronic pain [Daut, 1983).

The major domains include:

1. Description of pain: nature, location, frequency, and severity of pain in three areas (abdomen, back and back radiating into buttocks/ legs).
2. Description of symptoms due to enlarged organs ('mass effect').
3. Effects of pain and 'mass effects' on participant's physical, mental, and social well-being.

Although they seem similar, the SF-36v2, the HALT PKD Pain Questionnaire, and the Symptoms Checklist Form 5, *are* distinct. The SF-36v2 assesses how the disease, as a whole, affects one's health status, while the HALT PKD Pain Questionnaire specifically addresses how pain/symptoms from enlarged organs affect one's health status. The Symptoms Checklist contains a small number of questions about pain but does not characterize the nature, severity, or frequency of the pain nor its impact on the participant's experience.

It is suggested that the SF-36v2 and the HALT PKD Pain Questionnaire be administered after blood pressure has been measured, but before all other study procedures, in order to avoid affecting participants' responses to the questionnaires. The SF-36v2 (Form 38) will be administered *before* the Pain Questionnaire (Form 39), as it is important that the distinction of effects of the disease in general vs. effects of pain on quality of life are clear to participants when they are completing these forms.

11.3. **Primary Outcome Measures for Study B**

The primary outcome for Study B is a composite endpoint of time to the 50% reduction of baseline eGFR, ESRD (initiation of dialysis or preemptive transplant), or death.

Post Closeout Follow-up of Study B Participants: Once a patient reaches an endpoint of either a 50% decline in eGFR or ESRD (defined as the first event of starting dialysis or receiving a transplant), study medications, BP goal, and PCC visits will be discontinued. The site PI will taper/discontinue blinded study medication as follows:

If on 80 mg once daily, change to 40 mg once daily and monitor blood pressure daily for 1-2 weeks. If no change in blood pressure after 1-2 weeks, discontinue meds and continue monitoring blood pressure as below.

If on 40 mg once daily, discontinue and monitor blood pressure daily for 1-2 weeks.

If blood pressure is controlled (max 130/80) upon reducing dose or discontinuing study medication, no further intervention.

If blood pressure is not controlled upon reducing dose or discontinuing study medication, the PI will prescribe an increased dose of existing open label therapy and/or add other antihypertensive medications as appropriate.

The PI at each site will send a letter to the participant's primary physician notifying him/her of their patient's status in the study and informing him/her of the need to transition care of the participant for ongoing hypertension management and requesting them to monitor the participants as they stop study medication. Participants will be contacted annually to determine if ESRD has been reached. If the participant has not reached ESRD the most recent serum creatinine drawn by the PCP or nephrologist will be obtained. Once a participant starts dialysis or receives a transplant, he/she will be contacted annually to ascertain vital status only.

An addendum, to Consent Form B has been included in the Manual of Procedures (MOP) for all participants who reach a study endpoint. A Waiver of Consent is also included for participants who will not be returning to the PCC. A copy of the letter being sent to primary care physicians/nephrologists is also in the MOP.

11.3.1. **Ascertainment of Time to Event**

The outcome of time to the 50% reduction of baseline eGFR is based on the serum creatinine measurement obtained at each PCC follow-up visit and analyzed at Cleveland Clinic. Laboratory measurements to *confirm* the 50% reduction of baseline eGFR can be obtained from either Cleveland Clinic, or a Quest lab, as both are calibrated to the same standard.

11.3.1.1. **Confirming a 50% Reduction in eGFR**

A 50% reduction in eGFR from baseline must be confirmed by obtaining a repeat eGFR within two weeks of having obtained the original sample. The confirming sample may be obtained at the PCC, or at a Quest Lab. If the individual cannot return to the PCC, or does not live near a Quest lab, it is acceptable for the participant to obtain the sample at a local lab, as long as the sample can be centrifuged and shipped at room temperature to Cleveland Clinic within 24 hours of its having been collected. The 2-week confirmatory sample is required ONLY if the 50% reduction in eGFR from baseline is determined as the result of a study visit lab. If a 50% reduction in eGFR from baseline is determined as the result of a safety lab, it will not be considered an endpoint, and a confirmatory sample should not be drawn.

If the 50% reduction in eGFR is not confirmed, the full protocol will be continued until the next study visit. For safety, anytime GFR is <30 ml/min/1.73 m2, participants will be required to have serum creatinine and potassium drawn at three-month intervals. If a safety lab, drawn in between study visits, shows a 50% reduction in eGFR, it will not be considered an endpoint, and a confirmatory sample will not need to be drawn.

11.3.1.2. **Option to Dispute an Endpoint of 50% Reduction in eGFR**

If an investigator believes that a 50% reduction in eGFR from baseline is not a true endpoint, he or she has the option to dispute it by notifying the Endpoints Committee. Some of the reasons for disputing an endpoint include cyst infection/pyelonephritis, kidney stone obstruction, dehydration, medication error, and dietary non-compliance. The Endpoints Committee will adjudicate the disputed endpoint and then notify the investigator as to its validity. If the Endpoints Committee agrees the endpoint is not a true one, the participant will continue following the full protocol.

11.3.2. **Documentation of ESRD and Death**

The Recruitment and Retention Coordinator at each PCC will request supporting materials to document deaths, including hospital death summaries, death certificates, and/or an ESRD Death Notification Form (HCFA Form 2746) if appropriate. In case of death, study coordinators will request release of information from next of kin. To document ESRD, the run sheets of first dialysis treatments and/or ESRD Medical EvidenceReport (HCFA Form 2728) will be obtained, and/or participants will be contacted directly if a kidney transplant was received.

11.3.3. **Secondary Outcome Measures for Study B**

Secondary outcome measures include: i) rate of change in albuminuria; ii) rate of change in 24-hour excretion of aldosterone; iii) all-cause hospitalizations; iv) hospitalizations due to cardiovascular cause; v) the frequency of PKD related symptoms or medical conditions (e.g., ruptured renal cyst) as collected on the Symptoms Checklist (Form 5); vi) quality of life and pain measured using the SF-36v2 and HALT PKD Pain Questionnaire, respectively; and vii) adverse effects of medications. The methods of ascertainment and data collection are as described above in Section 11.2 and its associated subsections.

12. **STUDY SAFETY**

12.1. **Data and Safety Monitoring Board**

The NIH has appointed an independent Data and Safety Monitoring Board (DSMB), consisting of nephrologists with expertise in the areas of renal progression and clinical trials, statisticians, and experts in the treatment of hypertension. The DSMB previously approved the HALT PKD protocol, in principle, at a meeting held on January 29, 2003. The DSMB granted final approval to HALT PKD following a conference call held on October 31, 2005. Extension for Study A was approved by the DSMB in August, 2010. The extension for Study B was approved on April 30, 2012.

The DSMB will meet at least annually to review the progress of the study and a summary of adverse events, as well as to review other interim results. All substantive changes to the protocol require approval by the DSMB. Further details of interim analyses are provided in Section 13.10.

