A Clinical Research Study To HALT Progression of Polycystic Kidney Disease (HALT PKD)

Manual of Procedures (MOP)

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Chapter 1. Purpose of the HALT PKD MOP

The HALT PKD Manual of Procedures is a confidential document and may not be disclosed to any party without the prior consent of the HALT PKD Steering Committee. Once disclosed, the HALT PKD Manual of Procedures must be held in trust and confidence and used for only the purpose(s) agreed to by the HALT PKD Steering Committee.

The purpose of the HALT PKD Manual of Procedures (MOP) is to provide study investigators with one all−encompassing source to use as a guide in carrying out HALT PKD studies. The HALT PKD MOP includes sections on study organization and administration; subject recruitment; protection of human subjects; publications and communications; study design; screening, enrollment, randomization and follow−up; blood pressure management; study drugs; safety; blood handling; measuring primary and secondary outcomes; data management (forms, web−based data entry system, quality control/assurance, statistical design and analysis, and reporting); and personnel. The complete MOP will remain posted on the HALT PKD website (private access) for the entire length of the study and will be updated as necessary. Study investigators will also be able to print complete copies of the HALT PKD MOP directly from the website, as needed. The Data and Safety Monitoring Board will also have private access to the web−based HALT PKD MOP.

T*he online version of the MOP is the most recent and complete. The DCC will add changes as necessary and will notify study personnel when changes have been posted.* ***It is the responsibility of PCC personnel to ensure that all paper versions of the MOP are kept up to date.***

Chapter 2. Introduction and Background

2.1. Preface

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 enrolled in Study A will be followed for 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 the 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.

2.2. Background and Rationale

We propose to perform a large randomized clinical trial to determine the impact of intensive blockade of the rennin- 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 glomerular filtration rate (GFR) greater than 60 mL/min/1.73m_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.

2.2.1. 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

<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.

2.2.2. 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. Study A included individuals with GFR of 25−55 mL/min/1.73 m_2 treated with a low protein/low phosphorous diet versus regular protein diet and aggressive versus usual blood pressure control. Study B included individuals with GFR of 13−24 mL/min/1.73 $m_{2\ t}$reated with a very low protein/phosphorous diet supplemented by ketoacids or a low protein/low phosphorous diet and aggressive versus usual blood pressure control. Aggressive blood pressure control was defined as mean arterial pressure (MAP) </=92 mm Hg for age </=60 and </=98 mm Hg for age >60.

In patients with GFR between 25 and 55 mL/min per 1.73 m2, 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 m2, 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/1.73m2 (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.

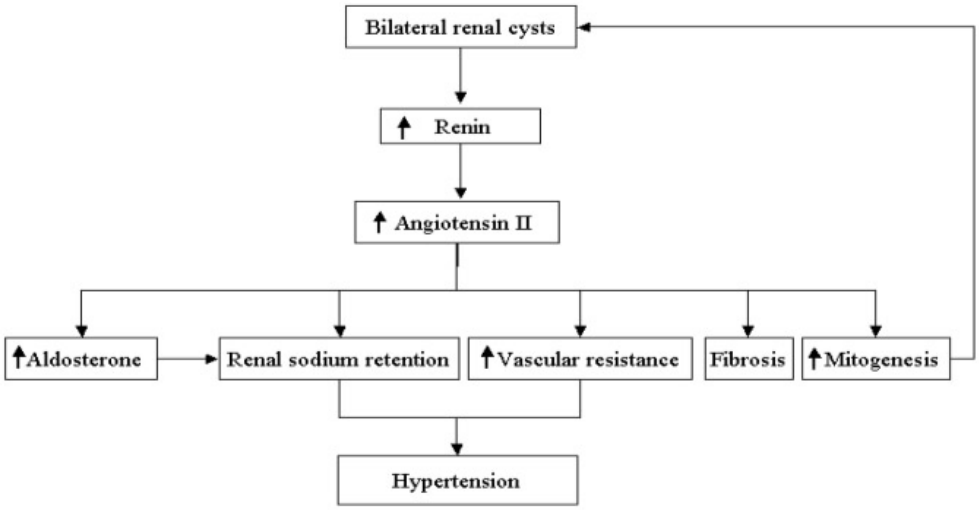
2.2.3. Molecular Pathogenesis of ADPKD

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)*.

2.2.4. 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−2997), (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−beta *(Ruiz−Ortega−1997)*. Recent experimental data in rats demonstrated that chronic low−dose angiotensin II infusion stimulated the production of TGF−beta 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−beta 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.

2.2.5. Renal Volume as a Marker of Disease Progression in Early Stages

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) provide convincing data showing 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 reassessed several years later. The studies also identify other variables that influence kidney and cyst growth and the relationship with function.

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. These data did not have the power to reach statistical 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 cm3/ 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 m_7. 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 renal and cyst volume 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 2−1. True and Measured Volumes of Balloon Phantoms

Location	Size	True	Volume	Measured Mean	Volume (SD)	Proportio n 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 2−2. Measured Clinical Variables of the Standardization Protocol Subjects

Variable	Mean + S.D.	Range
Height (cms)	175.75 +/− 16.51	167−200.5
Weight (kgs)	71.20 +/− 24.72	56.7−108.1
BMI (m2)	22.47 +/− 3.05	20.33−26.89
BSA (m2)	1.86 +/− .40	1.63−2.49
GFR ml/min/1.73m2	94.75 +/− 30.55	66−137

2.2.6. 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 2−3. Regression Model Predicting GFR: Effect of Age, Sex, Renal Volume and RBF

Source	F Value	P Value	R Value	P Value
Age	5.84	0.0172	-0.3899	0.0001
Sex	2.21	0.1397	0.0761	0.3894
Diagnosis of Hypertension	0.17	0.6839	-0.1883	0.0347
Total Corr Renal Blood Flow	27.54	<0.0001	0.5172	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.

2.2.7. 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), (Fernandez−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−1984)*. 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.

2.2.8. 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)*.

2.2.9. Use of ACE-1 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 *(KDOQI−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 Beta−Blockers were not. In summary, there is strong justification for the use of ACE−I in as the control agent for both early and moderately advanced ADPKD in the HALT PKD Study.

2.2.10. Rationale of 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 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 m_2, 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.

2.2.11. Summary

In summary, demonstration that rigorous treatment with a combination of ACE−I and ARB will attenuate renal disease progression and cardiovascular squeal 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.

2.3. Specific Aims

2.3.1. 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).

2.3.2. 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 ACE−I/ARB combination 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.

2.3.3. 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).

2.4. Synopsis of Study

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 Imaging (MR).

Study B will assess the efficacy of intensive RAAS blockade using ACE−I/ARB combination 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 3 months.

Chapter 3. Study Organization and Administration

3.1. Overview

The Polycystic Kidney Disease−Treatment Network (HALT PKD) includes seven Participating Clinical Centers (PCCs), the Data Coordinating Center, the Project Office at the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), a Steering Committee, and a number of subcommittees. Principal investigators and their staffs participate in the activities of the HALT PKD subcommittees, as does the NIDDK Program Director. An External Advisory Committee (EAC) has been formed and reports directly to NIDDK.

3.2. PKD-TN (HALT PKD) Steering Committee

The PKD−TN (HALT PKD) Steering Committee is charged with developing study procedures, protocols. It includes principal investigators from the participating clinical centers (PCC) and the Data Coordinating Center (DCC), as well as staff physicians from NIDDK. The PCC's and principal investigators (PI's) with responsibility for recruiting and following study subjects are: University of Colorado Health Sciences Center in Denver (Dr. Robert Schrier), Emory University in Atlanta, Georgia (Dr. Arlene Chapman), the Mayo Clinic in Rochester, Minnesota (Dr. Vicente Torres), and Tufts University−New England Medical Center in Boston, Massachusetts (Dr. Ron Perrone). Three additional participating clinical centers and co−investigators are Beth Israel Deaconess Medical Center in Boston, Massachusetts (Dr. Ted Steinman), the Cleveland Clinic Foundation in Cleveland, Ohio (Dr. Bill Braun), and Kansas University Medical Center in Kansas City, Kansas (Dr. Jared Grantham). The Data Coordinating Center (DCC), originally managed by Professor J. P. Miller at Washington University in St. Louis, began the transition of the DCC's 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's DCC led by Dr. James Bost (August 2008 – October 31, 2011), transitioned the DCC's Principal Investigator responsibilities to Dr. Charity G. Moore on November 1, 2011. Dr. Kaleab Abebe became the DCC's lead biostatistician on April 1, 2012.

All major scientific decisions are determined by majority from the voting members of the Steering Committee. Dr. Robert Schrier was elected as Chair of the Steering Committee, with Dr. Arlene Chapman elected as Vice−Chair. The Steering Committee has formed a number of subcommittees, made up of investigators and staff, which are described in Section 3.9 − Subcommittees. Each Steering Committee member, which now includes Dr. Michael Flessner (NIDDK Program Scientist), has a vote. Principal investigators attend all Steering Committee Meetings, with co−investigators invited at the discretion of PI's. Study coordinators and other ancillary staff may also be invited to attend Steering Committee meetings at the discretion of the PI's.

Contact information for Steering Committee members can be found on the HALT PKD website (https://www.halt−pkd.pitt.edu/web) under Research Teams Address Directory.

3.3. National Institute of Digestive & Diabetic & Kidney Diseases (NIDDK)

Dr. Michael Flessner serves as the NIDDK Project Scientist for HALT PKD and is a voting member of the Steering Committee. In her role as Project Officer, Dr. Flessner provides scientific support for the activities of the investigators. These activities include protocol development, quality control, interim data monitoring, final data analysis and interpretation, preparation of publications, and overall performance monitoring. Dr. Flessner is also responsible for forming and coordinating the activities of the HALT- PKD External Advisory Committee and subsequent Data Safety and Monitoring Board. He is the Executive Secretary of the DSMB.

Dr. Laura Moen joined the HALT PKD study in March, 2006, as NIDDK Project Officer, and worked with Dr. Meyers in carrying out the above−described activities. In July 2009, Dr. Marva Moxey−Mims assumed the position of NIDDK Project Officer. Dr. Michael Flessner became the NIDDK Project Scientist for HALT PKD in September 2010. Dr. Moxey-Mims continues as the NIDDK Program Officer. Drs. Laura Moen and Meyers are no longer affiliated with the HALT PKD Study.

3.4. 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 HALT PKD protocol requires EAC approval before the study can begin. Once recruitment is underway, members of the EAC will serve on the Data Safety and Monitoring Board (DSMB).

The EAC previously approved the HALT PKD protocol, in principle, at a meeting held on January 29, 2003. The EAC granted final approval to HALT PKD Study A during a conference call held on September 20, 2005. Final approval for HALT PKD Study B was granted during a conference call held on October 31, 2005.

The members of the HALT PKD EAC (DSMB) serving up to June 30, 2012 included: William Henrich, UT Health Science Center at San Antonio – Chairman

- ◊ Josephine Briggs, The National Institutes of Health
- ◊ Tom Greene, University of Utah
- ◊ Peter McCullough, William Beaumont Hospital
- ◊ Sharon Moe, Indiana University
- ◊ Michael Rocco, Wake Forest University
- ◊ James Shayman, University of Michigan
- ◊ Robert Toto, UT Southwestern Medical Center
- ◊ David Wendler, The National Institutes of Health, Clinical Center

As of July 1, 2012, the current members of the HALT PKD EAC (DSMB) include:

- ◊ James Shayman, University of Michigan – Chair
- ◊ Josephine Briggs, The National Institutes of Health
- ◊ Tom Greene, University of Utah
- ◊ Peter McCullough, William Beaumont Hospital
- ◊ Sharon Moe, Indiana University
- ◊ Michael Rocco, Wake Forest University
- ◊ David Wendler, The National Institutes of Health, Clinical Center
- ◊ Mary Leonard, Children's Hospital of Philadelphia

3.5. Data Safety and Monitoring Board

Once participant recruitment for HALT PKD begins, the External Advisory Committee (EAC) will become the Data Safety and Monitoring Board (DSMB). The charge of the DSMB is to regularly monitor study data, review and assess study performance, and make recommendations, as appropriate, to NIDDK in regard to: 1) performance of individual centers; 2) issues related to participant safety and informed consent, including notification of and referral for abnormal findings; 3) adequacy of study progress in terms of recruitment, quality control, data analysis, and publications; 4) issues pertaining to participant burden; 5) impact of proposed ancillary studies and sub−studies on participant burden and overall achievement of the main study goals; and 6) overall scientific direction of the study. NIDDK is responsible for organization and scheduling of DSMB meetings, while the Data Coordinating Center is responsible for providing the DSMB with the materials needed to complete its reviews. The DSMB will carry out its responsibilities for the duration of the HALT PKD studies.

- ◊ DSMB Charter

3.6. Data Coordinating Center

The HALT PKD Data Coordinating Center at Washington University in St. Louis had operational responsibility for the design, implementation, coordination and monitoring of all aspects of the study. The DCC has transitioned to the University of Pittsburgh in July 2009. The specific responsibilities of the coordinating center include:

1) Developing data collection forms, manuals, and recruitment and other study materials.
2) Developing and implementing study data management and communication systems.
3) Tracking, recruitment and adverse events.
4) Performing data management and quality assurance of study data.
5) Preparing data files and documentation for use by HALT PKD investigators and the larger renal community.
6) Developing and maintaining both the study and public web sites for HALT PKD.
7) Coordinating activities of central laboratories and repositories.
8) Reporting study benchmarks and results to the Steering Committee and DSMB.
9) Arranging and coordinating study teleconferences and meetings.
10) Providing biostatistical expertise to HALT PKD investigators and other users of study data.
11) Performing central training of study personnel and monitoring clinic performance.
12) Collaborating with HALT PKD investigators in producing, submitting, and tracking manuscripts in which to report study results.

3.6.1. Transition to the University of Pittsburgh

The Data Coordinating Center, originally managed by Professor J.P. Miller, at Washington University in St. Louis, began the transition of the DCC responsibilities to the University of Pittsburgh Center for Research on Health Care (CRHC) Data Center on 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 July 1, 2009. The University of Pittsburgh's 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's lead biostatistician on April 1, 2012.

3.7. Participating Centers

Responsibilities of Participating Clinical Centers include:

1) Collaborating in designing and monitoring of the study, including regularly attending Steering Committee meetings
2) Recruiting a specified number of participants for the study according to inclusion and exclusion criteria as stated in the study protocol.
3) Performing all study procedures according to protocol and collecting data in a standardized fashion.
4) Ensuring the safety, confidentiality and ethical treatment of study participants.
5) Collaborating in analysis and dissemination of study results.

Subjects are evaluated in person at one of seven participating clinical centers (PCC's), four led by HALT PKD principal investigators and three led by HALT PKD co−investigators. Each individual PCC is listed below.

- ◊ Beth Israel Deaconess Medical Center, Boston, Massachusetts
- ◊ Cleveland Clinic Foundation, Cleveland, Ohio
- ◊ Emory University, Atlanta, Georgia
- ◊ Kansas University Medical Center, Kansas City, Kansas
- ◊ Mayo Clinic, Rochester, Minnesota
- ◊ Tufts−New England Medical Center, Boston, Massachusetts
- ◊ University of Colorado Health Sciences Center, Denver, Colorado

Contact information for each PCC may be found in the HALT PKD Directory − Section 18.1 as well as on the HALT PKD website (https://www.halt−pkd.pitt.edu/web) under Research Teams Address Directory.

3.8. Project Management

The Project Manager and Research Program Coordinator for HALT PKD are responsible for overall operational management of the study and are based at the Data Coordinating Center (DCC).

3.8.1. Project Manager

The role of the HALT PKD Project Manager is to act as a liaison between investigators from the DCC, PCCs and NIDDK. Responsibilities of the Project Manager include coordinating and attending Steering Committee meetings and conference calls, as well as taking minutes for each, assisting in production of HALT PKD study forms and the HALT PKD Manual of Procedures, and creating and maintaining the HALT PKD website. *Contact information for the HALT PKD Project Manager may be found on the HALT−PKD website (https://www.halt−pkd.pitt.edu).*

3.8.2. Research Program Coordinator

The role of the Research Program Coordinator is to act as a liaison between study coordinators and the DCC. Responsibilities include coordinating and/or participating in the work of HALT PKD subcommittees, attending meetings and conference calls, assisting in production of HALT PKD study forms and the HALT PKD Manual of Procedures, and tracking all regulatory documents and IRB approvals across clinical sites. *Contact information for the HALT PKD Research Program Coordinator may be found on the HALT−PKD website (https://www.halt−pkd.pitt.edu).*

3.9. Subcommittees

The Steering Committee has established nine subcommittees and has appointed Chairs for each of them. These subcommittees have been established to address specific aspects of HALT−PKD and to provide information and recommendations to the Steering Committee in regard to the study. Additional subcommittees will be formed by the Steering Committee as required.