12.2. **Safety Monitoring**

From the drug washout period through the first 6 weeks of the study, changes in medications and/or doses will be frequent. Participants will be asked to monitor their blood pressure every 2-4 days and to contact the study coordinator immediately if BP readings are out of the accepted range given the phase of the study (as summarized in Table 7). Participants will also be instructed to contact the study nurse if they develop symptoms of hypotension (lightheadedness, postural lightheadedness). The frequency of home BP monitoring and of study visits may be increased, at the physician's discretion, for individuals with 'out- of-control' blood pressure that is difficult to manage. Serum creatinine, potassium and BUN will be measured at the PCC or at participants' local laboratories one week after initiation and after each increment in study drugs.

Serum potassium may be monitored more frequently in individuals with borderline hyperkalemia, at the discretion of the PI. In addition, Study B participants will be instructed on a low potassium diet. Study B participants, whose GFR is <30 mL/min/1.73 m^2 at the time of randomization, will be immediately referred to their primary nephrologist for more frequent follow-up than every 6 months (the HALT study visit frequency). As the study is ongoing, any participant in Study A or B, whose GFR falls to <30 mL/min/1.73 m^2, will also follow up with their primary nephrologist more frequently than at 6-month intervals. Participants who start the study with GFR <30 mL/min/1.73 m^2, or whose GFR drops below <30 mL/min/1.73 m^2 during the study, will be required to obtain additional safety tests (serum creatinine and potassium) at 3-month intervals.

At each PCC visit blood pressure will be measured using standardized, automated blood pressure equipment. This will calibrate the home blood pressure equipment. A panel of laboratory measurements will be obtained and reviewed for abnormal values, and the PCC will take appropriate action to address any abnormalities that are found. A computer routine at the DCC will query sites in regard to any abnormal PCC lab values that were not flagged as such by the PCC. The appropriate PCC will be notified of unflagged abnormalities by e-mail, with subsequent follow-up by the DCC to verify that appropriate action was taken. At each study visit, a systematic review of adverse events will be conducted, as described in greater detail under Adverse Events (Section 12.3). The Quality Control Subcommittee will review and discuss reports of adverse events (including SAEs, such as deaths and hospitalizations), serum creatinine doubling, and relevant safety parameters on a monthly basis, or earlier as necessary.

Individuals currently on a BP drug for a non-hypertensive indication will be allowed to enroll in the study. It is expected that some participants, while on-study, will develop a non-hypertensive condition for which BP medication is required. In such cases investigators will use their own judgment as to whether to keep or start a participant on a particular antihypertensive medication. The Quality Control Committee will follow cases of BP drugs being taken for non-BP indications. A computer routine will be set up to flag whether these medications were preexisting or began after the start of washout.

12.3. **Adverse Events**

12.3.1. **Definitions and Reporting of Adverse Events**

Adverse Events (AEs) are defined as any unfavorable symptoms, signs, or diseases temporally associated with participation in the HALT-PKD study that *may or may not* be related to study interventions. AEs can be symptomatic or asymptomatic and clinically-detected or ascertained from laboratory studies, diagnostic imaging studies or other testing. As in other large interventional trials in NIDDK (e.g., African American Study of Kidney Disease, AASK), a practical approach to possible side-effects has been adopted for HALT-PKD. In view of the extensive clinical history of the reagents to be used in these trials, both consent documents and symptom checklists have taken a targeted approach regarding the more common or concerning side-effects of medications. With this targeted approach, it is not necessary to list individually all possible drug-related side-effects on the AE reporting form (Form 5 - Symptoms Checklist) or to list uncommonly or rarely reported events in the consent document (although the consent explains that other effects could occur).

Because an event's relatedness to study medication cannot be determined with certainty after the start of medication, <u>all</u> adverse events will be reported on the study, from the screening visit up to thirty days after the last dose of study medication (whether masked or open-label drug). Participants who continue with modified participation after discontinuation of study medication will be followed for adverse events for 30 days after the end of their participation in the study (last study visit). AEs will be recorded every three months on a Symptoms Checklist (Form 5) - a checklist consisting of the most common or concerning side-effects of medications or of hypertension and/or hypotension. For AEs not present on the Symptoms Checklist (Form 5), the coordinator will enter a free text description.

Questions as to whether dose modifications and/or reporting of AEs as serious adverse events are needed have been included on the Symptoms Checklist and will be completed by the study coordinator or clinician. Designation of the relatedness of SAEs to treatment or study participation will be made by the study coordinator or clinician at the time of the event.

12.3.2. **Management of Adverse Events**

Adverse symptoms, or drug effects, will be recorded throughout the study. Due to a series of 8 episodes in 5 participants showing early acute renal insufficiency after introduction of ACE-I in ADPKD [Chapman, 1991], we will particularly monitor these events. The following table outlines the management of participants that develop anticipated adverse effects of study drugs. PIs will manage hyperkalemia and increases in serum creatinine per the guidelines below, which reflect the current standard of clinical care. Per Table 10 below all concerning lab values are to be reported within two weeks of collection. All lab values defined as serious, if verified, are to be reported within 24 hours, per section 12.4.2, unless they are due to an overt and clearly reversible issue as determined by the study investigator.

Table 10: Management of Adverse Effects of Medications

Event	Definition	Response	No Response to Prior Measures
Rise in serum creatinine (PCC to manage)	</=12 weeks of the start of ACE ± ARB: Serum creatinine increase >/30% and <100%, or 1.0 mg/dl. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Hold ACE ± ARB. 3. Exclude unrelated causes such as volume depletion, infected urine, other drug effect, obstruction. 4. If serum creatinine falls <30% and no other cause found, re-challenge at lower dose per PI discretion. 5. Data-enter all such values within 2 weeks.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.
	</=12 weeks of the start of ACE ± ARB: Serum creatinine increase >/=100%. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Hold ACE ± ARB. 3. Exclude unrelated causes such as volume depletion, infected urine, other drug effect, obstruction. 4. If serum creatinine falls <100% and no other cause found, re-challenge at lower dose per PI discretion. 5. Such occurrences may be reportable SAEs.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.
	>12 weeks of the start of ACE ± ARB: Serum creatinine increase >/=30% and <100% from most recent value PI must be informed immediately (<24 hours)	1. Notify participant. 2. Hold ACE ± ARB. 3. Exclude unrelated causes such as volume depletion, infected urine, other drug effect, obstruction. 4. If serum creatinine falls <30% and no other cause found, re-challenge at lower dose per PI discretion. 5. Data-enter all such values within 2 weeks.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.
	Anytime after start of ACE ± ARB: >100% of baseline average. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Repeat testing within two weeks (sample sent to central lab). 3. Data-enter all such values within 2 weeks.	If doubling confirmed, refer to Table 14-1. If no confirmation of doubling, no further action required.
Hyperkalemia (PCC to manage)	Potassium 5.6-6.0 mEq/l. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Exchange resins and/or diuretic. 3. Repeat testing. 4. If >5.0, implement 2-gram potassium diet, and/or Loop diuretic, and/or chronic sodium polystyrene sulfonate. 5. If repeat value still elevated, hold or reduce ACE ± ARB until K controlled on chronic therapy, rechallenge at reduced dose. 6. Data-enter all such values within 2 weeks.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.
	Potassium >6.0 mEq/l. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Exchange resin. 3. Hold ACE ± ARB. 4. Evaluate causes (admit to local ED if necessary) 5. Repeat test after evaluation and	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.

		treatment. If <,5.0, implement 2-gram potassium diet, and/or Loop Diuretic, and/or chronic sodium polystyrene sulfonate. 6. If repeat value still elevated, hold or reduce ACE +/- ARB until K controlled on chronic therapy, rechallenge. 7. Data-enter values 5.6-6.5 within 2 weeks. 8. K values >6.5 may be reportable SAE's.	
Cough	Dry, persistent (>2 weeks) cough worse at night, coincides with initiation of ACE ± ARB	1. Exclude infection, congestive heart failure, primary lung disease 2. Withdraw and re-challenge, noting whether cough reappears	Discontinue lisinopril and proceed to open-label therapy. Maintain blinding.
Angioneurotic Edema	Periodically recurring episodes of non-inflammatory swelling of skin, mucous membranes, glottis, viscera of sudden onset lasting hours to days	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.	N/A

Participants will be informed of the following non-acute issues to be handled by the PCP and/or nephrologist:

i. Referral to nephrologist for patients with GFR <30 mls/min if they don't already have one; need creatinine and potassium every 3 months.
ii. Phosphate is >5.5 mg/dl.
iii. Total Calcium is <8.0, or Calcium is >10.5 mg/dl Hematocrit <33%.
iv. Abnormal LFTs (screening only).
v. Elevated fasting glucose >126 (screening only).
vi. Any other lab result, physical exam finding or diagnostic imaging finding that requires further investigation and/or management by the PCP, at the discretion of the PI.

12.3.3. **Hyperkalemia**

Hyperkalemia is likely to be encountered in Study B participants and even some Study A participants. If there is a possibility of a falsely elevated measure due to hemolysis, potassium may be repeated before beginning treatment, as outlined in Table 10 above. Standard measures will be used to control potassium, including the use of exchange resins (sodium polystyrene sulfonate), furosemide, and dietary modifications; and if necessary, the participant may need to be brought into a local ER, to be decided by the PI. Because it may be difficult to obtain sodium polystyrene sulfonate on an urgent basis in some locations, all participants in Study B will be sent home with three 15g doses of sodium polystyrene sulfonate liquid suspension to be saved for later use, if needed. This may be deemed to be unnecessary at the discretion of the PI in cases such as participants are known to be hypokalemic and/or require KCL. Participants in Study A with high normal potassium or frank hyperkalemia will also be given three 15g doses of sodium polystyrene sulfonate at the Baseline Visit to be saved for later use, if needed.

12.5. **Serious Adverse Events (SAE)**

12.4.1. **Definition**

An SAE is defined as any undesirable experience meeting *one or more* of the following criteria, regardless of relatedness to study participation[1], occurring from the time a participant signs the informed consent (at the screening visit) until the end of the study[2,3,4].

1 Resulting in death.
2 Hospitalization- all hospitalizations, elective and non-elective, must be reported as SAEs. If a hospitalization is prolonged due to an event related to this study, this is also considered an SAE.
3 Life-threatening event- if the participant is at substantial risk of dying at the time of the event, or if continued use of a study medication[5] or study procedure[6] would result in the participant's death. Included in this definition are potassium levels of >6.5 mEq/L, and doubling of baseline serum creatinine within 12 weeks of beginning study medications.

4 Persistent or permanent harm or disability.
5 Exceeding the nature, severity or frequency of risk described in the protocol.
6 Congenital anomaly- if there is suspicion that exposure to a study medication[5] or proce- dure[6] prior to conception or during pregnancy resulted in an adverse outcome in the child.
7 Abuse of, or dependency on, study medication.
8 Any other important medical event, including new cancer diagnosis, which may jeopardize the participant, or may require intervention to prevent permanent impairment or damage or other outcome listed above.

[1] An event is "reasonably related to study participation" if it is or could reasonably be the result of or exacerbated by the use of study medication, whether masked or open-label, or any study procedure. While all SAEs are to be reported per the guidelines above, only those that are reasonably related to study participation will be counted as primary or secondary outcomes.
[2] The "end of the study" is defined as the "stopping date" or "x date," and not the "end of data close-out."
[3] Data analysis will separate out any SAEs occurring before the start of study medication from those occurring after.
[4] For the HALT PKD study, all serious adverse events that are reasonably related to study participation are, by virtue of their seriousness, unanticipated events which are not consistent with the risk information described in the protocol. Events are considered unanticipated by virtue of greater specificity (type or nature of an event) or greater severity (degree, frequency or outcome of an event; of a greater intensity than what has been previously observed). Examples of the latter: hypokalemia is an expected event, but cardiac arrest is unanticipated. Hypotension causing lightheadedness is an expected event, but a syncopal spell causing a trip to the ER for "fall" is unanticipated.
[5] The term "study medication" is defined as any medication, masked or open-label, used to control blood pressure from the time a participant signs consent until the end of the study, even if the participant was an early withdrawal from the study and even if the participant has withdrawn consent to continue in the study.
[6] A "study procedure" is any test or procedure required for the study (e.g., MR imaging for study A).

12.4.2. **Reporting Requirements**

All SAEs must be reported within 24 hours of study personnel learning of the event to the local PI and to the DCC via data-entry of SAE Report Form 13. Information not available at the time of the initial report should be submitted to the DCC as a follow-up report within 5 business days. All SAEs will be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. Reporting requirements for the FDA differ depending on their relatedness to study interventions, as follows:

SAEs that are reasonably related to study participation[1]:

Unanticipated: The DCC will notify NIDDK of SAEs that are drug-related and unanticipated within one business day of receiving the report, and all PIs within five business days (annually if anticipated). NIDDK will report all SAEs that are drug-related and unanticipated to the FDA within seven days of initial knowledge of the event. The DCC will prepare reports of such events for the DSMB at least annually.

Anticipated: NIDDK will report anticipated SAEs to the FDA at least annually, but these may need to be reported in a more timely fashion to local IRBs (usually 7 days but see local policy). PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by center.

Note: Adverse events that are "expected" appear as risks in the informed consent. Adverse events that are "unexpected" exceed the nature, severity or frequency of risk described in the protocol. Adverse events that are "unanticipated" are unexpected and reasonably related to study participation. Unanticipated adverse events must be added to the informed consent per Steering Committee discretion.

SAEs that are unrelated to study participation:

The DCC will prepare summary reports at least annually for the clinical centers, NIDDK, DSMB and FDA. PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by center.

SAEs that are related to study participation but are not related to study drug:

Some PCCs may require study-related, but not drug-related, SAEs (e.g., hypotension leading to fall) to be reported to their local IRB (usually within 7 days but see local policy). PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by institution.