All recommendations made by subcommittees must be submitted in writing to the HALT PKD Project Manager, who, in turn, will submit them to the Steering Committee for review and approval within a specified time frame. All subcommittee recommendations must be approved by the Steering Committee prior to implementation.

3.9.1. Blood Pressure - Vicente Torres, Chair

The Blood Pressure Subcommittee deals with the detailed protocols for all blood pressure measurements (in clinic, at home, ambulatory), as well as with the protocols for stepping through and augmenting study medications. During the conduct of the study, this Subcommittee will monitor the blood pressure measurements being obtained to compare with therapeutic goals.

☞ An email listserv has been established to facilitate EP Committee communication. Email may be sent to the EP Committee list at the following address: *haltendpoints@list.pitt.edu*

3.9.2. Clinical Coordinating and Retention – Theodore Steinman, Chair

The Clinical Coordinating and Recruitment Subcommittee deals with operational issues of the protocol from the perspective of the clinical staff. Particular attention is given to issues related to recruitment and retention of HALT PKD participants.

3.9.3. Endpoints – Dana Miskulin, Chair

The Endpoints Subcommittee established procedures and reviews endpoints in HALT PKD to assure that they target relevant PKD−related events and are appropriate reflections of PKD pathophysiology. Procedures will also be established to deal with therapeutic interventions that might alter study endpoints, e.g. cyst reduction surgery. The endpoint committee convenes monthly and reviews modified participation reports that outlines the cumulative totals and participants modified during the previous month. All recent endpoint determinations reached by 50% reduction in eGFR are reviewed in detail by the committee.

3.9.4. Executive – Robert Schrier, Chair

The Executive Subcommittee will hold regularly−scheduled conference calls in which to discuss the progress of the study, as well as to plan meetings of the Steering Committee and the DSMB/EAC. The Executive Subcommittee is made up of the Chair and Co−Chair of the Steering Committee, the PI of the Data Coordinating Center, and the NIH Project Officer.

3.9.5. Forms – Arlene Chapman

The charge of the Forms Subcommittee is to develop HALT PKD study forms. All proposed forms, as well as revisions to existing forms, must be reviewed and approved by the Forms Subcommittee and, subsequently, the Steering Committee prior to implementation.

3.9.6. Genetics – Peter Harris, Chair

The charge of the Genetics Subcommittee is to develop policies to govern the use of genetic data or samples from HALT PKD.

3.9.7. HALT/CRISP Liaison

The HALT/CRISP Liaison Subcommittee was formed to address issues affecting both the HALT PKD and CRISP studies. Its members include the NIDDK Project Manager, the Steering Committee chair from each study, and two investigators who participate in both studies.

3.9.8. Imaging – Ty Bae, Chair

The Imaging Subcommittee is charged with developing and implementing accurate and reproducible imaging techniques for measuring the primary and secondary outcomes for HALT PKD Study A. These primary and secondary outcomes are listed below:

1) Total Kidney Volume by MR (Primary)
2) Renal Blood Flow by MRA (Secondary)
3) Left Ventricular Mass by MR (Secondary)

The Imaging Subcommittee will also serve as the initial forum for decisions and appeals of imaging−related issues, and its recommendations will be referred to the Steering Committee for final decisions. Other responsibilities of the Imaging Subcommittee have been listed below:

- Develop protocols for imaging studies.
- Establish standardization of the imaging data. Formulate strategies to improve image data acquisition, collection, transmission, storage, and analysis.
- Evaluate the training of imaging technologists and quality controls.
- Assist the members with imaging-related technical supports

☞ An email listserv has been established to facilitate Imaging Committee communication. Email may be sent to the Imaging Committee list at the following address: *haltimaging@list.pitt.edu*

3.9.9. Publications/Ancillary Studies – Arlene Chapman, Chair

The responsibility of the Publications/Ancillary Studies Subcommittee is to establish policies and procedures for assigning working groups and approving HALT PKD−associated ancillary studies, abstracts, presentations, and publications prior to submission. All proposals for ancillary studies in which any HALT PKD resources will be used must first be reviewed and approved by the Publications/Ancillary Studies Subcommittee and then forwarded to the HALT PKD

Steering Committee for approval. No ancillary study may be implemented without having received prior approval from the Steering Committee.

The HALT PKD Ancillary Studies Policy is listed in Section 3.13.
The HALT PKD Publications Policy is listed in Section 6.1

3.9.10. Quality Control – Ronald Perrone, Chair

The Quality Control Subcommittee will review and discuss reports of visit completeness, adverse events (including SAEs, such as deaths and hospitalizations), serum creatinine doubling, and relevant safety parameters on a monthly basis, or earlier as necessary. Quality control of the data acquired and entered by the clinical centers, the central laboratories and the Data Coordinating Center are also under the purview of the Quality Control Subcommittee. Additionally, this subcommittee reviews all submitted protocol violations that occur study wide.

An email listserv has been established to facilitate Imaging Committee communication. Email may be sent to the Imaging Committee list at the following address: *haltqualcont@list.pitt.edu*

3.9.11. Closeout – Marie Hogan, Chair

This subcommittee will develop protocols to guide and monitor the implementation if the HALT PKD Clinical Trial closeout. The protocol will provide the framework for the participating clinical centers (PCC) in closing out all HALT PKD activities including: laboratories, CTRC clinics, pharmacies, radiology and clinical research offices. Included in the document will be a list of responsibilities to be managed by the Data Coordinating Center. Principal Investigators and research staff, along with a projected timeline of events outlining target dates for closeout procedures. Details on the transition of participants back to the care of a local PCP of nephrologist will be outlined. Refer to the Manual of Procedures (MOP) Chapter 17 for more information.

3.10. Revisions to Study Policies and Procedures

The HALT PKD Manual of Procedures was developed according to the study protocol. As HALT PKD moves forward, it is likely that revisions to the protocol may, on occasion, be necessary. **Any proposed change to the study protocol must be submitted, in writing, to the Steering Committee for review and approval. No change may be put into effect until Steering Committee approval has been granted, as well as IRB approval, if required.** Once a proposed change to the study protocol has been approved by the Steering Committee, the DCC will incorporate the change into the MOP. Revisions to the MOP that do not affect the protocol should be addressed as follows:

Minor Revisions

- Minor changes to the MOP will be made by the DCC and communicated to study personnel via e−mail. Minor revisions are items such as a change in a lab address or a change in study personnel.

Significant Revisions

- As study investigators gain experience and determine best practices, suggestions for changes in study policies or procedures are likely to result in significant revisions to the MOP. The steps involved in proposing and making a significant revision to the MOP are listed below:
  i. To suggest a change in study policies or procedures that does not necessitate revision to the study protocol, forward a draft of the proposed change, by e−mail, to the Project Manager.
  ii. The Project Manager will circulate the draft to the members of the Steering Committee and study coordinators for review.
  iii. Steering Committee members and study coordinators are to review the draft of the proposed change in study policy or procedure and forward their comments and suggestions to the Project Manager within two weeks.
  iv. The Project Manager will revise the draft proposal, based on comments and suggestions from Steering Committee members and study coordinators and forward the final proposal to the Steering Committee for approval.
  v. Once Steering Committee approval has been granted, the Project Manager will make the appropriate revisions to the MOP.

3.11. Laboratories

HALT PKD study samples will be collected and analyzed at a number of different laboratories as outlined in the study protocol. These include Participating Clinical Center (PCC) laboratories, Cleveland Clinic Foundation Reference Laboratory (CCF), The Biobehavioral Core Facility at the University of Pittsburgh Cancer Institute (UPCI), Quest Diagnostics Laboratories (nationwide), and local (hometown) laboratories. These laboratories are described in the subsections that follow. The Biobehavioral Core Facility, referred to here after as “UPCI, replaced Diagnostic Laboratory Facility (DLF) at Brigham and Women’s Hospital on June 1, 2010. In January of 2013, the processing of all study urine

samples was transferred to Cleveland Clinic Foundation Reference Laboratory (CCF).

For more information on collection and handling of serum creatinine samples, refer to Section 11.4 – Cleveland Clinic Foundation (CCF) Reference Laboratory – Serum Creatinine Measurements.

3.11.1. PCC Laboratories

PCC laboratories are those laboratories that are physically located at each of the seven clinical sites. All clinical sites utilize GCRCs when possible and appropriate. The GCRC staffs are responsible for collecting and handling blood and urine samples, as well as sending the samples on for analysis.

3.11.2. CCF Reference Laboratory

The Reference Laboratory at the Cleveland Clinic Foundation in Cleveland, Ohio, will serve as a central laboratory for HALT PKD. It will receive serum specimens and analyze them for creatinine. Costs for sample analysis will be handled centrally through the DCC. Contact information for the Reference Laboratory at the Cleveland Clinic Foundation may be found below.

Dr. Sihe Wang, HALT PKD Study, Cleveland Clinic Laboratories, 2119 E. 93rd Street, Cleveland OH 44106. Contact: Chris Sakenes, Phone: 216-448-8416 (office) 216-789-3955 (cell) Fax: 216-448-8130. Email: sakenec@ccf.org

3.11.3. Central Laboratory for HALT PKD Urine Samples

Diagnostic Laboratory Facility (DLF) at Brigham and Women's Hospital served as the central laboratory from the onset of the study until June 1, 2010 when the urine processing was taken over by Biobehavioral Core Facility at the University of Pittsburgh Cancer Institute (UPCI). UPCI served as a central laboratory for all HALT PKD urine samples until December 31, 2012. In January of 2013 the Reference Laboratory at the Cleveland Clinic Foundation in Cleveland, Ohio, assumed the responsibility for the receipt and processing of aliquots of 24-hour urine specimens. CCF is responsible for the analysis of urine aldosterone and urine chemistries (sodium, potassium, creatinine and microalbumin). All samples will be shipped from sites directly to CCF. Costs for sample analysis will be handled centrally through the DCC.

3.11.4. Local Laboratories: Quest and Hometown Labs

During the drug titration phase, each participant is required to obtain safety labs (potassium, BUN and creatinine) at the L2 and L4 visits for Study A and the L1, L2, L3, and L4 visits for Study B. A central billing account has been established with Quest Diagnostics Laboratories, a nationwide network; and those participants who live a great distance from their PCCs may obtain safety labs at a Quest laboratory. If there is not a Quest lab available to a participant, safety labs may be obtained at a local (hometown) laboratory. Results from Quest and local (hometown) labs will be faxed to the appropriate PCC

All lab orders for Quest for participants who live in California must be signed by Dr. Ted Steinman, as he is a licensed physician in that state.

For more information on procedures for obtaining labs at Quest and local (hometown) laboratories, refer to Section 11.3 – Local Laboratories: Quest Diagnostics and Hometown Labs. For more information on the study medication initiation and titration period, refer to Section 10.3.2.1-Initiation and Titration.

3.11.5. FedEx Shipping

Individual accounts were set up to be charged to when we ship the various samples obtained at study visits

- UPitt DCC account #165309723
- NIDDK Biosample Repository account #282009021
- NIDDK Genetics Repository account #276870645

- When shipping samples or forms for double data entry, log onto the FedEx account.
- Set up a shipment profile that includes the following information: the name of the recipient; detailed address; package and shipping details including service type (priority overnight); billing details including “bill transportation to Third party account # and reference “HALT PKD”; and email notifications to the recipient, the DCC and the coordinator name that a shipment has been sent and when it is delivered.
- When needing to ship, click on the appropriate profile, confirm the information or modify if necessary. Once that is done there is a button” to click that reads”ship”. The next screen shows the details of the shipment. Click ”ship” again and the shipping label is displayed. The shipping label includes the sender, addressee and the tracking number. Then print the label, which is placed on the package.
- The package can then be left at a FedEx drop box for pick up.

The coordinators should expect to receive email notification the following day that the package has been delivered. They can use the tracking number to check the delivery status if they do not receive the email.

FedEx may also be used when a participant obtains serum creatinine samples in his/her hometown that must be sent to Cleveland Clinic for analysis. Reasons for this scenario include:

1) the two serum creatinine samples, obtained at either the Baseline or F5 visit, are greater than 20% different from each other
2) 50% reduction in eGFR needs to be confirmed.

3.12. NIDDK Central Repositories

The NIDDK Central Repositories are made up of three separate, contract−funded components that work together to store data and samples from significant, NIDDK−funded studies. The three components are: 1) Biosample Repository (Fisher); 2) Genetics Repository (Rutgers); and 3) Data Repository (RTI). Dr. Rebekah Rasooly is the NIDDK Project Manager for the Central Repositories. Her e−mail address is rasoolyr@extra.niddk.nih.gov.

NIDDK has developed model language for informed consent forms that describes the repository and explains what will happen to samples and data that are collected. Informed consent for bio-samples may be obtained in the overall study consent, but a separate, written, informed consent document is recommended in order to draw genetic samples.

The Repositories will not contain any personal identifiers on samples or in datasets.

For more information on informed consent forms for samples that will be archived, refer to Section 5.3 – Informed Consent for Specimen Banking.

3.12.1. Biosample Repository

The Biosample Repository (Fisher BioServices) will gather, store and distribute biological samples from HALT PKD that are not being used for the active conduct of the study. As defined by the HALT PKD protocol, blood and urine samples will be designated for the Repository at the time of collection or sample processing and then shipped, frozen, via FedEx, to Fisher BioServices to be archived. *The FedEx Ship Manager online system will be utilized in shipping samples to Fisher BioServices.*

Stored samples will be made available to the study if needed. However, any use of these archived samples by HALT PKD investigators is considered to be an ancillary study and requires prior approval from the HALT PKD Steering Committee. During the proprietary period, the HALT PKD Steering Committee will control access to the samples, and the DCC will work with Fisher BioServices and will be the primary contact in regard to the samples. Once the proprietary period ends, RTI, the Database Repository, will have the data associated with the samples and will become the primary contact point in regard to the samples. Contact information for the Biosample Repository (Fisher BioServices) may be found below.

Heather Higgins NIDDK Repository Fisher BioServices Building 6, Suite 400 20301 Century Boulevard Germantown, MD 20874 Phone: (240) 686−4703 Fax: (301) 515−4049 E−mail: bio−NIDDKRepository@thermofisher.com or heather.higgins@thermofisher.com.

For more information on procedures for the Biosample Repository at Fisher BioServices, refer to Section 11.6.2. – NIDDK Biosample Repository – Blood and Section 11.6.3 – NIDDK Biosample Repository – Urine.

3.12.2. Genetic Repository

The Genetics Repository (Rutgers) will receive and process blood samples for genetic analysis. Samples of whole blood will be collected and shipped, via FedEx, to the Repository, where immortalized cell lines will be created, from which DNA will be prepared. The FedEx Ship Manager online system will be utilized in shipping samples to Rutgers University.

During the proprietary period, the HALT PKD Steering Committee will control access to the samples. The DCC will be the primary contact in regard to the samples. Once the proprietary period ends, RTI, the Database Repository, will have the data associated with the samples and will become the primary contact point in regard to the samples.

Contact information for the Genetics Repository (Rutgers) may be found below.

Dr. Douglas Fugman/Genetics Rutgers Univ/Cell Repository Div. Life Sciences − Nelson Labs 604 Allison Road, Rm. C120A Piscataway, NJ 08854−8082 Tel: (732) 445−1498 Fax: (732) 445−1149. E−mail: fugman@biology.rutgers.edu

For more information on procedures for the Genetic Repository at Rutgers, refer to Section 11.6.1 − NIDDK Genetic Repository.

3.12.3. Data Repository

The NIDDK Data Repository at Research Triangle Institute (RTI) will gather, store and distribute incremental or finished datasets from HALT PKD. It will also be responsible for helping the DCC prepare databases and incremental datasets for archiving and for carrying out restricted queries of stored databases. In general, the Data Repository (RTI) will receive all data collected by the DCC, provided that subjects have consented to having his/her data included in the repository. No personal identifiers will be sent to the repository. Contact information for the Data Repository (RTI) may be

found below.