Table 11: Summary of Reporting Requirements for Serious Adverse Events

Reporting from PCC to DCC: **An event is serious if it is or results in**	**Study Related**	**Report to PI + DCC (Form 13)**	**Report to Local IRB** (may vary by site)
Death or Hospitalization	Yes	24 hrs	5 business days
	No	24 hrs	5 business days
Life-threatening, resulting in permanent disability, requiring intervention to prevent impairment, exceeding nature, severity, or frequency described in protocol, congenital anomaly, abuse of or dependency on study medication, any other important medical event, including new cancer diagnosis, which may jeopardize the participant, or may require intervention to prevent permanent impairment or damage or other outcome listed above	Yes	24 hrs	5 business days
	No	24 hrs	Annually

Reporting by DCC to:	**NIDDK**	**PI→IRB[#]**	**QCC**	**DSMB**	**FDA**
Study-Related SAEs	1 business day*	5 business days	Monthly, except 1 business day*	5 business days	% *
Unrelated SAEs	Annual Summary	Annual Summary	Monthly	Annual Summary	%

*SAEs that are both drug-related and unanticipated: NIDDK will report to FDA within 7 days of initial knowledge. %Expected SAEs, and those that are both unanticipated and unrelated to drug: DCC submits annual summary reports to FDA. #PIs are responsible for reporting SAEs to local IRBs per site-specific guidelines.

1. Staff at the PCC where the event occurs will report all SAEs to the DCC within 24 hours of learning of the event, and report it to their IRB per institutional guidelines.
2. DCC reviews SAE report and sends electronic notification to Boehringer Ingelheim by the end of the next business day, or within 24 hours if the report is received before a weekend or holiday.
3. DCC reviews SAE reports. If study related, the DCC sends electronic notification to all PCCs (including the reporting PCC) within five days of the original report with a reminder of their responsibilities for reporting. All unrelated events will be reported to PIs at least annually.
4. PIs at all *other* PCCs (where the event did not occur) are responsible for reporting the event to their IRB per institutional guidelines.
5. DCC Reports to NIDDK and DSMB as listed in Table 11 above.
6. DCC reports events to the FDA as listed in the Table 12 below.

Table 12: Summary of FDA Reporting Requirements

Event	Anticipated/Unanticipated?	FDA Reporting Requirement
Study- **AND** Drug-Related	Anticipated/Expected	Annual Report
Study- **AND** Drug-Related	Unanticipated	NIDDK reports to FDA within 7 days of initial knowledge
Study-Related **BUT** unrelated to drug	Anticipated/Expected	Annual Report
Study-Related **BUT** unrelated to drug	Unanticipated	Annual Report
Unrelated to Study	N/A	N/A

12.4.3. **Participant Management in the Event of an SAE**

The need to discontinue or modify doses of medications will be left to the discretion of the PI. Unmasking the study group assignment will occur only if a pregnancy or other unusual circumstance occurs, but unmasking is not anticipated for most SAEs.

12.5. **Drug Interaction of Telmisartan and Digoxin**

Coadministration of Telmisartan and Digoxin, both metabolized by the liver, can lead to an increase in the peak concentration of Digoxin by up to 50%. If a participant is taking Dogoxin, the level is to be checked at the baseline visit and results must be available before the start of study medication.

Digoxin levels will also be checked, along with potassium and BUN/ Creatinine (i.e., safety labs), between titration of ACE-I and Telmisartan/ placebo in the first 8 weeks of the study. Dose adjustments for digoxin will be made, if needed, by the PI. Digoxin levels should stabilize once a steady dose of telmisartan is reached, anticipated at the final titration step, L4 safety lab, but continued testing will be arranged if levels continue to flucuate. Digoxin levels will be followed every 6 months thereafter. If there are changes in telmisartan/placebo over the course of the study, digoxin levels will need to be rechecked within a week of the dose adjustment.

12.6. **Modified Study Follow-up**

Per the intent- to-treat principle, every effort must be made to follow each participant enrolled until the end of the study or death. Table 13 below outlines procedures to be followed for participants who meet primary endpoints or withdraw prematurely from part or all of the study. In cases for which follow-up must be modified, it is recommended that sites obtain the participant's consent for modified follow-up (per local policies). A checklist has been drafted to clarify participants' options and responsibilities.

To continue on study medications, participants *must continue to be followed at the PCC at least every six months*, including all required lab work. Participants continuing to take study medications will be required to monitor their blood pressure at home and complete telephone visits three months after each PCC visit. However, these participants may opt out of imaging studies, urine collections, specimen banking and/or questionnaires.

If participants do not agree to six- month follow -up visits at the PCC, study medications will be discontinued and each participant will be asked to indicate the intensity and frequency of follow-up they are agreeable to from among the four options listed below. Participants who stop taking study medications will *not* be required to complete home blood pressure monitoring, safety labs, telephone visits, or questionnaires, and participants may opt out of imaging studies.

1) *Annual visits to the PCC* and completion of the usual activities of the annual visit, including blood work. No urine collections will be required, but participants may choose to provide urine samples. Participants will be given the option to complete 6-month lab testing at a lab near their home, and if agreeable, arrangements will be made for serum creatinine to be analyzed centrally.

2) *No study visits but regular lab work and blood pressure*. The participant agrees to have lab work drawn for HALT PKD at 6- or 12-month intervals and to have blood pressure checked by his/her PCP/ nephrologist at 6- or 12-month intervals. HALT PKD will arrange for serum creatinine to be shipped to the central lab for analysis. Study personnel may continue to contact a participant by telephone to obtain interim medical history and/or other pertinent information. The participant will be asked whether he/she is agreeable to a single PCC visit at the end of the study.

3) *No study visits but consent to release of medical records* The participant gives consent for study personnel to contact him/her and/or, gives consent to release medical records from the PCP or nephrologists office (local serum creatinine and blood pressure).

4) *No study visits and refusal for release of medical records.* The participant will be asked to give consent to HALT PKD to check vital status via Social Security Number.

Table 13: Follow-up After Primary Endpoints, Early Withdrawal or Modified Participation

Event	***Continue Masked Drugs?***	***Follow-up Visits***
50% reduction of baseline eGFR (Study B)	No	No: contact annually to determine whether ESRD has been reached. If ESRD has not been reached, then obtain the most recent serum creatinine drawn by the PCP or nephrologist. Once participant starts dialysis or receives transplant, contact annually to ascertain vital status.
ESRD (Study A)	No	Study drugs and BP goals are discontinued, but Q3 month telephone and Q6 PCC visits with completion of all forms and MR imaging as per protocol.
ESRD (Study B)	No	No; Vital Status Only [b]
Transplant (Study A or B)	No	No; Vital Status Only [b]
Cyst Reduction / Nephrectomy (Study A)[a]	Yes	Study Protocol without renal MR/ MRA. Cardiac MR and other protocol continue.
Cyst Reduction / Nephrectomy (Study B) [a]	Yes	Full protocol
Pregnancy (>12 weeks)	Resume 3 months postpartum and post lactation	Stop all study meds, transfer care to PCP, but continue to follow Q3 month (phone/clinic BP, all AEs, no imaging). Participants may re-enter the study 3 months after a pregnancy of >12 weeks duration or immediately after lactation (whichever is later).
Pregnancy (<12 weeks)	Resume 2 months postpartum	Stop all study meds, transfer care to PCP, but continue to follow Q3 months (phone/clinic BP, all AEs, no imaging). Participants may re-enter the study 2 months after a pregnancy of <12 weeks duration.
Serious Adverse Event [a]	Yes	As per full protocol of respective study
Participant refuses home BP monitoring but agrees to study visits Q 6 months [a]	Yes	All investigations scheduled for the respective PCC visit.
Participant refuses clinic visits	No	Participant to choose desired level of follow-up and provide written consent for such. Obtain local bloods, central serum creatinine and BP from PCP/nephrologist.
PI discontinues study drug for health/safety reasons	No	Continue 6 month PCC visits, completion of forms, labs and MRs per protocol
Participant moves to a different	Yes	Transfer care to the nearest HALT-PKD PCC. However, participant

HALT region[a]		does have the option to continue follow-up with the original PCC.
Participant lost to follow-up without knowledge of study personnel	If participant reappears	1. Exhaustive efforts to contact the participant 2. Continued follow-up from point of reappearance 3. Check vital status with Vital Statistics via SS # and USRDS (via SS#) if all else fails

[a] Once the GFR falls to <30 mL/min/1.73 m^2, participants will have more frequent follow-up visits with their primary nephrologists than every 6 months (the HALT study visit frequency). For these participants, the study requires additional safety testing (serum creatinine and potassium) at three- month intervals. Dose modifications may be made by the treating nephrologist (e.g. for hyperkalemia/ fluid overload) and these will be tracked at the 3-month telephone or 6-month visits to the HALT PCC. The HALT Study will continue to provide study medications until participants reach a 50% reduction in eGFR from baseline, ESRD, transplant, death or another reason for termination of drugs ensues.

[b] Vital Status ascertained through 6-month telephone follow-up.

12.6.1. Modifications in Follow-Up in the Event of Pregnancy

Because ACE-Inhibitors and ARBs are harmful to a fetus in the second and third trimesters, pregnancy is an exclusion criterion. Prior to randomization, every effort should be made to exclude participants who intend to become pregnant over the course of the study. For the rare participant who becomes pregnant after randomization, study drugs must be stopped. However, pregnancy is not considered a stopping point for study participation (participants need not be permanently withdrawn from the study).

12.6.1.1. Pregnancy Prior to Randomization

If a female participant signs the study consent and completes all eligibility criteria at the screening visit, she may be enrolled to the study and start the drug washout period. If the participant becomes pregnant prior to the baseline visit, she will not be randomized but will be considered a screen failure, even if she has already been enrolled and/or intends to terminate the pregnancy. Study medications must be discontinued immediately and a Screen Failure Form (Form 14) must be completed and data-entered as soon as possible. The participant will be referred to her primary care physician (PCP) for management of the pregnancy and will not be followed under intent-to-treat. Such participants can be screened for the study again but must wait a minimum of 3 months after termination of a pregnancy of >12 weeks duration or immediately after breastfeeding stops (whichever is later) or 2 months after termination of a pregnancy of <12 weeks duration.

12.6.1.2. Pregnancy after Randomization

If a female participant becomes pregnant *after* she has been randomized and is *currently* pregnant at the time study staff learn of the pregnancy, study drugs must be stopped immediately and the Study Medication Form (Form 11) must be completed and data-entered as soon as possible. The participant will be referred to her PCP for management of the pregnancy and hypertension. With β-HCG screening at baseline and in women who have missed a regular menstrual cycle, all participants should be identified within the first trimester, minimizing teratogenicity. Should the woman and her doctor decide that study medications should be unmasked (ARB versus placebo), the study arm assignment will be unmasked upon receipt of written permission from the PI. For all pregnancies, the event must be reported on the Symptoms Checklist (Form 5 - #5b). Modifications to study drugs and follow-up are described below. Follow-up will be the same, irrespective of whether study arm assignment remains masked or not.

Required Modifications for Pregnant or Lactating Participants:

1. Study drugs (ACE-IARB or ACE-I/placebo) therapy must be discontinued immediately.
2. All other study medications must be discontinued and participant care transferred to the PCP.
3. Pregnant or lactating participants will continue to be followed every three months by telephone (adverse events and medications only) and every six months at the PCC (for all required tests).
4. Pregnant or lactating participants will *not* be imaged (due to gadolinium). Home BP monitoring is not required.
5. Participants may re-enter the study, without being rescreened or reconsented, at 3 months after termination of a pregnancy of >12 weeks duration or immediately after breastfeeding stops (whichever is later) or 2 months after termination of a pregnancy of <12 weeks duration.

In rare circumstances, where life-threatening illness or complication precludes ongoing participation, the participant may be withdrawn from the study, at the discretion of the PI. For most participants however, modified participation in the study will continue as described above.

Planned or Spontaneous Abortion After Randomization: If the participant becomes pregnant after she has been randomized, but has had a planned or spontaneous abortion by the time study staff learn of it, study medication need *not* be discontinued nor should follow-up be modified. The event (abortion) must be reported on Symptoms Checklist Form 5 (other event).

13. STATISTICAL ANALYSIS

13.1. Statistical Power and Sample Size Calculations for Study A

The statistical model for testing the treatment effect in Study A is the random coefficients model of Laird and Ware [Laird, 1982]. To compute the necessary sample size/power we need to estimate the average rate of change in total kidney size, the standard deviation of the slopes (σ_s) across participants, and the standard deviation of the noise (σ_n, deviations around the linear trajectories for each participant). Because the variance in the measurement errors appear to be closer to a constant coefficient of variation and the variability in kidney sizes from baseline to year 1 in CRISP appears to be greater for those with larger kidneys at baseline, we have worked on the $\log_{10}$ scale which translates into a % change in kidney size.

Using the CRISP data for those who were diagnosed as hypertensive at baseline (snapshot of 12/22/03), we have observed a mean change of .0230 or a 5.4% increase. The standard deviation of the noise (σ_n) was estimated to be 0.019 and the standard deviation of slope across individuals (σ_s) to be 0.018.

Looking at the main effects and using the method of Lefante (Lefante, 1990) and the protocol of measuring kidney size at baseline, 2 years, and 4 years, and 5 years, we have calculated the necessary sample size (each group) for various effect sizes for a powers of .80 and .90, with a significance level of .05 (2- tailed):

Power Calculations for Study A with year 5 extension for ALL subjects

Proportion Slowing	% Increase in Active Group	Total N Power=0.80	Total N Power=0.90
0.20	4.32	520	696
0.25	4.05	333	445
0.30	3.78	231	309
0.35	3.51	170	227
0.40	3.24	130	174

Although there are 4 cells in the design, if there is no interaction we can combine cells within rows or columns so that the effective sample size would be all of those randomized to the aggressive blood pressure goals versus all of those randomized to conventional blood pressure goals. Similarly, we can combine all of those randomized to ACE-I/ARB with all of those randomized to ACE-I. If we use these calculations for each of the two hypotheses for Study A tested independently, then we will have a power to detect an effect size of slowing the progression by 25% (e.g. from 5.4% to 4.05%) at a power of .953 with the 558 recruited participants. If we assume no follow-up information for 15% of those recruited, then the remaining 475 participants would achieve a power of .918 for each of the hypotheses.