Phil Cooley RTI−NIDDK Database Repository Box 12194 Research Triangle Park, NC 27709 Tel: (919) 541−6509 Fax: (919) 541−6178 E−mail: pcc@rti.org.

3.13. Ancillary Studies Policy

3.13.1. General Policy

To enhance the value of the Polycystic Kidney Disease Clinical Trials Network, HALT Study, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. In order to protect the integrity of the HALT Study and other studies that arise from the Polycystic Kidney Disease Clinical Trials Network, the Publications and Ancillary Studies Committee and the Steering Committee must review and approve all proposed ancillary studies before their inception or submission of a proposal for external funding consideration.

3.13.2. Definition of an Ancillary Study

An ancillary study is one based on information from the HALT Study participants or in other studies of the Polycystic Kidney Disease Clinical Trials Network in an investigation or analysis which is relevant to, yet not described in the Study protocol, and derives support from non−HALT or PKD Clinical Trials Network funds. A typical ancillary study will propose the collection of additional data not collected or analyzed as part of the routine HALT Study data set. Ancillary studies may be submitted by the investigators within the HALT Study or by investigators without a prior relationship to the HALT Study. Ancillary studies require external (non−PKD Clinical Trials) funding to cover all associated costs. Examples include studies funded by investigator−initiated NIH research awards (RO1s), grants from academic institutions (K12s) or private sources (e.g. private foundations, the PKD foundation, pharmaceutical companies). Any ancillary study must have sufficient funding to cover the costs incurred to process or ship samples and for tasks such as sample selection, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into the combined PKD Clinical Trials Network database.

3.13.3. Requirements and Procedures for Approval of an Ancillary Study

3.13.3.1. Overview

Participation in, and approval of an ancillary study is subject to review by the HALT PKD Clinical Trials Publications and Ancillary Studies Committee, and formal approval by the PKD Clinical Trials/HALT Steering Committee. Under specific, selected conditions (e.g. an imminent funding deadline), the Executive Committee may serve as the proxy for the Steering Committee, although this is expected to be a relatively uncommon situation. Approval by the Steering Committee requires four of six votes in favor of the proposal. Dissenting voters must provide the explicit reason for their dissent. Any issues of concern to dissenting voters are shared with the applicant and opportunities for clarification provided. All sites (Participating Clinical Centers, Data Coordinating Center, NIH) agree to cooperate with approved ancillary studies regardless of their individual vote. Ancillary study investigators must receive approval of their concept, and then engage in detailed budget and scientific planning in cooperation with participating clinical center investigators and the Data Coordinating Center (DCC) before submitting their grant to any funding agency. Potential ancillary investigators are encouraged strongly to discuss potential proposals with the Chair of the Publications and Ancillary Studies Committee, or the Study Chair of the Steering Committee prior to submitting a concept proposal. All outside investigators with an interest in ADPKD and expertise in clinical research will be allowed to submit to the Publications and Ancillary Studies Subcommittee for review. *All HALT PKD Clinical Trials Network ancillary study proposals must include at least one HALT PKD Clinical Trial investigator as a co−investigator.* Willingness to include additional HALT investigators as co−investigators of the ancillary study is mandatory, and potential ancillary investigators must document that they have contacted the Principal Investigators of all Participating Clinical Centers to determine their interest in participating in the ancillary study. If another site wishes to participate in the ancillary study, they may contact the proposing Investigator directly with the assistance of the Chair of the Publications/Ancillary Studies Committee, if needed.

3.13.3.2. Proposals for Ancillary Studies as Part of training or Career Awards

See additional information later in this policy specifically dedicated training grant submissions. The HALT Study investigators and the NIH anticipate that the HALT Study will be an important resource for career development and training among members of the academic community. Therefore, proposals for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources require special consideration. These funding mechanisms typically provide funding only for investigator effort, not additional data collection, and as such, these proposals will generally propose research questions and analyses that could be considered part of the core HALT Study. In these cases, consideration of what analyses will be authorized could present a conflict with the interests of the HALT investigators. Evaluation should consider the scientific gain to the HALT study from the addition of the proposed ancillary analyses as well as the training and career development opportunities afforded to the applicant by the proposed ancillary study.

Evaluation in the case of proposals to be funded through training grants is limited to trainees of HALT study

investigators, as the quality of the analyses will be greatly dependent on the mentor identified in the training grant. In the case of faculty career awards, evaluation of ancillary study applications will need to consider the anticipated scientific contribution of the applicant, including their ability to perform data analyses that may not be able to be performed at the DCC without additional funding. Further, willingness to adhere to the requirements of the Publications and Ancillary Committee with respect to authorship will be particularly important.

The review process will have several steps. The first step is submission of the HALT PKD Ancillary Study Proposal Form. This may occur up to one year before an anticipated submission date. Proposal concepts should be registered on the HALT website. Once the proposal form is submitted, the next step is review of the proposal and approval by the Publications and Ancillary Studies Committee. The concepts for the proposed ancillary study should be summarized in 2−4 pages and submitted as part of the HALT PKD Ancillary Study Proposal Form.

3.13.3.3. Considerations for Approval

1) The proposed study must meet requirements of the highest scientific merit.
2) Participant burden
    - The proposed study must be acceptable to the participants (e.g. time, discomfort, privacy).
    - The proposed study must not interfere with other parts of the main HALT Study.
    - The proposed study must not hamper continued participation in the main HALT Study.
    - The proposed study must put minimal demand on scarce HALT Study resources such as blood samples.
3) The proposed study must require the unique characteristics of the HALT Study cohort to accomplish its goals.
4) The investigators must have adequate resources to effectively complete the project, including:
    - Sufficient budget and personnel.
    - Staff having the requisite expertise to meet the objectives of the project.
5) The ancillary study investigators must agree to return the complete ancillary data set back to the HALT Study if requested by the HALT Study Steering Committee.
6) The proposed study must not interfere with the completion of the main objectives of the HALT Study.
7) The proposed study must not adversely affect participant cooperation or compliance with the HALT Study.
8) The proposed study must not create a serious diversion of study resources (personnel, equipment or study samples) or investigator/staff time, either locally or centrally.
9) The proposed study must not jeopardize the public image of the HALT Study.
10) Documented involvement of the HALT investigators as part of the research team.

3.13.3.5. Proposal Format

The following elements must be included in an ancillary study proposal. Before submitting the proposal for the first review within the Publications and Ancillary Studies Section, each Investigator must consider the possible participation of other HALT centers. The HALT PKD website will have a link haltsteer@list.pitt.edu to register the concept an Investigator wishes to pursue with an ancillary study. Registration of this concept generates an electronic message sent to all HALT sites and broadcasts the Investigator's interest in developing the protocol. There will be times when the study cannot accommodate all interested sites because of budgetary constraints. It is important that adequate communication exists before sites are included/excluded. The Steering Committee will ultimately arbitrate any process in which a dispute arises regarding an ancillary study and site exclusion based on budget (or any other) constraints.

The HALT PKD Ancillary Study Proposal Form must be completed and submitted to the Publications and Ancillary Studies Committee, at least 6 weeks before a funding application deadline. The completed HALT PKD Ancillary Study Proposal Form must include the following information:

A. Identifiers

1) Initiating investigators, collaborators, HALT Study co−investigator if indicated.
2) Confirmation of participation status of all HALT Participating Clinical Centers and the DCC
3) Planned starting date and project timeline.
4) Funding plans and estimated cost.

B. Design and Methods

1) Brief background and rationale
2) Study questions or hypotheses.
3) Specific data collection methodology, including questionnaires and coding forms, if available.

C. Specific answers to the following questions

1) What is the expected burden to participants? What are the specific time burdens, discomfort and expected participation rates?
2) What HALT Study core data and/or analyses are needed for the ancillary study?

3) Is blood or other biologic samples (either fresh or from the HALT Study's repository of stored samples) required? What will be the quantity of specimens needed?
4) What collaboration with HALT Study investigators is planned? With whom? Have the collaborating investigators approved the proposal?
What, if any, follow−up is needed? Specify length of time and events to be ascertained.
5) How many participants are required?
6) How will the ancillary study be funded? Would any additional un−reimbursed work or personnel time be expected of the HALT Study? How will the ancillary study budget cover demands on HALT Study personnel time and Study resources?
7) Where will the data analyses be conducted?
8) How will the confidentiality and other aspects of protection of human subjects be maintained?
9) When and in what form will a complete data set be returned to the HALT Study?

D. Data or Specimen Requirements:

1) Data needed from HALT Study analysis files.
2) Specimens needed from HALT Study repositories, specifying type and amount.

E. Handling of HALT Study Data and Specimens*:*

1) Disposition of stored samples from main study and those processed by ancillary study.
2) Disposition of ancillary study data at the conclusion of the ancillary study.

3.13.4. Changes to Proposed Study

Once an ancillary study is approved, if a change occurs in the structure or concept of the study, then a revised proposal must be disclosed to the Publications and Ancillary Studies Committee, for review and approval. If the changes are substantial, the Ancillary Studies Committee may submit the proposal for approval by the HALT PKD Clinical Trials Steering Committee for approval.

3.13.5. Proposal Budget

The investigator applying for an ancillary study must supply all additional funds needed to successfully complete the study. The Publications and Ancillary Studies Committee will be concerned with both the obvious and the hidden costs to the HALT Study entailed by an ancillary study. Provision of funds for these expenses is essential − an ancillary study cannot begin without such fiscal support to the core study. The need for such support must be stressed in research grant applications since this support is a mandatory ingredient. Such costs include, but are not limited to:

1) If work is to occur on site, rental of appropriate clinic, lab and office space.
2) If subject recruitment outside of main exams is anticipated, subject coordinator to arrange subject appointments.
3) Personnel, equipment and supplies necessary to complete the project.
4) Statistical and data management staff for coordinating the additional data management and analyses.

3.13.6. Human Subjects/Data Confidentially

Confidentiality of HALT participants must be guaranteed. Individually identifiable data may not be released. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main HALT Study. IRB approval of the consent is not necessary in order to submit to the Publications and Ancillary Study Committee.

1) Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.
2) A copy of the IRB approval letter for the ancillary study is to be sent to the Data Coordinating Center. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the HALT Subject Study record. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the HALT DCC.

The principal investigator of an ancillary study is responsible for presenting the study to the Publications and Ancillary Studies Committee or Steering Committee as appropriate, monitoring the study to assure continuing compatibility with HALT Study and serving as a liaison to the HALT Steering Committee. The HALT Steering Committee monitors the development of the ancillary studies, receipt of funding, initiation dates, and progress. A written progress report on ancillary studies must be made annually to the Steering Committee and the Monitoring Board.

3.13.7. Analysis and Publication of Results of Ancillary Studies

Analyses of ancillary studies within HALT can be undertaken in three specific ways: i) Analysis can take place at the DCC and be conducted under the supervision of its biostatistician−investigators, ii) datasets could be released for analysis by external investigators when approved by the Publications and Ancillary Studies Committee and the DCC; iii) ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical centers may be

situations in which release of data for analysis deserves special consideration. Under these circumstances, the investigator of the ancillary study will provide interim reports on analyses to the DCC to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database and to ensure the quality of analytical approaches.

Proposals for manuscripts resulting from all ancillary studies shall be submitted for review to the Publications and Ancillary Studies Committee and require approval by the Steering Committee before establishment of a writing committee or a submission for publication or presentation. It is anticipated that principal investigators of approved ancillary studies will lead at least one scientific paper emerging from the ancillary study analyses as specified in the HALT Publications Policy. Each manuscript and abstract would be expected to include a HALT investigator. The phrase "HALT Study" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts will also contain an appendix listing HALT investigators deemed appropriate.

3.13.8. Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful. Such reporting should follow standard HALT protocol for notification of participants.

3.13.9. Handling of HALT Data and Specimens

At the time of distribution of HALT specimens and/or information, the HALT Collaborating Investigator, with help from the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the HALT data at the collaborating institution is the responsibility of the ancillary study Principal Investigator, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, and files of HALT data are returned or deleted, as established at the outset of the collaboration. An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the HALT DCC at the conclusion of the data analysis and publication of the main (ancillary) study hypothesis. This transfer is the responsibility of the ancillary study HALT Principal Investigators. Once transferred back to the HALT DCC, these ancillary data will become part of the aggregate HALT PKD Clinical Trials Network database. Subsequent access to these data will be governed by the Steering Committee.

3.13.10. Site Responses to Ancillary Study Submissions

The Steering Committee ballot for each ancillary study will contain a section in which the interest of each site in participating in the ancillary study is formally registered. In addition to voting either "No," "Yes,", or "qualified Yes" (with attached comments), each site should indicate one of three levels of desired involvement, as shown below in a hypothetical ancillary study ballot:

3.13.10.1. Example of HALT PKD Ancillary Study Ballot – Distributed January 27, 2004

Ancillary Study Title: Finding Meds for HALT PKD

Please check one of the following responses and include detailed explanations where appropriate. Please forward electronically, your completed ballot to the Project Manager by March 14, 2004. No response will be considered approval. Please "cc" your email comments to Dr. Arlene Chapman.

_____***Yes***, I approve the above Ancillary Study.

_____***Yes***, I approve the above Ancillary Study with the following modifications:

_____***No***, I do not approve the above Ancillary Study (please explain below):

Our Proposed Site Participation:

_____***No Interest***

_____***Partial Interest*** (scientifically engaged, wish to contribute intellectual content, but do not wish to perform additional data collection at our site; no budgetary needs).

_____***Full Interest*** (scientifically engaged, wish to contribute intellectual content and to collect data at our site; include in budgetary considerations as appropriate below).

a. _____Data collection and investigator salary support.

b. _____Investigator salary support alone.

3.13.11. Ancillary Studies Submissions – Training Grants

We recognize the need to both protect the integrity of the core hypotheses and yet provide for research training in junior members of our various institutions. The ancillary submission form includes a box to check for "Training Proposal" which will alter the philosophy of the review process within the Publications and Ancillary Studies Subcommittee as well as

the Steering Committee.

When a Training proposal is submitted, a paragraph from the mentor(s) indicating briefly their credibility as mentors in the proposed training area, and their commitment to the individual is required. Attaching a CV of the mentors is welcomed, but not necessary. Hopefully we can establish a CV link in the HALT website so that when the proposal circulates the mentor's CV(s) could be easily accessed if a reviewing individual is interested. Since "hypothesis overlap" is likely, if not probable, a paragraph in the proposal dealing with whether, and exactly how, the overlap is to be handled is necessary. Since this is a process, the "requirements" for this paragraph are vague, and guidelines for this are necessarily general. The paragraph should acknowledge where overlap exists. When substantial overlap exists, how this proposal will add to HALT as well as to the development of the research aim(s) should be explained. It is strongly recommended to contact and discuss these proposals within the Publications and Ancillary Studies Subcommittee. We encourage ancillary proposals, and we all want to foster training in nephrology. However, there will be circumstances in which the overlap with primary hypotheses is too large to be considered approvable by the Steering Committee. It is best to discuss the proposals candidly with members of the Steering Committee when this is anticipated.

When the proposal circulates through the Publications and Ancillary Studies Subcommittee, the Training Proposal box tick will generate the following checklist in addition to the usual considerations for any ancillary proposal:

_____ Does the hypothesis overlap with core hypotheses in HALT, and has rationale supporting why the overlap is reasonably been presented?

_____ Is the mentor(s) clearly identified and do they appear to possess the expertise and commitment to train the candidate?

_____ Will the proposal require resources clearly beyond those typically available in a training award, and does the mentor have such resources available?

3.14. Information for Study Personnel

3.14.1. Training

The Data Coordinating Center (DCC) is responsible for training all HALT PKD personnel in the correct procedures for carrying out the study and conducted a two−day training workshop at Washington University in St. Louis on Wednesday and Thursday, July 6−7, 2005, for all HALT PKD study coordinators. Principal investigators reviewed the HALT PKD Protocol and Manual of Procedures during the Steering Committee meeting on Friday, July 8, 2005, in St. Louis. The DCC is responsible for assuring that procedures are carried out in a consistent, standardized manner and is also responsible for monitoring procedures at each PCC and proposing remediation measures for sites or individuals that do not meet acceptable performance levels. The DCC Research Program Coordinator will participate in conducting site visits at PCCs periodically during the course of HALT PKD to ensure that consistent, standardized procedures are being followed. Her activities will be overseen by the Quality Control Subcommittee.