Power Calculations for Study A with year 5 extension for ALL subjects

Proportion Slowing	% Increase in Active Group	Power N=558	Power N=475
0.20	4.32	0.827	0.764
0.25	4.05	0.953	0.918
0.30	3.78	0.992	0.980
0.35	3.51	0.999	0.997
0.40	3.24	>0.999	>0.999

13.2. **Analytic Methods for the Primary Outcome of Study A**

The two treatment factors (ACE-I/ARB vs ACE-I; normal vs. aggressive BP control) will each be tested at a significance level of .05 (2-tailed).

The participants will be seen and imaged at years 0, 2 ,4 and 5, giving four measurement points for the primary outcome variable of total kidney volume (TKV). Other variables that will be measured include a variety of blood and renal chemistry indicators (i.e., serum creatinine, GFR).

Analysis of these data will primarily utilize random regression methods. To improve the stability of the estimation process and reduce the impact of larger KVs on the overall assessment process, log (KV) will be examined. With four time points, there is enough data to establish the overall slope for the individual and some measure of uncertainty, assuming linearity of the measure. If the changes are assumed to be quadratic, the shape of the line could be determined at the cost of the measurement of uncertainty. Thus, linearity will be assumed unless the evidence for quadratic change is strong. A Laird and Ware linear mixed model will be used to model the trajectory of lnTKV between groups. There will be fixed effects for time, group (ACE-I vs. ACE-I + ARB; low BP vs. standard BP), and their respective interaction. The intercept and slope will be allowed to vary randomly, but the latter random effect may be removed if there is a lack of slope variability.

Using the methods of Laird and Ware (Laird, 1982) and others based on this notion, several important comparisons can be made to test the main hypotheses:

Hypothesis 1 (involving the ACE -I/ARB vs. ACE-I comparison) will be tested by random regression methods. The primary test of the hypothesis will involve a contrast comparison of the slopes of the random regression lines between these two conditions.

Hypothesis 2 (involving the normal vs. low BP comparison) will be tested by a contrast comparison of the slopes of the random regression lines between these two conditions.

In both of these comparisons, a variety of important covariates will be introduced. These include age, sex, and baseline GFR. These all attempt to statistically equate the groups over possible important differences, although these are not expected to be large by random assignment (this will be monitored during the randomization phase). Although missing data are not expected to be an overly large problem (assuming that the participant population for this disease is very enthusiastic about the study), the random regression methods are somewhat robust to this problem. Obtaining two of the four observations of the primary outcome variable is essential, however.

One important issue is the lack of the existence of an interaction between the two factors. The power estimates depend on this assumption, since pooling over groups is assumed, and the existence of a significant interaction would make such pooling questionable. For this reason, an interim analysis will be performed to examine evidence for the interaction at a point at which roughly half of the cases have been accrued. If the evidence for a significant and crossing interaction is found, the Steering Committee will consider the situation. Note that pooling would still be valid, if the interaction is of the divergent (rather than crossing) type.

13.3. **Analytic Methods for the "Primary" Secondary Outcome of eGFR**

The two treatment factors (ACE-I/ARB vs ACE-I; normal vs. aggressive BP control) will each be tested at a significance level of .05 (2-tailed).

CKD-EPI eGFR will be calculated using serum creatinine measurements, which will be obtained at the baseline, F5 visit, F12 visit, and at every subsequent 6-month visit. This will yield 11 measurement points for the secondary outcome variable of eGFR.

Analysis of these data will utilize random regression methods. With 11 time points, there is enough data to establish the overall slope for the individual and some measure of uncertainty, assuming linearity of the measure. If the changes are assumed to be quadratic, the shape of the line could be determined at the cost of the measurement of uncertainty. Thus, linearity will be assumed unless the evidence for quadratic change is strong. A Laird and Ware linear mixed model will be used to model the trajectory of eGFR between groups. There will be fixed effects for time, group (ACE-I vs. ACE-I + ARB; low BP vs. standard BP), and their respective interaction. The intercept and slope will be allowed to vary randomly, but the latter random effect may be removed if there is a lack of slope variability.

Using the methods of Laird and Ware (Laird, 1982) and others based on this notion, several important comparisons can be made to test the main hypotheses:

Hypothesis 1 (involving the ACE -I/ARB vs. ACE-I comparison) will be tested by random regression methods. The primary test of the hypothesis will involve a contrast comparison of the slopes of the random regression lines between these two conditions.

Hypothesis 2 (involving the normal vs. low BP comparison) will be tested by a contrast comparison of the slopes of the random regression lines between these two conditions.

In both of these comparisons, a variety of important covariates will be introduced. These include age, sex, and baseline GFR. These all attempt to statistically equate the groups over possible important differences, although these are not expected to be large by random assignment (this will be monitored during the randomization phase). Although missing data are not expected to be an overly large problem (assuming that the participant population for this disease is very enthusiastic about the study), the random regression methods are somewhat robust to this problem.

One important issue is the lack of the existence of an interaction between the two factors. The power estimates depend on this assumption, since pooling over groups is assumed, and the existence of a

significant interaction would make such pooling questionable. For this reason, each interim analysis will include examination of significant interaction effects. If the evidence for a significant and crossing interaction is found, the Steering Committee will consider the situation. Note that pooling would still be valid, if the interaction is of the divergent (rather than crossing) type.

13.4. **Analytic Methods for the Secondary Outcomes of Study A**

Similar to analyses used for the primary outcome, the effects of the two treatment factors (ACE- I/ARB versus ACE-I; normal versus aggressive BP control) on the secondary outcomes will be tested at a significant level of 0.05 (2-tailed). Besides these treatment factors, the important covariates such as age, gender and baseline GFR will also be included within each analysis to statistically adjust for their possible impacts. The actual choice of statistical methods for each secondary outcome depends on the variables of interest.

To assess the association between treatment factors and adverse events of study medication, logistic regression will be used [Seber, 1989]. The primary interest is to model the relationship between those predictive factors and the probability of occurrence for each type of adverse event. A significant effect means that the probability of the adverse event is different among the factor levels.

To evaluate the impacts of the treatment factors on all-cause or cardiovascular disease-specific hospitalizations, Cox regression model for recurrent events will be used [Prentice, 1981]. The outcome of interest in this model is time to event (hospitalizations). The method takes a conditional approach to handle recurrent events, i.e., assuming that a participant is not at risk for the 2^{nd} event unless he/she has experienced the 1^{st} event. The interest of this method is to marginally compare the hazards of hospitalization between two conditions for each treatment factor (ignoring the existence of the other factor). An alternative choice is the method by Anderson and Gill [Anderson, 1982]. This model provides an easy way to handle recurrent survival data, but it has a relatively strong assumption that the events are of the same type and independent. We will fit both types of models and if the results are concordant will report the Anderson and Gill model results since this methodology is more readily available in statistical packages. If the results are discordant we will carefully examine the fidelity of the data to the underlying model and report that model where the assumptions appear to be best satisfied.