3.14.2. Certification

Certifications will be granted in each of the following five areas to study coordinators who have completed training and demonstrated proficiency in carrying out applicable policies and procedures: 1) web−based data−entry system; 2) blood pressure measurements; 3) study medication; 4) central laboratories and repositories; and 5) image acquisition and data−transfer. Study coordinators must be certified in all five areas. Study coordinators should keep a record of their certification.

Once fully certified, study coordinators are authorized to train additional study personnel in areas appropriate to their involvement with the study, as well as train and certify additional study coordinators. Study personnel are to review relevant sections of the Manual of Procedures and coordinators must pass a written test and demonstrate blood pressure procedures for certification. Each PCC will be given a DVD containing portions of the initial training session held in St. Louis. This will serve as an additional aid to training study personnel. Study coordinators should keep a record of the training and certification for all study personnel at the site.

3.14.3. Data Collection Forms Completion

Data collection forms may be completed by a certified study coordinator or by other designated personnel, defined as individuals having completed training and demonstrated proficiency in carrying out the policies and procedures applicable to the task(s) they are performing for the study.

The signature of a study investigator must be included on the appropriate cover sheet to verify that he/she reviewed and approved the completed forms within a packet. The study investigator's signature must also be present on completed data collection forms for which PI signature is specifically required (e.g. SAE Form 13).

3.14.4. Request Tracker - (N/A - no longer in use)

Request Tracker (RT) is an automated system set up by the DCC to monitor, prioritize, answer, and document requests pertaining to HALT PKD. The DCC uses RT as a tool to assist in tracking requests, responsibilities, and tasks.

Both web and e−mail interfaces can be used with RT.

A username and password are required to access RT, and these are set up by the HALT PKD Project Manager for new personnel when they join the study. RT accounts for existing study personnel may be requested by sending an email to the HALT PKD Project Manager.

rt−haltpkd−study@rt.biostat.wustl.edu - Use this Request Tracker queue to make general requests or to report problems pertaining to the HALT PKD protocol, study procedures, regulatory issues, supplies, etc.

rt−haltpkd−data@rt.biostat.wustl.edu - Use this RT queue to request specific tasks and to report problems pertaining to the Web Data Entry System (WDES) and/or data−collection forms.

rt−haltpkd−report@rt.biostat.wustl.edu - Use this RT queue to request specific reports, as well as to make requests for analysis. This queue should also be used to notify the DCC of any problems pertaining to the reporting system.

rt−haltpkd−samples@rt.biostat.wustl.edu **-** Use this RT queue to notify the DCC of any problems pertaining to samples for central labs and repositories, sample shipments and test results.

To initiate a request through RT, the user has two options: one is to send an e−mail to the appropriate RT queue (as shown above), and the other is to use the RT web interface to select a queue and create a ticket. When a ticket is created, either by email or through the web interface, a ticket number is assigned to the request and a confirmation of the newly−created ticket is emailed to the requestor. The subject line of the email, which includes the RT ticket number, must be used in all subsequent correspondence pertaining to the request.

Once a new ticket is created, the appropriate individual at the DCC will work on the request and will get in touch with the requestor to ask questions, if necessary. Once a request is resolved, the DCC will close the ticket, and RT will email a confirmation to the requestor to let her know that the ticket has been closed. All correspondence between the DCC
and the requestor is saved in the history of each ticket for future reference. To view the history of a ticket, log into the RT web interface and search for the relevant ticket number.

3.14.4.1. RT Requests Via Web Interface

In addition to creating and responding to RT tickets by e−mail, users can access it through the web interface at the following address: http://rt.biostat.wustl.edu. A link to the RT web interface can also be found on the Investigator Home page of the HALT PKD website. A screenshot of the log−in page is included below:

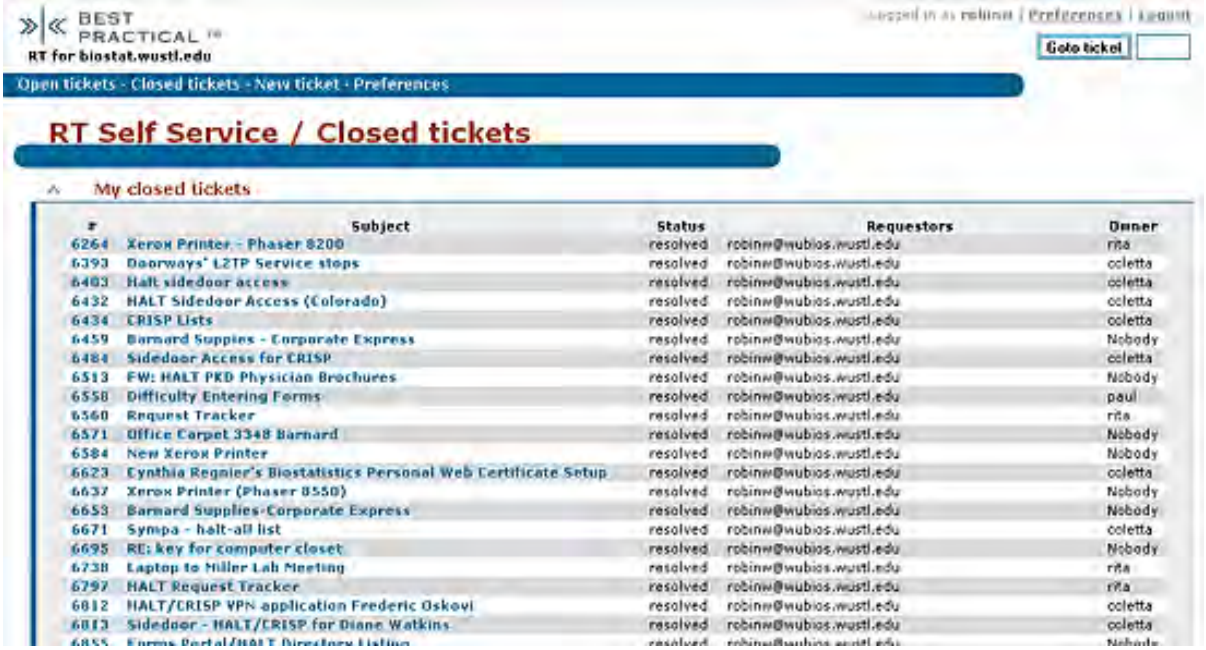
3.14.4.1.1. Open Tickets

Once a requester logs in, he/she will see his RT home page, which includes a list of open tickets. The home page also presents options for viewing closed tickets, creating a new ticket, and changing preferences.

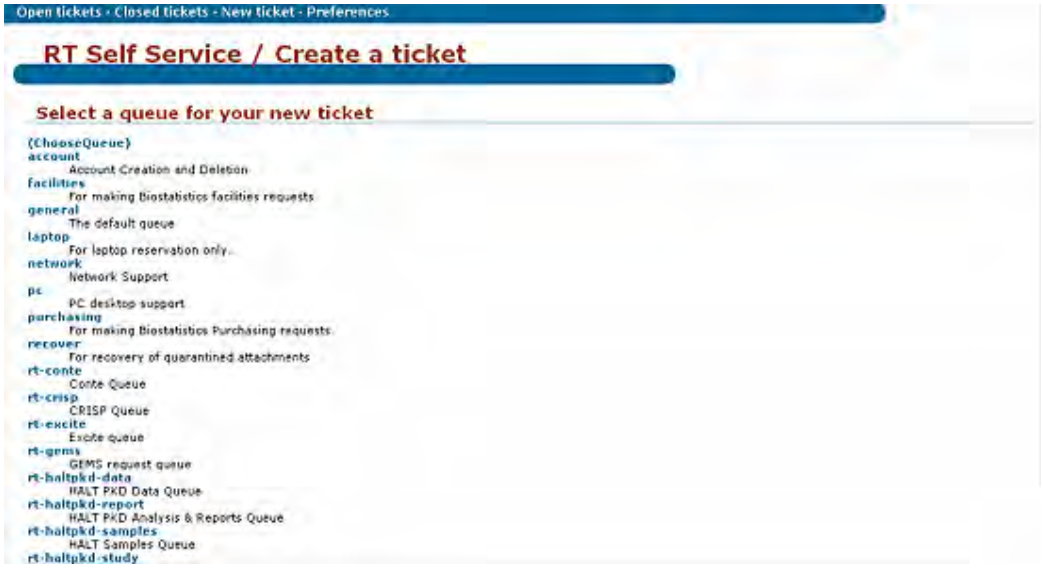
The user's open ticket number and subject line. Clicking on a ticket will open that ticket's history. Where the user may view and reply to correspondence.

3.14.4.1.2. Closed Tickets

The user's open tickets are listed by ticket number and subject line. Clicking on a ticket will open that ticket's history for review. When a request has been completed, the requestor will receive an e−mail indicating the ticket has been resolved.

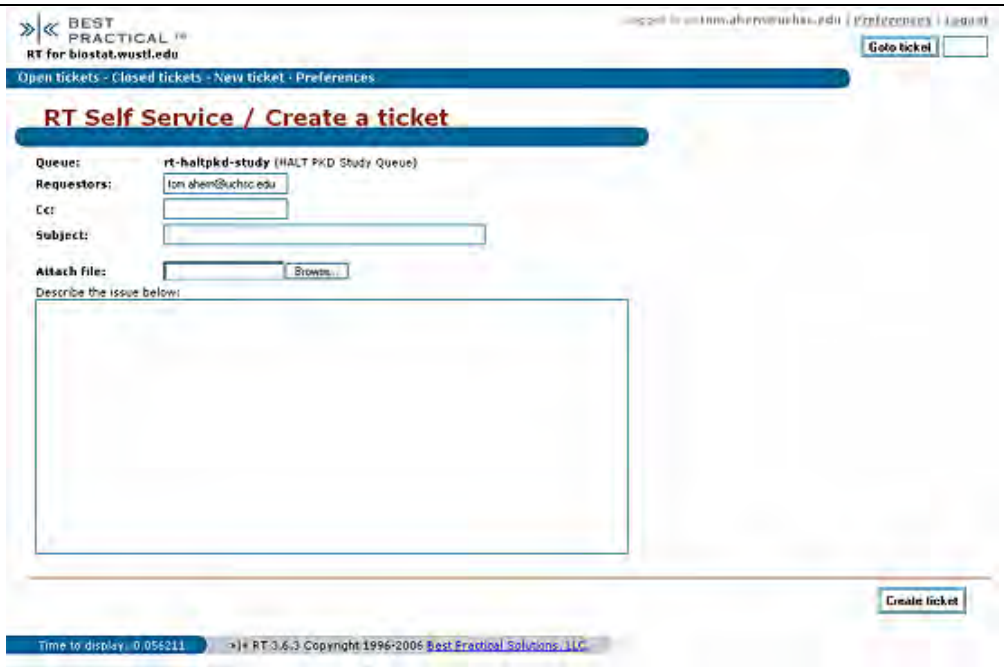


3.14.4.1.3. **Create a New Ticket**



Click on "New ticket" to open the "Create a ticket" page, which contains a list of all RT queues. Select the appropriate queue from the four listed for HALT PKD and click on it to open a blank ticket.

You'll see there are a number of other queues to choose from besides those for HALT PKD. These additional queues are for other projects and should be disregarded.



The queue you selected will be listed, and your email address will appear in the "Requestor" field. Fill in the "Subject" line with the most specific information possible. Include information specific to the problem; and if your request is:

* in regard to a participant, be sure to enter the HALT−ID number.
* in regard to a particular form, be sure to enter the form number.
* in regard to sample, be sure to enter the HALT−ID and accession number.

After entering the subject, describe the issue in the free text field, including as much information as possible about the request. If you were working in WDES when you encountered a problem, please take care to completely describe the HALT−ID, the form you were working on, and exactly what you were doing when the problem occurred. Always include the HALT−ID and visit code or date of action. This will greatly assist the DCC in troubleshooting the ticket. Again, please be very specific.

3.14.4.1.4. Preferences

If desired, you can change your RT password. Just click on Preferences and enter the new password information. Your password should be at least 8 characters long and include alphabetical characters (both upper and lower case), numbers, and symbols ($, *, @, !, ~, etc.).

3.14.4.2. RT Requests Via Email

One way to create a Request Tracker ticket is to email a request to one of the HALT PKD, RT queues (a list of email addresses for the RT queues can be found above at the beginning of Section 14) .Choose the queue according to the nature of the request. Again, please be as specific as possible in describing the subject and the issue.

As soon as the ticket has been created, RT emails a confirmation to the requestor that includes the ticket number.

All subsequent correspondence pertaining to the ticket may take place via email. Just use the "Reply To" button in your email application to reply to the ticket. Be sure the subject line, including the ticket number, is as descriptive of the problem as possible.

The email ticket confirmation includes a hyperlink to the ticket history on the web, so users may elect to use the web interface for further correspondence regarding a ticket. If the user is not logged in, the link will go to the RT login page, and the user will be redirected to the ticket as soon as he/she has logged in.

3.14.4.3. Making Effective RT Requests

When making an RT request, the subject line of the request needs to be as specific to the content of the request as possible. This allows requestors to easily find open tickets should follow−up on a request be required. When creating a ticket regarding forms, please list items for only one form per ticket, and include the form number in the subject line (e.g., "Form1 − can't change date") and always include the HALT−ID and applicable visit code or date of action.

The more information included in your request or trouble report, the quicker your problem can be solved. Also, by including the most complete information possible, the need to email back−and−forth for more details will be reduced, which will result in quicker resolution of your ticket.

We suggest you delete past correspondence from your tickets when sending replies, as this keeps the history of your tickets cleaner and much easier to read.

All past correspondence exists in the history of the ticket; so if past correspondence is not deleted, it gets repeated in each subsequent reply. This makes it cumbersome scroll through the ticket to find the current information because one has to go through the past correspondence in every reply that exists for the ticket.

3.14.5. Email Lists

Several email listservs have been established to facilitate communication between HALT PKD study personnel. When a message is emailed to one of these lists, a copy of it will be delivered to all study personnel who are subscribed to that particular list. The HALT PKD website includes links to the Halt−All Steering Committee and Study Coordinators email lists.

HALT PKD Study Personnel - haltall@lists.pitt.edu
HALT PKD Steering Committee - haltsteer@list.pitt.edu
HALT PKD Coordinators - haltcoord@list.pitt.edu
HALT PKD Blood Pressure Committee - haltbldprs@list.pitt.edu
HALT PKD Endpoints Committee - haltendpoints@list.pitt.edu
HALT PKD Imaging Committee - haltimaging@list.pitt.edu
HALT PKD Quality Control Committee - haltqualcont@list.pitt.edu
HALT PKD Forms Committee - haltforms@list.pitt.edu
HALT PKD Publications Committee – haltpubanc@list.pitt.edu
HALT PKD Closeout Committee – haltcloseout@list.pitt.edu

To add or remove an individual from one of the above lists, please email a request to the HALT PKD Project Manager.

3.14.6. Setting up New HALT PKD Personnel - (N/A - no longer in use)

A number of tasks must be done by the DCC when new study personnel begin on HALT PKD, so it is very important to notify the HALT PKD Project Manager as soon as possible upon learning that someone new will be working on the study. All new personnel are required to complete a University of Pittsburgh registration form and fax it to the DCC. A temporary password will be sent by email.

The DCC will arrange the following for new study personnel:

Access to HALT PKD Website − In order to access the private sections of the HALT PKD website, it is necessary to print a HALT PKD Web Access Request Form, fill it out, and submit it by fax (314) 362−3440 to the HALT Project Manager. She will set up the access and then send an email notification that includes the assigned username and password.

Side door Certificate − In order to access the HALT PKD Web Data Entry System (WDES), a side door certificate must be installed in each user's browser. Please note that if a computer is used by more than one person to enter data in WDES, each must install separate side door certificates in the browser. Also, if an individual uses more than one web browser, the side door certificate must be installed in each browser. To request a side door certificate, print a side door Request Form, fill it out, and submit it by fax (314) 362−3440 to the HALT PKD Project Manager. Once the side door certificate has been generated, it will be forwarded to the user by email, along with Side door Installation Instructions for importing the certificate into a web browser.

Both the Web Access Request Form and the side door Request Form cannot be accepted without the signature of the principal investigator.