For the other secondary outcomes (renal blood flow, left ventricular mass, albuminuria, aldosterone excretion and quality of life), random regression methods of Laird and Ware will be used [Laird, 1982]. In a similar approach to the analysis of the primary outcome, this method intends to compare the slopes of random regression lines between the two levels within each treatment factor. Exploratory data analyses will be conducted first for each outcome to see whether data transformations are needed so that the appropriate statistical assumptions for the model are met. For example, a logarithm scale may be used.

13.5. **Effect Modification in Study A**

We postulate differential effects of the two interventions (ACE-I/ARB combination therapy versus ACE-I monotherapy and two levels of blood pressure control) on cystic progression in specific subgroups noted to have faster rates of kidney growth in the literature. Interaction terms will be devised to test the following hypotheses:

a) Younger participants have lower absolute changes in kidney volume and interventions may not be as efficacious as in older participants. (Interaction: Age $\leq$30 vs. > 30*Intervention)
b) Males have been noted to have larger kidneys than females at a given age [Fick-Brosnahan, 2001] and may derive greater benefit. Results will be examined by gender and by gender for age (Interaction: gender *age <30 vs. $\geq$30)
c) Interventions may be more efficacious in faster growing kidneys. (Interaction: baseline kidney volume to be categorized based on baseline distribution* Intervention)
d) More aggressive growth in childhood may be associated with a greater response to the interventions (Interaction: In participants <30 y old, baseline kidney volume >75^{th} percentile vs. <75^{th} percentile *Intervention)

e) Interventions may be more efficacious in kidneys with reduced function (Interaction: >80 mL/min/1.73 m^2 vs. <80 mL/min/1.73 m^2 * Intervention)

13.6. **Power and Sample Size Calculations for Study B**

The power calculations for Study B were based on an analysis of the serum creatinine values in 134 ADPKD cases from MDRD whose initial GFR values were in the same range as the proposed study (MDRD Study A). The serum creatinine values were translated into estimated GFR values (eGFR) based on the 4-variable MDRD equation. We fit the Laird and Ware model to this data with a mean intercept of 34.9 [Laird, 1982]. The average slope was -0.342/month (-4.1/year). The standard deviation for the intercepts was 8.57 and 0.1956 for the slopes. The residual standard deviation was 2.1836.

We then conducted a Monte Carlo simulation of the trial in which the eGFR values were generated according to the proposed protocol using the random components from model fit from the MDRD data. Because the mean eGFR in the MDRD cohort was 34.9 at the beginning of the study and Study B participants must have an eGFR in the range of 30-60, we assumed that the initial eGFR values were uniformly distributed over the allowable range. We used an average slope of -.35/month. Because of concern that the slope estimate from MDRD might be too aggressive, we also used mean slopes of -.30 and -.25. We assumed that there were duplicate measures at baseline. We assumed that 400 participants would be recruited (200 in each treatment group) at a uniform rate over a period of 3 years. We assumed that follow up would continue until the last participant had been enrolled for 5 years. Thus individual participants were followed for between 5 and 8 years, with an average of 6.5 years of followup. If an eGFR at any visit was less than 50% of that for the baseline for that simulated participant, then a repeat creatinine was generated with the same expected value. If the mean of the triggering value and the repeat value were less than 50% of baseline then an endpoint was declared. The rate of reaching endpoints was compared in the two groups using a log rank test. The study, with the specified sample size, was then repeated 1000 times for each set of parameters and the empirical power calculated. The average 8-year survival rate (life table method) was also calculated as was an average hazard rate.

For the two group power calculations, the ACE-I monotherapy control group was assumed to have the rate of decrease in eGFR values seen in MDRD and the ACE-I/ARB group to have varying slowing of that rate. The observe powers were:

Reduction	8-Yr Survival		HR	Power
	Control	Treatment		
Slope = -0.25				
0.25	.442	.562	.70	.74
0.30	.442	.589	.65	.86
0.35	.444	.611	.60	.95
0.40	.442	.632	.56	.98
Slope = -0.30				
0.25	.352	.492	.67	.88
0.30	.352	.519	.61	.96
0.35	.353	.547	.57	.99
0.40	.353	.575	.51	>.99
Slope = -0.35				
0.25	.269	.419	.65	.94
0.30	.267	.453	.58	.99
0.35	.268	.485	.53	>.99
0.40	.267	.524	.48	>.99

The rows with power >.90 are shaded in gray. Using an average slope similar to that seen in MDRD (-0.35) we will have power >.90 with this design to detect a slowing in the rate of change of eGFR by 25%. If we assume a slower slope of -0.30 we will have power to detect a slowing of 30% and even if it is as shallow as -0.25 we will have adequate power to detect a slowing by 35%.

We also conducted sensitivity analyses and obtained similar results if we used either the log of creatinine or the reciprocal of creatinine as the parameter to be modeled. Results were also not different if we used a normal distribution of baseline eGFR with a mean of 45 (same as used above) with a standard deviation of the intercept of 8.57, corresponding to the variability seen in MDRD.

As for Study A, if we assume a 15% dropout rate, then we would need to recruit a total of 470 (235 in each group).

13.7. **Analytic Methods for Primary Outcomes of Study B**

Each participant will be treated in one of two conditions:

1. ACE-I/ARB + standard BP control
2. ACE-I + standard BP control

The primary outcome variable for Study B is a composite endpoint of time to the 50% reduction of baseline eGFR, ESRD or death. Participants will be followed until the end of the study (5-8 years). Participants who do not reach one of the three endpoints at the end of the study will be considered to be right-censored.

The analysis method for this arm will primarily involve survival methods. The distribution of time to event will be summarized by Kaplan-Meier product limit estimators. Proportional hazards (Cox) methods for comparison of survival times with censored observations will be used to compare the difference between two arms. Age, sex, and baseline GFR will be used as covariates. Clinic will be entered as a stratification variable.

An important issue in Study B is the assumptions for the trajectory of eGFR over time. The possible number of events (and power estimates) will depend on these assumptions. For this reason, an interim analysis will be performed, when all participants have had at least one year of follow-up, to examine these assumptions and, thus, determine the necessity of possible remedy measures (i.e., extending the follow-up period to increase the power).

13.8. **Analytic Methods for Secondary Outcomes of Study B**

Analyses of the secondary outcomes in Study B (including rate of change in eGFR, albuminuria and aldosterone excretion, all- cause hospitalizations or hospitalizations due to cardiovascular cause, frequency of PKD-related symptoms or medical conditions, quality of life and pain measurement, as well as adverse effects of medications) will employ similar strategies as those used for the secondary outcomes in Study A, except that all participants in Study B will be under standard BP control and the comparison will be made between ACE-I/ARB and ACE-I alone.

One potential problem is that the analysis of eGFR slopes may be complicated by the existence of both acute and chronic effects as indicated by MDRD and AASK. For this reason, two samples (1 hour apart) for serum creatinine will be drawn at visits B1 (baseline) and F5 (4th month) as indicated in Section 6. The data will first be thoroughly examined. If a different slope is suggested in the initial few months, the values from F5 rather than B1 will be used as the initial measurements in the Laird and Ware random regression model for the rate of change in eGFR.