- Subscription(s) to Appropriate Email List(s)
- Registration in WDES Database
- Request Tracker Access
- Addition to Study Personnel Page on HALT PKD Website
- Addition to Study Personnel Section of HALT PKD Manual of Procedures (MOP)
- Addition to clinicaltrials.gov, if the new staff person is replacing one of the individuals listed on that site.

3.14.7. Departing Staff Personnel

Notify the HALT PKD Project Manager as soon as possible after learning that an individual is leaving the study, as the items listed above in Section 14.6 must be reversed for a departing staff member.

- Personnel listing will be removed from HALT website and MOP.

3.15. Certification of Participating Clinical Centers

Once clinical centers have received local IRB approval of the current (10.10.2005) protocol and informed consent documents, study personnel may begin conducting prescreening telephone interviews and scheduling initial PCC visits. However, participants should not be seen for screening prior to NIH approval of study budgets.

Prior to the start of enrollment, each PCC will need site certification. To certify a PCC, a certified study coordinator is to complete the Site Readiness Checklist and fax it to the DCC. The PCC Regulatory Checklist and Study Supplies Checklist should also be submitted to the DCC as supporting documentation. The DCC will need to review and approve certification of the site prior to the first screening visit.

Chapter 4. Participant Recruitment

4.1. Recruitment Goals and Timeline

The objective of the recruitment process is to identify individuals who have been diagnosed with ADPKD and who have GFR's of either >60 ml/min/1.73 m_2 (Study A) or 25−60 ml/ min/ 1.73 m_2 (Study B). A further objective will be to recruit subjects who will make themselves available for the entire follow−up period and who will likely be compliant with study protocols and visit schedules.

Approximately 548 participants for Study A and 470 participants for Study B will be required. With an anticipated ratio of screened−to−enrolled participants of 5:4, each PCC will need to screen approximately 307 participants − 165 participants for Study A (GFR >60 ml/min/1.73 m_2) and 142 participants (GFR 25−60 ml/ min/ 1.73 m_2) for Study B.

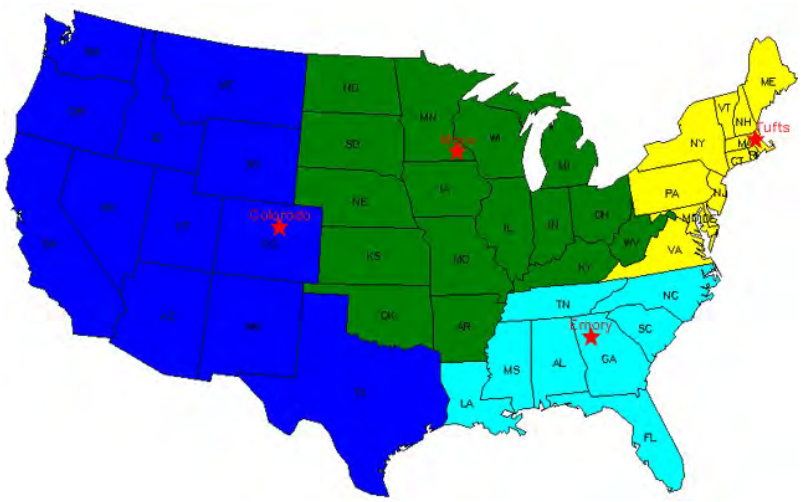
4.2. Methods for Recruitment

Recruitment strategies will target participants residing within and outside of the immediate vicinity of the PCC. Due to the high motivation of PKD participants and their families, efforts aimed at recruiting family members through the PKD Foundation, and from nephrology, general medicine, urology and transplant (for relatives) clinics are likely to be successful strategies. Recruitment strategies have been divided into physician and community sources.

Pamphlets for Patients and Physicians

A brochure has been developed for potential participants that summarizes the purpose of the study and some eligibility criteria and lists study sites and general commitments required for participation. A map of the United States has been divided into four regions, as seen below, with participants referred to clinic sites according to the state in which they live. The study brochure includes telephone numbers for all PCCs, so participants can contact the PCC nearest their home state. Potential participants may also contact the HALT PKD Project Manager, Robin Woltman, as her address, phone number, and email address are also noted on the brochure.

Figure 4−1. HALT PKD Catchment Map



The Polycystic Kidney Disease Foundation

The PKD Foundation sent a letter to its nationwide membership announcing the HALT PKD study, and has also publicized the study in its publications, such as *PKD Progress*. 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 initiation of the study will stimulate additional interest in the study within the ADPKD community. The PKD Foundation has posted study information on their website and also sends targeted, blast emails to individuals from its database.

Web−Based Advertising Strategies − (N/A − no longer in use)

The DCC has developed a website (www.pkd.wustl.edu/pkdtn) to provide the public with a summary of the HALT PKD study and its purpose. Access to the website follows any keyword search for PKD and is linked to the PKD Foundation Home Page, as well as to the NIH−NIDDK home page. From the public website, potential participants can email inquiries for more information to the HALT PKD Project Manager. The Project Manager is to respond to each inquiry via e−mail, forwarding copies of the correspondence to the PCC to which the potential participant should be assigned according to the catchment map.

Mass Media/Public Advertisements

Principal investigators at each PCC will advertise the study through 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, brochures, and web−based materials must be approved by the Institutional Review Board at each PCC.

Referral from Physician Clinics

A personalized letter and a 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 brochures will be distributed among outpatient nephrology, urology, and general medical clinics and dialysis units (the latter for recruitment of family members).

A summary of recruitment strategies is shown in Table 4.1.

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

Table 4−1. Specific Recruitment Strategies for Physician and Community Sources

4.3. Source Populations

Each of the four principal investigators has established his/her own specialized referral center for ADPKD patients. Estimates of numbers of patients identified through existing databases at individual PCC's as being potentially eligible to participate in HALT PKD studies are as follows:

The University of Colorado

Since 1985, 1474 members of 463 ADPKD families have participated in clinical studies at the University of Colorado. Of these, 969 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. The PCC has been contacted by an additional 644 families (unrelated to the 463 families above), that have expressed interest in participating in future clinical studies.

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.

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 affected family members have been identified. Of these patients, 284 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 patients. 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 there are 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 300−400 families with ADPKD, each likely to have 1−2 affected family members who may be eligible for the study

Tufts University/New England Medical Center

Tufts−NEMC has subcontracted with Beth Israel Deaconess Medical Center (BIDMC), also in Boston, to achieve the recruitment goals required. A review of administrative databases at New England Medical Center and three Rhode Island Hospitals within 45 minutes driving distance of NEMC, identified 400 ADPKD patients older than age 18. After excluding patients with ESRD, greater than 64 years of age, and 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 an estimated 689−1380 ADPKD patients and in Massachusetts between 6300−12000. 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 NEMC, has agreed to advertise the study in its 43 dialysis units within the Northeastern states, which will serve to notify and recruit family members to the study. Other dialysis providers in the area will also be contacted. Finally, there have been over 40 affected individuals who have contacted the PCC since August 2002, expressing interest in participating in the study, even though advertisements or other active recruitment strategies have not been used to date.

4.4. Determination of Eligibility

Eligibility for HALT PKD studies is to be determined by specific inclusion/exclusion criteria, as described in Section 7.2 − Eligibility.

Refer to Section 8.2 − Pre−Screening for procedures governing the prescreening visit.

4.5. Recruitment Monitoring

The DCC and each study site will keep a close tally on the expected and achieved numbers of participants enrolled at study sites over time. The number of individuals 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 proven most effective. To ensure the study populations reflect the 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 contact clinics and physicians servicing minority populations.

Forms documenting successfully recruited participants, i.e. those who have signed their informed consents and meet eligibility criteria, will be submitted to the DCC to allow for tracking of local recruitment rates. A monthly report, including both successfully recruited individuals and individuals who have entered the baseline phase of study, will be sent to each PCC and to the NIH to assess recruitment at the sites.

A Pre−Screening Activity Report Form will be completed and data−entered by the study coordinator at each PCC on a monthly basis. The purpose of this form is to track the number of participants who begin the pre−screening process each month, as well as to track numbers of participants according to referral sources. Also, participants who enroll in the study but who fail to qualify during the baseline visit will be accounted for and the reason for their ineligibility stated. Each PCC should track the number of participants that contact its site to express interest in the study, as well as the reasons why potentially eligible participants decline participation. The study coordinator should note this information in a log book for future reference. These log books will be reviewed during site visits to take place at regular intervals throughout the study.

4.7. Follow-Up and Retention Measures

After the first year, study visits at the PCC will occur every six months through 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 a review of unscheduled medical encounters, hospitalizations, and the 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. Blood pressure measurements and a physical exam will also be done. Participants will also review their home blood pressure records by telephone with a study coordinator every three months, starting the third month after enrollment (F5). These telephone visits will allow study coordinators to maintain contact with participants, thereby helping to maintain their commitment to the study.

The HALT PKD Contact Information Form solicits demographic information on individuals, such as spouse, alternate contact and emergency contact, plus information on who may be able to help locate a participant who has

changed residence without notifying the clinic. This information is to remain in a locked file for use by the clinical center only and will not be entered into the study database. Every effort should be made to encourage participants to return for all follow−up visits and to maintain contact with participants who do not attend follow−up visits or who become inactive. Potential barriers to retention of participants, such as parking, transportation and clinic hours, will be identified and addressed. Clinics will be proactive in identifying the concerns of individuals about continued participation in the study and will take preventive action to maintain active participation. Inactive participants who do not return for clinic visits will be followed whenever possible by telephone and mail for vital status and key outcome measures.

Retention and follow−up activity reports will be made available to clinical sites by the DCC. The data system will provide clinic staffs with lists of participants who are due for follow−up contacts/visits. The DCC will closely monitor participant retention and adherence to the visit schedule, creating reports in which frequency of late and missed visits are detailed. These visit completeness reports will be reviewed by the Quality Control Committee at their regular teleconference meetings. Starting in May of 2012, the DCC will generate a monthly “At Risk Participant Report”. This document utilizes data from the visit completeness report to identify participants that have missed recent PCC appointments or those that utilized the “remote visit” option for the last visit. The report is site specific and highlights PCC visit attendance histories that put the participant at risk for modification. This report is provided so sites may focus scheduling efforts on the “at risk” participants and decrease the incidence of modification. Since January of 2012, the issue of participant retention appears as a recurring agenda item during all Clinical Coordinating and Recruitment Subcommittee regular monthly teleconference calls. The CCRC will formulate clinic−specific responses to emerging retention issues.

For strategies on how to maintain full participation in HALT PKD, refer to the cheat sheet Strategies for Full Participation. For guidelines on how late or missed visits are to be addressed, refer to Section 8.16 – Target Visit Dates, Acceptable Visit Ranges and Missed Visits and/or Section 13.5 – Protocol Deviations/Major Violations.

Chapter 5. Protection of Human Subjects

5.1. IRB Reporting Requirements

The Institutional Review Board (IRB) at each PCC must approve the HALT PKD protocol, informed consent documents, and recruitment materials prior to recruiting participants to the study. All revisions to these materials must also be submitted to and approved by each site's IRB.

5.2. Informed Consent for HALT PKD

Refer to Section 18.4.1 – Model Consent Forms and Section 18.4.2 – Model Assent Forms to review samples of informed consent and informed assent documents required from participants who wish to take part in HALT PKD. Please refer to Section 19 – Addendum Consents for Study A & B and waver of consent for Study B.

In order to be eligible for HALT PKD, each participant must be willing to sign **two** study−specific statements of informed consent for either Study A or Study B. **Two** informed assent forms are to be used for participants of ages 15−17 (Study A only). Please note that the IRBs at BIDMC, Emory and KUMC have given these sites permission to obtain only **one** informed consent document to cover the entire study (either A or B).

Two Informed Consents Required: The *first* informed consent document must be reviewed and signed by the participant prior to beginning the screening visit and is applicable to the screening visit and drug washout, up to and including urine collection prior to the baseline visit. The *second* informed consent document must be reviewed and signed by the participant prior to the baseline visit and is applicable to the baseline visit through the end of the study.

One Informed Consent Required (BIDMC, Emory, KUMC): The informed consent document must be reviewed and signed by the participant prior to beginning the screening visit and is applicable to the screening visit, drug washout, and baseline visit through study−end.

Each participant is required to review and sign the appropriate informed consent document(s) prior to beginning the screening visit and some institutions may require re-consenting annually thereafter. Participants must also review and sign any IRB−approved revisions of informed consent documents. Once an individual who has signed an informed assent form reaches the age of 18, he or she is no longer considered a minor (as defined by FDA) and is required to sign an informed consent form prior to the next study visit. The DCC will notify study coordinators electronically when a participant reaches the age of 18 to remind them to obtain the now adult participant's informed consent. In February of 2012, the DCC confirmed that all participants consented as underage subjects had reached the age of 21 years and were re-consented as adults.

The fully−executed informed consent document(s) confirms that participants have been made aware of the risks and benefits involved in participating in HALT PKD and have agreed to accept the risks and benefits and take part in the study. If it is necessary or desirable for a participant to modify his or her participation in the study, it is *strongly* recommended that consent for modified participation be obtained and documented in a way that is acceptable to each

site's IRB.

For more information on modified participation, refer to Section 5.5 – Modified Participation.

Each PCC must obtain IRB approval of its site−specific informed consent documents prior to beginning the study and annually thereafter. Any revisions made to informed consent documents must be submitted to the appropriate, site−specific IRB for approval. It is recognized that site−specific IRBs have official responsibility for determining informed consent procedures for each PCC. Copies of all IRB approvals (including amendments and renewals) must be promptly sent to the DCC.

Model informed consent documents have been developed by the DCC to assist the PCCs in ensuring that all required components, written at the appropriate reading level, are included in site−specific informed consents. In addition to information regarding the study itself, informed consent documents must include the following:

1) Appropriate consent language to address obtaining samples for purposes of specimen banking
2) Language to inform participants that a Certificate of Confidentiality is in effect and to present participants with a fair and clear explanation of the protection afforded them by such Certificate.
3) Language pertaining to informing the participant's primary care physician (PCP) of the participant's study involvement and any abnormalities or other concerns.
4) Language regarding the sharing of study data. Informed consent documents must inform participants of the sharing of information about them, through the NIDDK Central Data Repository, with other investigators who may wish to study kidney disease in future. Additionally, consent documents must offer participants who were previously enrolled in the CRISP study the option to share information and samples collected for CRISP with HALT investigators.

5.3. Informed Consent for Specimen Banking

Refer to Section 18.4 – Model Consent/Assent Forms to review samples of the model informed consent and model informed assent documents required from participants in order to obtain genetic samples.

5.3.1. Bio-samples

Each participant enrolled in HALT PKD will be asked to provide blood and urine specimens for banking at the NIDDK Biosample Repository (Fisher) for use in future studies. Specific consent language pertaining to specimen banking must be included within each site−specific HALT PKD informed consent document, and the recommended text has been included within the DCC model informed consent document.

5.3.2. Genetic Samples

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.

For information on obtaining and shipping specimens to the NIDDK Repositories refer to Section 11.6 – Archived Specimens.

If the participant was enrolled in the CRISP study and previously provided a genetic sample for the NIDDK Genetic Repository, a second sample will not be obtained. Instead, the participant will be asked to consent to the sample being shared with HALT PKD investigators.

5.3.2.1. Genetic Consent after F5

Refer to section 11.6.1 for additional information.

5.4. Informed Consent for Sharing Information

Each participant is required to name a primary care physician (PCP), other than a study investigator, as indicated on the appropriate consent document. Participants will also indicate on the consent document whether he/she authorizes HALT PKD to communicate with the named 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. If participants have granted authorization, PCCs may directly inform PCPs of any abnormalities or concerns over the course of the study.

At the Screening visit, participants who were previously enrolled in the CRISP study will be given the option, as indicated on the appropriate consent document, to share information and samples collected for the CRISP study with

HALT PKD investigators. Informed consent documents are to include language regarding the sharing of participant information (after it has been stripped of personal identifiers), through the NIDDK Central Data Repository, with other investigators who may wish to conduct studies related to kidney disease in future.

5.5. Informed Consent for Modified Participation

All randomized participants are to be followed until death or until the end of study. Modified participation occurs when a randomized participant: a) refuses or is unable to do all of what is required for the study but is willing to do some of what is required; or b) refuses or is unable to participate in the study at all. Under the intent−to−treat policy, all such participants must continue to be followed, as much as possible, until death or until the end of the study. The participant's chart must contain source documentation of the decision to modify participation, including the level of continued participation chosen by the participant (one of four available options). When the level of participation changes, Modified Participation Form 28 must be completed and data−entered within two weeks of the event leading to the change. However, this form need not be data−entered when a study endpoint is met.

It is desirable that modified participation be streamlined in such a way as to meet the endpoints of the study, while sufficiently reducing participant burden. To this end, Section 8.18 outlines the plan for modified participation. In addition, a Modified Participation Checklist has been created, as an optional tool, to aid in clear and consistent interpretation of the guidelines for modified participation across sites, as well as to serve as source documentation if permitted by the institution. It is strongly recommended that study coordinators administer the Modified Participation Checklist to ensure that participants understand the requirements associated with the level of modified participation they have chosen. It is also strongly recommended that participants be re-consented in a manner consistent with the policies of each institution's IRB.

If approved by the local IRB, it may be possible to re-consent participants through use of the Modified Participation Checklist, rather than through use of an IRB−approved, informed consent document.

For further information, refer to Section 8.18 − Modified Participation and/or Section 14.2 − Early Termination of Study Drugs or Follow−Up

5.5.1. No Contact Policy

Occasionally sites have participants who, for whatever reason, do not contact the PCC for extended periods, despite coordinators' best efforts to reach them. For these situations, the study has adopted the policy that once a single visit has been missed, participants are given a period of 6 months of non−contact before considering them to have withdrawn their consent.

1) Coordinators will make regular attempts to contact participants, at least biweekly, during the first month, either by phone, email or U.S. Postal Service, and at least monthly during subsequent months.
2) Toward the end of the six month period of no contact, the coordinator will send a certified letter to the participant in a final attempt to contact and schedule a visit.
3) If no response from the subject is received within 6 months of repeated efforts to contact them, the participant will be considered “lost to follow up” and to have withdrawn consent to participate in the study.
4) Modified Participation Form 28 should then be completed, selecting the options 3a. “Participant has withdrawn consent, not otherwise specified” and 5d “refuses all follow up”.
5) The terms “lost to follow up” should be documented in Form 28 comments detailing the site’s attempt to contact the participant.
6) The Form 28, question 3m “other” is not used to document a “lost to follow up” participant
7) Once the participant has been modified ad withdrawn, the coordinator should make no further attempt to contact the participant
8) When filling out Form 28 Q4 “drug stop dates” on the “lost to follow up” participants, the drug use information is commonly unknown.

To Document the Drug Stop Date on Withdrawn Participants:

- Use the most conservative date
- Calculate the last known date which the participant was known to be using study drugs based on the amount of drug supplied at the last PCC visit.

5.6. Tracking System for Regulatory Documents

The DCC monitors each site to assure local IRB renewals are completed and regulatory compliance is maintained is maintained. The DCC will send email reminders regarding renewal submissions two months prior to the current renewal expiration date. The DCC will provide sites with copies of the most recent DSMB minutes, the DSMB Executive Summary (Study A and B) and a list of site SAEs occurring within the past renewal period for IRB submission. Regulatory documents being tracked include local IRB approvals of the study protocol, amendments to the study protocol,

informed consent documents, IND 1572, Certificate of Confidentially, Investigators Curriculum Vitaes, financial disclosure documentation, and recruitment materials. Copies of all IRB−approval letters must be sent to the HALT PKD Research Program Coordinator at the DCC. Copies of all IRB−approved informed consent documents, whether new or revised, must also be forwarded to the Coordinator. Once the IRB approved documents are received, they will be stored electronically within the DCC database.

Required regulatory documents to be on file within the DCC include the following: **Items 5−9 do not require IRB approval.*

1) Official documentation of the IRB registration number and assurance ID number.
2) IRB approval of the current HALT PKD protocol (Final Version: 05.03.2012).
3) A copy of all IRB−approved consent and assent forms required by the PCC.
4) A copy of any brochures, flyers, advertisements, etc., approved by the local IRB for recruiting purposes.
5) Documentation of conflict of interest and financial disclosure of all investigators
6) Documentation of PCC's policy on frequency of Dinamap calibration.
7) BP Monitor Calibration Log Form 34 (at the frequency required by the PCC).
8) Documentation of the institution's normal ranges for required lab tests.
9) HALT certification of study personnel.
10) IND 1572 Certificate signed by the PI

5.7. Investigational New Drug (IND) Approvals

An IND is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug to humans. This authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.

The FDA has approved separate INDs for HALT PKD Study A and Study B. In Study A the IND was originally applied for because the drug telmisartan is not approved for use in children. However, as telmisartan is not approved for use in treating PKD, the FDA also chose to issue an IND for Study B. The IND numbers for both studies are as noted below:

- Study A: IND 73,036
- Study B: IND 72,729

5.8. Participant Confidentially

Participant confidentiality is protected thorough a multi−tiered approach to assure compliance with the requirements of the Privacy Act, the Privacy Rules of HIPAA, and with all other applicable laws that protect the confidentiality of health information. Each participant is to be informed of the purpose of the study and consented for participation in all aspects of the protocol through use of IRB−approved consent documents. Participants must sign an authorization (along with the informed consent document) for public release of their data.

At the time of registration, each participant is assigned an identification number. Participants are identified only by number in the study database and generated reports and, in general, only group data will be published. If individual participant data are published, no identifying information will be included. The data management system is highly secure with multiple levels of controls on access. The medical records of the participants in the HALT PKD study are confidential and must be de-identified prior to submission to the DCC for endpoint committee adjudication. Specific study−related information may be made available to the FDA, study sponsors, the NIH, or other regulatory agencies but will be de−identified.

5.8.1. HIPPA Compliance

Only individual PCCs and the Washington University DCC have access to identifiable protected health information (PHI) for study participants. All participant data will be maintained in locked file cabinets and/or on secure, password−protected computers at each PCC and at the Washington University DCC, with access limited to HALT PKD researchers and staff. Each PCC will have access to PHI of only its own site−specific participants.

The disclosure of individual health data to the general public or affiliated external researchers will comply with the provisions of the HIPAA Privacy Rule. Clinical data and images will be de−identified prior to disclosure, according to the rules and prescribed mechanisms for doing so in Sections 164.502(d), 164.514(a)−(c). Data values that have the potential for unmasking participant identity will not be available on the public−use data set or will be made available only as calculated variables that cannot be uniquely mapped back to raw values. These include clinic locations, dates of hospital admission, information about parents or siblings, and rare medical conditions.

5.8.2. FDA Certificate of Confidentially – Study A

The DCC, on behalf of HALT PKD, applied for and received a "Certificate of Confidentiality" (COC) from the Food & Drug Administration (FDA) to cover Study A (05−76−CDER). The purpose of the Certificate of Confidentiality is to

protect participant genetic data and other sensitive data from involuntary disclosure of the identities of research participants. The COC was effective on the date of issuance, September 23, 2005, and expires on the date on which the IND application is terminated or withdrawn.

The FDA Certificate of Confidentiality does not govern a disclosure for which the participant gives permission or a researcher's voluntary disclosure of the identifying characteristics of research participants, but only protects participants from compelled disclosure of identifying characteristics. For example, a researcher is not prevented from making voluntary disclosure of personally identifiable information related to child abuse or a participant's threatened violence to self or others. However, if a researcher expects to make such voluntary disclosures, the consent form should clearly indicate this [21 CFR 50.25(a)(5)]. The Certificate of Confidentiality also does not govern disclosure of study information without personal identifiers.

5.8.3. FDA Certificate of Confidentially - Study B

The DCC, on behalf of HALT PKD, applied for and received a "Certificate of Confidentiality" (COC) from the Food & Drug Administration (FDA) to cover Study B (08−148−CDER). The purpose of the Certificate of Confidentiality is to protect participant genetic data and other sensitive data from involuntary disclosure of the identities of research participants. The COC was effective on the date of issuance, November 24, 2008, and expires on the date on which the IND application is terminated or withdrawn.

The FDA Certificate of Confidentiality does not govern a disclosure for which the participant gives permission or a researcher's voluntary disclosure of the identifying characteristics of research participants, but only protects participants from compelled disclosure of identifying characteristics. For example, a researcher is not prevented from making voluntary disclosure of personally identifiable information related to child abuse or a participant's threatened violence to self or others. However, if a researcher expects to make such voluntary disclosures, the consent form should clearly indicate this [21 CFR 50.25(a)(5)]. The Certificate of Confidentiality also does not govern disclosure of study information without personal identifiers.

Every research project that includes human research participants must explain how identifiable information will be used or disclosed, regardless of whether or not a Certificate is in effect.

5.8.4. Sidedoor Certificate - (N/A - no longer in use)

Sidedoor is a reverse proxy web server that has been set up to ensure that all protected health information (PHI) and study data are securely transmitted over the Internet and remain privileged and confidential. Sidedoor requires installation of a user−specific certificate in each web browser the individual will use, and the presence of the certificate, combined with a username and password, allows access to the HALT PKD Reports page and Web Data Entry System (WDES). Once sidedoor has been installed in a browser, it is transparent to the user. The DCC is responsible for issuing sidedoor certificates and must receive a completed VPN/Sidedoor Request Form from any HALT PKD staff member who needs to access study PHI.

To request a sidedoor certificate, the HALT PKD staff member must complete a VPN/Sidedoor Request Form, and the applicable principal investigator (PI) must sign the request form to authorize the DCC to create the certificate. Once the PI has signed the completed form, it needs to be faxed to the HALT PKD Project Manager. She will forward the request form to the network administrator at the DCC, who will then create the sidedoor certificate and email it to the user, along with complete instructions for installation in a web browser. When individuals resign from HALT PKD, they should delete the certificate from both their web browser(s) and computer file system (.p12 file).

Each sidedoor certificate is specific to the user, as well as specific to the web browser, so each HALT PKD staff member must install his/her own certificate in all browsers that will be used to access study data.

HALT PKD staff members are expected to accept personal responsibility for maintaining the security of the study. Usernames and passwords must **not** be shared with any other individual.

Users must **not** share their sidedoor access with any other individual. Using another individual's sidedoor connection is a security violation and, if discovered, may result in the user being prohibited from accessing the HALT PKD website.

5.9. Safety Monitoring

A number of activities will be undertaken to minimize risks to HALT PKD participants and to ensure their safety over the course of the study. These activities include: 1) screening evaluations of potential participants to determine whether it is safe for them to take part in the study; 2) monitoring safety during drug washout, drug titration and telephone and clinic examinations; and 3) providing selected results from study assessments to participants and/or their physicians when there are health and safety implications.

For more specific information on safety monitoring, refer to Section 13 - Safety

5.9.1. Definition and Reporting of Serious Adverse Events (SAE)

For complete guidelines on reporting SAE's, refer to Section 13.8 – Serious Adverse Events (SAE).

5.9.1.1. Definition of an SAE

A study 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 (before the screening visit) until the end of the study. [2][3][4] Some study SAEs may also reach the threshold of requiring reporting to your local IRB. Sites will follow local IRB policy and procedures for reporting serious adverse events within their institutions.

- ***Resulting in Death*** − All deaths must be reported as SAEs.
- ***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.
- ***Life−threatening*** − If the patient 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 patient'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.
- ***Resulting in significant, persistent or permanent harm or disability.***
- ***Exceeding the nature, severity or frequency of risk described in the protocol.***
- ***Congenital anomaly*** − If there is suspicion that exposure to a study medication or procedure prior to conception or during pregnancy resulted in an adverse outcome in the child.
- 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.

5.9.1.1.1. Hospitalization for 23 Hour Observation or Pregnancy

The following admissions qualify as study serious adverse events:

- Participant admissions for an overnight "23 hour observation"
- Pregnant participants admitted for labor and delivery
    - Form13-study SAE comments should include documentation of the infant's health status noted on the maternal medical record obtained for adjudication or obtained from the participant's verbal report. Any congenital malformations or complications of the labor and delivery should be documented.

Coordinators will obtain a HIPAA release form from the participant, request the discharge summary for that admission and submit a serious adverse event Form 13 and hospitalization Form 30.

Emergency room admissions per se, without subsequent admission to the hospital, do not require the submission of a serious adverse event report unless these otherwise meet the criterion for a severe adverse event.

5.9.1.2. SAE 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 Form13. Information not available at the time of the initial report should be submitted to the DCC as a follow−up report in a timely fashion. All SAEs will be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE version 3.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. In October, 2010 the University of Pittsburgh DCC converted the CTCAE version 3.0 to CTCAE version 4.0. Reporting requirements for the FDA differ depending on their relatedness to study interventions as follows:

SAEs that are reasonably related to study participation*:*

- *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.

☞ 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. Principal investigators 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.

Chapter 6. Publications and Communications

6.1. Publications Policy

The policy of the PKD Clinical Trials Network concerning publications and presentations is designed to achieve five objectives:

1) To assure timely publication of the results of studies of the PKD Clinical Trials Network to the appropriate professional audiences.
2) To avoid premature publication of results that might compromise performance of the study (such as publishing trends before they become statistically convincing) or that might compromise the ability to publish results in high−quality peer−reviewed journals (such as premature release to the lay press).
3) To maintain high standards of quality of all materials published by the PKD Clinical Trials Network.
4) To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees.
5) To assure attribution of credit to all professionals participating in studies within the PKD Clinical Trials Network.

To accomplish these ends, it is the policy of the PKD Clinical Trials Network that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Study Chairman, after consultation with the Publications/Ancillary Studies Subcommittee Chair, to specifically−appointed writing committees, and that all such materials must be reviewed and approved by the Publications/Ancillary Studies subcommittee and/or the Steering Committee prior to publication.

A listing of the members of the Publications/Ancillary Studies Subcommittee may be found on the HALT PKD website (https://www.halt−pkd.pitt.edu).

6.1.1. Scope of Policy and Exception for Local Publicity Materials

All materials to be presented orally or submitted for publication or dissemination by individuals associated with the PKD Clinical Trials Network or dealing with any aspect of a study within the PKD Clinical Trials Network must receive prior review and approval by the Publications/Ancillary Studies Subcommittee and/or Steering Committee with the following exception:

Material prepared for publicity purposes, either nationally or within the recruitment region of a PKD Clinical Trials Network Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the PKD Clinical Trials Network Study and its objectives, need not be reviewed by the Publications/Ancillary Studies Subcommittee. Such material must be limited to a background discussion of the scope of the study (e.g. in the HALT PKD study: the issue of blood pressure control as a treatment for progressive renal disease and a description of the PKD Clinical Trials Network study organization, objectives, and entrance criteria) and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously un-presented and unpublished outcomes from a PKD Clinical Trials Network study or generate a citable professional reference.

6.1.2. Source for Suggestions for Publications

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

A HALT PKD Manuscript / Presentation Proposal Form must be completed and submitted to the PAS Subcommittee for any proposal that pertains to presentation and analysis of NEW data.

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

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

6.1.3. Assignment of Writing Committees

The Study Chair, upon receipt of a recommendation for preparation of a topic for publication, and after confirming that the topic does not overlap with a previous assignment to another writing committee, and discussion with the PAS Subcommittee Chair, will appoint the Chair of a new writing committee to prepare the publication. Appointments of writing committee chairmanships will be made in an equitable fashion to all professionals−physicians, clinical coordinators, statisticians, and others − in a fashion that recognizes the special contributions of each member of the PKD Clinical Trials Network study to its performance.

Upon appointment of the Chair of a new writing committee, the PAS Subcommittee Chair will notify each collaborating center, including clinical centers, the DCC, the NIH, and the central laboratories, of the new writing committee, soliciting indications of interest to be on that writing committee. If more individuals express interest than is practical to assign to a committee, the Study Chair, after discussion with the PAS Subcommittee Chair, shall make final assignments of the members of the committee.

In all cases, writing committees dealing with an issue that requires analysis of data by the Data Coordinating Center will have a member of the DCC assigned to it.

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

6.1.4. Classes of Reports for the PKD Clinical Trials Network

There are four classes of reports for the PKD Clinical Trials Network:

Class A

- Reports of the major outcomes of the studies − It is assumed there will generally be only one or two such reports derived from each phase of the Study. Generally these reports will be prepared by the Writing Committee appointed by the PAS Subcommittee Chairman, with the Study Chair as Chair of the writing committee.

Class B

- Reports addressing in detail one aspect of the PKD Clinical Trials Network Studies, but in which the data are derived from the entire study.