13.9. **Effect Modification in Study B**

Differential effects of ACE-I/ARB can be assessed using interaction terms defined by factors that have been associated with faster rates of progression in the literature. We propose to test for interactions between the intervention and age (age <45 vs. older than 45), gender, baseline level of renal function (e.g., above vs. below mean), and baseline level of albuminuria.

13.10. **Randomization**

Participants will be randomized *once* baseline eligibility criteria have been satisfied, and the participant has consented and been enrolled to the study. A web-based data-entry system will be used to enter the participant's demographic information and assign the participant to a study arm based on a random number generated at the time of data-entry. Randomization within each study will be stratified by study site, age (less than vs. greater than equal to 30 for Study A; 45 for study B), gender, race (Black, Non-Black), and level of renal function (less than vs. greater than equal to 75 mL/min/1.73 m^2 for Study A; 45 mL/min/1.73 m^2 for study B).

13.11. **Interim Analysis**

The time periods for the proposed studies are relatively long. During the period after the start of the study and prior to the designated endpoint, results will be monitored by the Data Coordinating Center, in conjunction with the DSMB, to ensure that data being obtained are scientifically valid and that participant safety is maintained. At each DSMB meeting, beginning 12 months after enrollment starts, interim results will be examined by the DCC and presented to the DSMB to determine whether conclusive and definitive results, which overwhelmingly point to one conclusion, have been obtained. For this purpose, a Lan-DeMets spending function [Lan, 1989] will be defined to ensure that the "peek" does not bias final conclusions. Data analyses will be reported that compares assumptions made for sample size calculations (e.g. rates of change in the control group) with accumulating data. All investigators (other than at the DCC) will remain masked to these interim efficacy results, to ensure that their continued participation is not affected.

14. **Data Collection and Quality Control Procedures**

The Data Coordinating Center (DCC) will be responsible for the data management system (DMS). The DMS is a web-based data-entry system (WDES) (front-end) and a fully-featured relational database (back-end). Study data will be collected at each clinical site on specially-designed study data collection forms to achieve as close to "real time" data-entry as possible.

14.1. **Participant and Form Tracking and Data-Entry Process**

As HALT-ID numbers and dates of registration are logged into the system, the master database will generate participant schedules and identify expected data collection forms and their associated due dates. Data collection forms will be programmed such that data-entry screens closely resemble the original paper forms. The data-entry clerk will enter data into the DMS from each data collection form. Fields will be set to exclude implausible entries. Missing values will generate queries requiring resolution. Queries will be tracked by the DMS. Even though the multiple steps described above reduce errors in data acquisition and entry, the data will undergo additional cleaning processes. A full database back -up will be performed daily using a network tape back- up system. The web application and databases will reside on different servers, with all servers behind a firewall. Access to WDES from outside the DCC will be restricted by the use of role-specific userid/passwords and by use of side door, a secure, reverse-proxy web server. Side door may be accessed only if a user-specific .p12 Certificate issued by the DCC has been successfully imported into a user's web browser. The DCC staff will control all queries and reports from the database.

14.2. **Forms Design and Manual of Procedures**

The Steering Committee will assist the DCC with development of effective data collection forms and a study Manual of Procedures to ensure the highest possible data quality. Form features will include assistance with selection of valid, reliable measurements that are least burdensome to participants, development and testing of reliability measures, pretesting of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open-ended questions, etc.) and smooth flow (clear skip patterns) to reduce missing data.

14.3. **Adherence**

Adherence to study medications and blood pressure goals will help ensure the study has the stated power to detect the effect size specified in the sample size calculation. Participants unlikely to understand the importance of maintaining follow up, as well as strict adherence to study medications and blood pressure goals for the entire duration of the study, or who are unable or unwilling to make the required visits during the screening and baseline periods, will not be enrolled and/or randomized. Those that fail to comply with blood pressure monitoring during the screening period may also be excluded. Participants will be asked to bring their pill packages to every follow-up visit to allow pill counts to be performed. Participants that miss scheduled study visits (either telephone or study site visits) will be contacted in a timely fashion by a study coordinator. Practical measures to minimize inconvenience (i.e. parking or stipends, if possible), maintaining communication with referring physicians, and other means of maintaining direct communication with the participant (follow-up and thank you cards after visits, birthday and holiday cards, small gifts) will assist in promoting adherence. Six-month follow-up visits will also aid in retaining study participants.

14.4. **Training, Retraining and Certification**

Since consistency of application of the study protocol is critical to acquiring high-quality data, all study coordinators will attend a project initiation meeting and undergo a competency-based training program and certification process prior to enrolling participants. Study coordinators will be required to review the Manual of Procedures and complete and pass scenario-based competency tests. Study coordinators will be observed conducting randomly-selected protocol duties during site visits (see below), at least twice during the study. These observed duties will be evaluated through use of checklists. Retraining will be conducted as necessary.

14.5. **Site Visits**

The Data Coordinating staff will lead site visits at each PCC at least twice during the conduct of the study. The review will include examination of all study procedures (control and intervention group), verification that the randomization system is being used correctly and that study group assignments are accurate, review of completed data collection forms, and review of procedures used to resolve queries. A specific site visit checklist will be used, and a report will be generated after the visit has been completed. The PI will be responsible for ensuring that any deficiencies noted during the site visit are corrected to the satisfaction of the Steering Committee.

14.6. **Laboratory Quality Control.**

Laboratory measurements used in assessing the primary outcome of doubling of serum creatinine will be measured through the Cleveland Clinic Foundation Reference Laboratory, which will be calibrated to the MDRD study lab, enabling use of the MDRD prediction equation for conversion of serum creatinine values to eGFR. Laboratory measurements to confirm a 50% reduction in eGFR from baseline can be obtained from either Cleveland Clinic or a Quest Lab, as both are calibrated to the same standard. Results from Cleveland Clinic will be sent directly to the DCC and then forwarded to the PCC within 24 hours.

15. Anticipated Problems and Solutions

15.1. Lower than Expected Study Enrollment

The DCC and study sites will keep close tallies on the expected and achieved numbers of participants enrolled over time at study sites. The means by which recruited participants learned of the study will be traced so that future resources may be directed to strategies that have been most successful. Direct contact with potential participants will be arranged through educational/informational sessions to be advertised in local hospitals and nephrology clinics, through PKD Foundation meetings, or through the PKD Foundation website. Television exposure through interviews on local news stations or public broadcasting will be arranged, as these have been shown to be highly effective in other studies. PCC recruitment coordinators will arrange visits to nephrology clinics/dialysis units outside the immediate vicinity of PCCs in efforts to increase recruitment.

15.2. Attrition and Non-Compliance

At the time of screening and potential enrollment, the importance of the longitudinal aspect of the study will be emphasized. Participants who do not believe they will be able to complete follow-up will be discouraged from enrolling. The study coordinator will identify non-compliant participants by lack of adequate blood pressure control at office visits, absence of home BP records, missed study visits, and failure to refill prescriptions for study drugs. More frequent contact (once every two weeks) will be made with those participants who are felt to be non-compliant.

15.3. Missing Data

As described in 14.1 above, the DMS will identify data collection forms that are expected, as well as their due dates. In the event of missing data, notifications and reminders will continue to be sent to PCCs until outstanding data issues have been resolved.

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