Class C

- Reports of data derived from a subset of centers by investigators of the studies within the PKD Clinical Trials Network (e.g., sub−studies or ancillary studies) or originally conceived analyses of data from entire studies of the PKD Clinical Trials Network (original analyses).

Class D

- Reports of investigations initiated outside of the PKD Clinical Trials Network, but uses data or samples collected by a study within the PKD Clinical Trials Network. The investigators may be PKD Clinical Trials Network or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the PKD Clinical Trials Network itself.

6.1.5. Authorship

The authorship policy of the PKD Clinical Trials Network must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire PKD Clinical Trials Network professional staff. Thus, all reports, of whatever Type, must give recognition to all the participants of the PKD Clinical Trials Network studies (e.g.: HALT PKD), and reports of Types A and

B must give primary recognition to the entire study professional staff. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of results of the PKD Clinical Trials Network. The PKD Clinical Trials Network authorship policy attempts to recognize each of these goals. The authors of PKD Clinical Trials Network publications will be listed as detailed below for each type of publication.

6.1.5.1. Type A – Publications

Abstracts: From the PKD Clinical Trials Network, e.g. HALT PKD study, presented by XXXX. (This will usually be determined by the Study Chair).

Papers: From the PKD Clinical Trials Network (e.g. HALT PKD study[1]).

[1]The PKD Clinical Trials Network Participant Box, detailed below, must be included in these papers.

6.1.5.2. Type B – Publications

Abstracts and Papers*:* From the PKD Clinical Trials Network HALT PKD study[1], prepared by [Chair of the writing committee, other members of the writing committee listed alphabetically].[2]

[1]The PKD Clinical Trials Network Participant Box will be included in all papers if this can be arrange with publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts. [2] It will be stated in a footnote that the names of the writing committee are listed alphabetically after the name of the committee chair.

6.1.5.3. Type C and D – Publications

Abstracts and Papers*:* By [members of the writing committee in any order acceptable to them] and the PKD Clinical Trials Network HALT PKD study.[1]

[1]The Participant Box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. In type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

6.1.5.4. Listing of Professional Participants in the PKD Clinical Trials Network Participant Box

The PKD Clinical Trials Network Participant Box for each phase will list all professionals that have participated in a study within the PKD Clinical Trials Network for a minimum of one year in that phase. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "PI" followed by the other center staff listed alphabetically. Each participant is to be listed only by his/her professional and academic degrees and not by the specific position that he/she holds in the study. The centers are to be listed in the following order:

1. NIH
2. Study Chair
3. Data Coordinating Center
4. Clinical Centers (in alphabetical order)
5. Central Laboratories (in alphabetical order)

Prior to the publication of any papers from any phase of a study from the PKD Clinical Trials Network, each center will be asked to confirm and approve the listing of the personnel from that center in the PKD Clinical Trials Network Participant Box.

6.1.6. Acknowledgement of Support and Reprint Addresses

Acknowledgment of grant support is to be used in all papers reporting results of the PKD Clinical Trials Network study. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The PKD Clinical Trials Network is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, through cooperative agreements.

The Merck agreement requires 30 days company review prior to a publication submission and 5 days company review prior to an abstract submission. The Boehringer Ingelheim agreement requires that the company receive a copy of publications after their acceptance for publication.

The following information regarding reprint requests should be included in all papers prepared by the PKD Clinical Trials Network. The NKUD Clearing House will maintain an inventory of all PKD Clinical Trials Network publications and will actually mail out the reprints.

Requests for reprints should be addressed to: National Kidney and Urologic Diseases Clearing House Box NKUDIC Bethesda, MD 20892.

6.1.7. Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time a writing committee is constituted by the Study Chair, the Publications/Ancillary Studies Subcommittee will establish a timetable for completion of the writing assignment that takes into account deadlines for publication, the amount of time required for data analysis, other commitments of the Coordinating Center, and priority of the publication. These deadlines may differ based on the complexity of data analysis; however, once the required analysis has been determined, these materials should be available to the writing committee within three weeks.

The Chair of the Writing Committee should provide the Chair of the PAS Subcommittee with a general outline of the proposed publication, within a month of receiving its assignment, to permit the Publications/Ancillary Studies Subcommittee to identify any overlap with the assignments of other writing committees and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the Publications/Ancillary Studies Subcommittee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Study Chair. The Chair of the Publications/Ancillary Studies Subcommittee will report at each meeting of the Steering Committee on the progress of the various writing committees.

6.1.8. Review of Abstracts and Presentations by the Publications Committee

1) The writing committee that wants to submit an abstract, give a talk, or submit other material for which there is an explicit submission deadline, shall contact the Chair of the PAS Subcommittee. If data analysis is required by the DCC in order to submit an abstract or presentation, this notification must be made at least 6 weeks prior to the deadline. In the event that the Chair is unavailable, an Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of three members of the Publications/Ancillary Studies Subcommittee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be mailed by the submitter directly to the subcommittee. This material must be submitted no later than fourteen (14) days prior to the deadline for submission.
2) The members of the subcommittee shall review the material and notify the Chair solely of the approval or disapproval. If there is unanimous approval, the PAS Subcommittee Chair (or Alternate Chair) shall inform the submitter that he/she has PKD Clinical Trials Network approval for the submission. In the event of a split vote for approval, the issue will be reviewed by the Publications/Ancillary Studies Subcommittee Chair (or Alternate Chair) with the Chair of the Steering Committee (or in his/her unavailability with the Vice Chair of the Steering Committee) whose decision will be binding.
3) All materials submitted for approval in this fashion will be distributed by mail, together with notice of the disposition, to all members of the Publications/Ancillary Studies Subcommittee, the Chair of the Publications/Ancillary Studies Subcommittee and to the Chair of the Steering Committee. All approved materials will also be forwarded to the NIH Trial Coordinator and, for record purposes, to the Principal Investigator of the Data Coordinating Center and will be distributed to the entire membership of the Steering Committee at the next meeting of that Committee as an Appendix to the report of the Publications/Ancillary Studies Subcommittee.
4) In the case of abstracts or other similar written material, the entire material to be submitted must be sent by the submitter for review by the appointed subcommittee.
5) In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.
6) Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation. Normally this review will be done by the same subcommittee of the Publications/Ancillary Studies Subcommittee that reviewed the initial abstract.

6.1.9. Review of Papers by the Publications Subcommittee

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Subcommittee for formal review by the entire Committee. If there is a deadline for submission of a formal paper that does not require analysis by the DCC, it is the responsibility of the submitter to be certain it is submitted to the Chair of the Publications/Ancillary Studies Subcommittee, PAS subcommittee, at least 30 days prior to the deadline, to permit such review. *If data analysis is required of the DCC prior to submission of the paper, the Chair of the PAS Subcommittee must be notified at least 6 weeks prior to the 30 day−deadline to allow for adequate analysis*. This review will be conducted as follows:

1) The Publications Chair, with the PAS Subcommittee, shall appoint a panel of three primary reviewers, two of whom must be PAS Subcommittee members, and one of whom may be any professional member of the PKD Clinical Trials Network with appropriate expertise. The Publications Chair shall distribute the material to all members of the Publications/Ancillary Studies Subcommittee and to the Principal Investigator of each center participating in the PKD Clinical Trials Network. The three members of the review panel shall each prepare and send to the Publications Chair a written critique of the submitted material for distribution to the entire Publications/Ancillary Studies Subcommittee. The PI's of the various clinical centers will be given a deadline of 14 days by which any comments or critiques that study participants at their center may wish to make to the chair of the Publications/Ancillary Studies Subcommittee. This mechanism will assure that each professional participating in the PKD Clinical Trials Network will have an opportunity to review any materials that will be submitted for publication bearing his/her name as a participant and co−author.
2) The chair of the Publications/Ancillary Studies Subcommittee shall schedule a meeting of the Subcommittee (generally by conference call), including review of papers and other non−time critical materials as Agenda items. The reviews of the panel members and any comments received from the center PIs will be distributed to the Subcommittee with the agenda.
3) *While discussion of the submitted papers and other materials will be led by the three appointed reviewers, all members of the Subcommittee will be invited to participate and all shall vote on final disposition.*
4) In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re−review), non−acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.
5) The chair of the Publications/Ancillary Studies Subcommittee shall be responsible for communicating the decision of the Subcommittee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non−acceptance of the material as submitted, but with suggestions for revision and resubmission, he/she and the writing committee may agree not to proceed with a report to the Steering Committee at that time, pending revision and resubmission.
6) If there is a recommendation for approval or final approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the Chair, Publications/ Ancillary Studies Subcommittee, shall report this outcome in writing to the Steering Committee for final action. In the case of a dispute between the Publications/Ancillary Studies Subcommittee and the author(s), the Chair, Publications/Ancillary Studies Subcommittee, shall provide a copy of the submitted material and a summary critique to the Steering Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.
7) The authority to grant final approval for a formal scientific paper of the PKD Clinical Trials Network rests with the Steering Committee.
8) All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the Steering Committee. All materials receiving final approval by the Steering Committee will also be forwarded to the NIH Trial Coordinator and for record purposes to the Principal Investigator of the DCC.
9) In the event that editors of a scientific journal to which an approved PKD Clinical Trials Network scientific manuscript is submitted request a revision to a paper, the revisions should be submitted to the Publications/Ancillary Studies Subcommittee to review the revision, and every effort will be made to expedite such repeat reviews.

6.1.10. Criteria for Review of Materials by the Publications Subcommittee

All materials submitted to the Publications/Ancillary Studies Subcommittee will be reviewed for acceptability on two grounds:

1) Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved PKD Clinical Trials Network materials reflect well on clinical studies.
2) Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the studies within the PKD Clinical Trials Network or compromise the eventual publication of any findings in high− quality peer−reviewed journals. In this latter regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer−reviewed journal.

6.1.11. Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all official publications and presentations of studies from the PKD Clinical Trials Network, separated into the following categories:

Peer−reviewed papers accepted and published in professional journals.

- Invited editorials, reviews, chapters and books.
- Abstracts published in citable journals
- Other presentations at regional or national meetings that do not result in a citable abstract.

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

6.1.12. Acknowledgement and Acceptance of PKD Clinical Trials Network Policies on Publications

To assure that all professionals involved with the PKD Clinical Trials Network know and understand the policies governing PKD Clinical Trials Network studies and to preclude the possibilities of misunderstandings after initiation of any studies, each professional member will be given a copy of this document and asked to sign a Statement of Understanding, listing the major provisions of this document and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding is to be returned to the Data Coordinating Center for record purposes. A copy of the Publications Policy and signed Statement of Understanding is to be kept by the PKD Clinical Trials Network professional participant for reference.

6.2. HALT PKD Website

The Data Coordinating Center (DCC) developed and maintains the HALT PKD website, which is password protected content accessible to only study personnel. The address of the HALT PKD website is: *https://www.halt−pkd.pitt.edu/web*.

6.2.1. Content Restricted to Study Personnel

The HALT PKD website is restricted to study personnel and has several distinct components dedicated to management and coordination of the study: administrative resources, data−entry system support, forms tracking, querying and editing, and reporting. The administrative component of the web site includes the following features: study protocol, study personnel directory, meeting and conference call minutes, subcommittee minutes and reports, Manual of Procedures (MOP), data collection forms. Reports will be posted on the web to provide an accurate picture of the progress of the study, including recruitment tables, within window visit completion rates, retention rates, forms submission and completion rates, data query and edit completion rates (pending, addressed, timeliness), and other QA reports as needed. Multi−tiered support is provided for website users, including written procedures and technical support via e−mail or telephone. Study documents (MOP, forms, reports, etc.) are available for download in various formats, including MS Word (.doc) and portable document format (.pdf).

6.2.2. Content for Public Access – (N/A – no longer in use)

The portion of the HALT PKD website accessible by the public includes a brief description of the purpose of the study and hyperlinks to participating sites, the Polycystic Kidney Disease Foundation (PDKF), and to the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The public can also access the HALT PKD study brochure, which includes a more complete description of study goals and objectives, as well as some inclusion/exclusion criteria and information on how to contact the HALT PKD Project Manager and participating clinical centers. The public portion of the website is expected to expand as the study progresses.

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.

6.3. Public Relations

The HALT PKD Project Manager has been primarily responsible for public relations duties during the development phase of HALT PKD. At present, these duties pertain mainly to responding to requests for more information from potential participants. As the study progresses, a more defined public relations policy will be established.

Chapter 7. Study Design

7.1. Study Timeline

7.1.1. Development Phase

During the Development Phase, the HALT PKD Steering Committee wrote and finalized the study protocol and its associated policies and procedures. This Manual of Procedures (MOP), which includes well−defined procedures for the HALT PKD studies, as well as training and certification procedures for clinical personnel, was produced during the Development Phase. Parameters to be assessed at the Central Laboratories have been outlined. The Data Coordinating Center (DCC) designed and programmed the study database during this phase.

Prior to moving to the Recruitment Phase of HALT PKD, the study protocol must be reviewed and approved by the Data Safety and Monitoring Board (DSMB). The long−term study cannot move into its operational phase until the DSMB and NIDDK concur that recruitment may begin.

During the Development Phase, outlays of funds have been, primarily, for appropriate levels of salary support for investigators during development of the HALT PKD protocol and MOP and for travel to Steering Committee meetings.

7.1.2. Recruitment Phase

Just prior to beginning the two−year Recruitment Phase, training of study staff will take place to ensure the protocol is carried out uniformly across participating clinical sites (PCCs) and to provide certification for study procedures. During the Recruitment Phase, potentially eligible participants will be identified through a pre−screening process and invited to PCCs for screening and baseline assessments, and those individuals who are determined to be eligible to participate in HALT PKD will be randomized and enrolled to either Study A or Study B. Note that no exceptions to established eligibility criteria will be allowed.

During the Recruitment Phase, the DSMB will meet annually to review the status of recruitment and interim outcomes and will then recommend to NIDDK whether the study should continue. The DSMB will also review any subsequent trials proposed by the Steering Committee.

7.1.3. Study Phase

Concurrent with recruitment, follow−up of all study participants will be conducted in a standardized fashion over regular intervals, as outlined in the participant schedule. Further interventions will be developed, as necessary, during this phase, as an ongoing process, as determined by the results of pilot and feasibility studies. The major activity during the Study Phase will be manuscript preparation and follow−up clinic visits. Follow−up and data collection on study participants will continue throughout the Study Phase, as defined by the study protocol. Manuscripts on interim findings from HALT PKD will be prepared and submitted for publication, per the guidelines of the study Publications Policy. The last follow−up visits for study participants will be scheduled during the final two months of this Study Phase.

7.1.3.1. Participant Schedules

Tables 7−1 and 7−2 summarize the study visits that are to take place between the screening visit and the end of the study, with shaded columns representing visits to the PCC. At the first visit, S (Screening), subjects will be consented for Screening and Drug Washout (B0) and trained to monitor blood pressure at home. Screening lab measurements will be drawn. After review of the labs drawn at the S visit, the study coordinator will contact participants by telephone to initiate a 2−4 week drug washout period, if required. During the drug washout period, labetalol will be substituted for current blood pressure medications. (Clonidine will be used in cases of participants for whom beta−blockers are contra−indicated).

At the Baseline visit (B1), participants will be consented for baseline and beyond (Study A or Study B). Baseline lab measurements will be obtained, participants will be randomized, and the treatment regimen will be initiated and masked study drug(s) dispensed. If the results of central serum creatinine values do not require repeat sample collection, participants can be instructed to begin the treatment regimen (B2 visit).

Study drugs will be incremented over three subsequent visits (F1−F3), two weeks apart, to be conducted by telephone. Serum potassium, creatinine and BUN will be checked between dose increments at the PCC or a local lab.

After 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 4th month (F5) and 12th month (F12) in the first year and every 6 months thereafter. After the first year, serum creatinine will be measured centrally every 6 months for participants enrolled to both studies. Study A participants will undergo MRI imaging at baseline, 24, 48 and 60 months. For each Study A participant, the "end of the study" was defined as the F48 visit, or its "target visit date" if that visit is not completed. However, Study A will be extended until July, 2014, rather than the closing date of January, 2013. All participants will continue on the study until July, 2014, even if they reach their 60 month visit at an earlier date. Participants will be triaged out of the study at their clinical visit prior to July 2014. This extension will allow all participants to reach their 60month visit, prior to the end of the study. Study B participants "end of the study" is defined as the F84 visit,

or when the last participant enrolled has been followed for 48 months.

Table 7−1. Schedule of Assessments − PS−F5 Visits

Visit Code	PS	S@	B0	B1	B2	L1	F1	L2	F2	L3	F3	L4	F4^	F5
Time Point		K	−2 wk	0 wk	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 Questionnaire				x										
MR/MRA/Cardiac MR (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		xE										xE
Total Electrolyte Panel: Na, K, Cl, CO2, BUN		x												x
Partial Electrolyte Panel: K, BUN, Creatinine**C**				xA		xB		x		xB		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												
B−HCG Urine Pregnancy **F**		x												
Digoxin				xL		xBL		xL		xBL		xL		
24−Hr Urine Collection **H,#**		#		x#										x#
Genetic Sample**G**														x
Specimen Banking **I**				x										xJ

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.*

C=*At B1, must use PCC for K+BUN, central lab for creatinine. May use PCC outside lab during titration(L1-L4).*

***D*=PCC lab must be used at S visit, Cleveland Clinic (Quest, if necessary) at all other visits. Confirm baseline results before starting randomized drugs.**

***E*=TWO samples drawn at B1 & F5 (>1 hour apart), shipped same day to Cleveland Clinic. 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. Genetic sample is shipped at room temperature on the day of collection to the NIDDK Genetic Repository at Rutgers.**

***H*= Urinary Aldosterone + Urine Chemistry samples (Na, K, creatinine, microalbumin) are batch−shipped to BMCF at Hillman Cancer Center, Pittsburgh, PA.**

***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.**

***J*=At F5, archival samples include urine (fresh + 24−hour) and optional genetic sample (G above), but not serum or plasma.**

***K*=S visit must be within 10 weeks of randomization (B1).**

***L*=Participants on Digoxin must have levels tested at B1, with safety labs (L1−L4), every 6 months and 1 week after any change in ARB/placebo.**

***M*=Glucose is fasting at the Screening Visit, random at all other visits annually.**

#=Containers and instructions for 24−hr urine collection may be sent home with participant for next visit.

***=**Some sites require a second consent for the B1 visit (baseline and beyond).

^=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 7−2. Schedule of Assessments − Following F5 Visit

Visit Code	F7	F10	F12	F15	F18	F21	F24~	F36~	F48~	F60~	F72~	F84	F96&
Time Point													
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
Background Questionnaire													
QOL + Pain Questionnaire			x				x	x	x	x	x	x	x
MR/MRA/Cardiac MR (Study A only)							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, CI, CO2, 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	
Glucose **M**			x				x	x	x	x	x	x	
CBC with PLT			x		x		x	x	x	x	x	x	
PCC Random/Spot Urine: Microalbumin+Creatinine													
B−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

D*=Cleveland Clinic 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 CCF*

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 at Fisher.*

L*=Participants on Digoxin must have levels tested at B1, with safety labs (L1−L4), every 6 months and 1 week after any change 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 next visit.*

~*Note: After F24, continue 3 month phone calls, 6 month PCC visits as during the second year until the end of study.*

%*=Study A participants may continue past the F48 visit as noted in section 10.1 of the protocol. Continue following all Study B participants through F84.*

7.1.4. Close-Out Phase

During the final six months of the study, final data analyses and preparation of manuscripts on the findings from the study will take place. PCCs, the DCC, and all central facilities will be closed out over the course of the last two months of the HALT PKD close−out phase.

7.2. Eligibility (Inclusion/Exclusion Criteria)

7.2.1. Study A

7.2.1.1. Inclusion Criteria

The following criteria will be used to determine eligibility for Study A.

1) In subjects 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, equated 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 greater than or equal to 130 mm Hg and/or a diastolic blood pressure of greater than or equal to 80 mm Hg on three separate readings within the past year, or by the current use of antihypertensive agents or diuretics for blood pressure control. *(JNC−VII−2003)*

4) Informed consent.

7.2.1.2. Exclusion Criteria

Please note that no exceptions to established eligibility criteria will be allowed.

1) Currently pregnant or intention of becoming pregnant in the subsequent 4 years.
    a. Women who have had a pregnancy of more than 12 weeks duration (past the first trimester) must wait a minimum of 6 months postpartum, miscarriage or abortion before screening and must not be lactating at the time of screening.
    b. For a pregnancy of 12 or fewer week's 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 greater than or equal to 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 greater than or equal to 126 mg/dl or a random non−fasting glucose of greater than or equal to 200 mg/dl (in accordance with ADA recommendations for diagnosis of diabetes. *(Report−2003)*)
5) Serum potassium greater than 5.5 mEq/L for participants currently on ACE−I or ARB therapy; greater than 5.0 mEq/L for participants *not* currently on ACE−I or ARB therapy.
6) History of angioneurotic edema or other absolute contraindication with ACE−I or ARB. Intolerable cough associated with ACE−I has been defined as cough that developed within six months of initiation of ACE−I in the absence of other causes and resolved upon discontinuation of the ACE−I.
7) Indication (other than hypertension) for beta−blocker or calcium channel blocker therapy (e.g. angina, past myocardial infarction, arrhythmia), unless approved by the site principal investigator.

    Please note that only participants taking a "relatively small dose" of a beta or calcium channel blocker may be enrolled in HALT PKD, as this would not be expected to significantly impact BP nor put participants at greater risk (a change in consent is not required). Individuals on a large dose of beta or calcium channel blocker must continue to be excluded from the study.

8) Systemic illness necessitating NSAIDs, immunosupressant 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 less than 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 greater than or equal to 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 creatinine supplements within three months prior to the screening visit.
15) Congenital absence of a kidney.
16) Known allergy to sorbitol or sodium polystyrene sulfonate (kayexalate).

Exclusions specific to the MR measurements of Total Kidney Volume:

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 greater than 159 kg (350 lbs) or untreatable claustrophia.

7.2.2. 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:

7.2.2.1. Inclusion Criteria

1) A diagnosis of ADPKD as described in item 1 of Exclusion Criteria for Study A.
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 *(Levey−2000)*

4) Hypertension or high−normal blood pressure, defined as systolic blood pressure greater than or equal to 130 mm Hg and/or diastolic blood pressure greater than or equal to 80 mm Hg *(JNC−VII−2003)* on three separate readings within the past year or the current use of antihypertensive agents or diuretics for blood pressure control.
5) Informed consent.

7.2.2.2. Exclusion Criteria

Please note that no exceptions to established eligibility criteria will be allowed.

1) Currently pregnant or intention of becoming pregnant in the subsequent 4−7 years.
   a) Women who have had a pregnancy of more than 12 weeks duration (past the first trimester) must wait a minimum of 6 months postpartum, miscarriage or abortion before screening and must not be lactating at the time of screening.
   b) 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 procedures or partial nephrectomy will not preclude participation in Study B.3. Documented renal vascular disease.
3) Spot urine albumin−to−creatinine ratio of greater than or equal to 1.0 and/or findings suggestive of kidney disease other than ADPKD.
4) Diabetes requiring insulin or oral hypoglycemic agents or a fasting serum glucose of greater than 26 mg/dl or a random non−fasting glucose of greater than or equal to 200 mg/dl (in accordance with ADA recommendations for diagnosis of diabetes). *(Report−2003)*
5) Serum potassium greater than 5.5 mEq/Lfor participants currently on ACE−I or ARB therapy; greater than 5.0 mEq/L for participants not currently on ACE−I or ARB.
6) History of angioneurotic edema or other absolute contraindication with ACE−I or ARB. Intolerable cough associated with ACE−I as defined above. Intolerable cough associated with ACE−I has been defined as cough that developed within six months of initiation of ACE−I in the absence of other causes and resolved upon discontinuation of the ACE−I.
7) Systemic illness necessitating NSAID use or immunosupressant or immunomodulatory medications
8) Systemic illness with renal involvement.
9) Hospitalization for an acute illness in past 2 months (not including elective admissions).
10) Any serious comorbid condition for which life expectancy is less than 2 years.
11) History of non−compliance, drug or alcohol dependence within the past year or other psychiatric disturbance that would preclude successful completion of the study.
12) Known presence of unclipped cerebral aneurysm greater than or equal to 7 mm in diameter.
13) Indication (other than hypertension) for beta−blocker or calcium channel blocker therapy (e.g. angina, past myocardial infarction, arrhythmia), unless approved by the site principal investigator

    Please note that only participants taking a "relatively small dose" of a beta or calcium channel blocker may be enrolled in HALT PKD, as this would not be expected to significantly impact BP nor put participants at greater risk (a change in consent is not required). Individuals on a large dose of beta or calcium channel blocker must continue to be excluded from the study.

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 the HALT−PKD study, or creatinine supplements within three months prior to the screening visit.
15) Known allergy to sorbitol or sodium polystyrene sulfonate (kayexalate).

7.3. Statistical Power and Sample Size Calculations

7.3.1. 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 percent change in total kidney size, the standard deviation of the slopes ($\sigma_{s)}$ 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, 4 years, and 5 years, we have calculated the necessary sample size (each group) for various effect sizes for powers of 0.80 and 0.90, with a significance level of 0.05 (2-tailed).

Table 7−3. Study A − Statistical Power and Sample Size

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	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

7.3.2. 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 25−60, 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 of3 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 follow up. 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:

Table 7−4. Study B − Statistical Power

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**	**.619**	**.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	**.267461**	**.524726**	**.4844**	**>.9900**

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).

7.4. Endpoints

7.4.1. Study A

The primary outcome for Study A is the percent change in kidney volume assessed by MRI at baseline, 24, 48 and 60 months follow up. 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 (Study A "primary" secondary outcome): 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 (Form5); ix) adverse effects of study medications.

7.4.2. 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. 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.

7.5. Methods for Analysis of Primary Outcomes

7.5.1. 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, F24, F48 and F60, 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). The "primary" secondary outcome of eGFR will be calculated using serum creatinine measurements, which will be obtained at the baseline, F5 and F12 visits 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 primarily utilize random regression methods. To improve the stability of the estimation process and reduce the impact of larger TKVs 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. The model intercepts will not be constrained, as they should be roughly equivalent by chance.

A Laird and Ware linear mixed model will be used to model the trajectory of ln TKV 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,N.M. and J.H. Ware Random effect models for longitudinal data. Biometrics, 1982. 38:963-974.),* 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)*

Hypotheses 1 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)*

Hypothesis 2 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, 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.

7.5.2. 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. Study B participants will be followed until the last clinic visit prior to July 2014 resulting in 5-8 years of follow up with the average length being 6 ½ years. Participants who do not reach one of the four 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).

7.6. Methods of Analysis of Secondary Outcomes

7.6.1. 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 [*Seber1989*]. 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 2nd event unless he/she has experienced the 1st 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.

7.6.2. 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 (>/= 2 hours 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.

Chapter 8. Participant Visits

8.1. Overview of Study Visits

Participants will be prescreened during a brief telephone interview. The Screening (S) and Baseline (B1) study visits, as well as all six−month (F5, F12, etc.) study visits, will take place at participating clinical centers (PCCs). Additional follow−up visits are to be conducted by telephone every two weeks during drug titration and then at three months after each PCC visit. Each participant's interval blood pressure readings, adverse events, concomitant and study medications, changes in contact information, and any necessary lab results are to be reviewed at all study visits. Each PCC is to report all pre−screening visits on the monthly Pre−Screening Activity Report Form 1. PCCs are to report B2 visits and all clinic visits on HALT PKD Visit Tracking Form 40 on the day of the visit or by 9:00 a.m. (local time) the day after the visit at the latest.

Schedules of the assessments required at each visit may be found in Section 8.4 − Schedule of Assessments for Screening, Baseline and Follow−Up Visits.

For guidelines on how late or missed visits are to be addressed, refer to Section 8.16 − Target Visit Dates, Acceptable Visit Ranges, and Missed Visits and/or Section 13.5 − Protocol Deviations/Major Violations.

8.1.1. Definition of Study Visits

All events that take place in HALT PKD will be associated with a Visit Code, with the exception of blood draws and changes in study medications that occur between planned visits; and each Visit Code is associated with a Date of Visit and a Visit Range.

8.1.2. Guidelines for PCC Visits

All PCCs should follow the guidelines below for all participant visits to the clinical center.

8.1.2.1. Scheduling Visits

PCC visits are to occur in the morning at screening (S), baseline (B1), four months (F5), and annually (whenever MR imaging and/or 24−hour urine samples are required). The guidelines described below apply to all morning visits. However, at six−month visits (beginning with F18), PCC visits may occur in the afternoon (between noon and 5:00 p.m.). Prior to afternoon visits, participants may eat a normal breakfast and a light lunch. To ensure standardized evaluations when MR imaging is required (Study A participants only), it is suggested that afternoon visits occur 22−28 hours after the last dose of study medication. Second−line antihypertensive mediations taken on a twice−daily schedule should be held the evening before any visit that includes MR imaging (B1, F24, F48, F60).

8.1.2.2. Dietary and Medication Restrictions

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.

In most cases, it is advisable that a GCRC dietician give guidelines for food portions <1.3 g/kg/d (~91 Grams of protein, ~11.4 ounces of meat) to participants. However, in cases where access to a dietician is not practical, the PI may use his or her discretion on this point.

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.

When imaging is required (B1, F24, F48, F60), Study A participants should be instructed to hold morning doses of all antihypertensive medications until after renal blood flow imaging has been acquired (to reduce the hemodynamic effects).

Study A participants who take second−line antihypertensive medications twice daily, should be instructed to hold those medications the night before any visit that will include imaging exams (B1, F24, F48, F60). Study B participants do not need to hold any antihypertensive medications prior to clinic visits.

Refer to Section 11.5.2.2 − Medication Restrictions for a complete list of drugs with potential nephrotoxicity.

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.

Additional Dietary Instructions for PCC Visits:

- *Screening*: Fast (water only) for 8 hours prior to the visit.
- *Baseline and F5 visits*: A light meal prior to the visit is acceptable. The only acceptable fluids on the morning of the visit (after midnight up to the second serum creatinine collection) are coffee, milk, juice, soft drinks and water.
- *All 6− and 12−month visits*: A light meal prior to the visit is acceptable. The only acceptable fluids on the morning of the visit (after midnight up to the time of sample collection) are coffee, milk, juice, soft drinks and water.

8.1.2.3. Self-Reporting Questionnaires

HALT PKD uses three self−reporting questionnaires. They are Quality of Life Questionnaire Form 38 (SF−36v2), HALT PKD Pain Questionnaire Form39, and Symptoms Checklist Form 5 (the last being partially completed by the participant, and then reviewed by the coordinator). It is suggested that all self−reporting questionnaires be administered after blood pressure is measured, but before all other study procedures, in order to avoid affecting the participant's responses to the questionnaires. It is critical that the Quality of Life Form (SF−36) and Pain Questionnaire be completed by the patient without any assistance from staff who may influence responses.

Quality of Life Questionnaire Form 38 (SF−36v2) must be administered before the Pain Questionnaire (Form 39), as it is important that the distinction of effects of the disease in general, versus effects of pain, on quality of life is clear to patients when they are completing the forms. However, the order of administration of the Symptoms Checklist relative to these forms is not as critical, though it would make sense for this form to follow the others.

It is important to emphasize the distinction between the SF−36 and the HALT−PKD Pain questionnaire and Symptoms Checklist Form 5. The SF−36 assesses how the disease as a whole affects one's health status, while the pain questionnaire specifically addresses how pain and/or symptoms from enlarged organs affect one's health status. The Symptom Checklist also asks questions about pain, but does not go into detail about the nature, severity, frequency and impact of pain on daily activities, as does the pain questionnaire.

Suggested instructions when administering self−reporting questionnaires: "Here are two questionnaires for you to fill out. The first asks about your overall wellbeing and the quality of your life." Point out the title and form number. "The second questionnaire asks you specifically about any pain or abdominal fullness you may experience." Point out the title and form number. "These are two very different questionnaires, although some of the questions may seem similar to you. We ask that you fill them out in this order; first the Quality of Life Form (38), then the Pain Questionnaire (Form 39)." Place Form 38 on top of Form 39 and hand them to the participant. When the participant has completed forms 38 and 39, give him/her Form 5 to complete yes/ no columns and any comments. While the participant is completing Form 5, the coordinator should review forms 38 and 39 to ensure that all required questions were completed (do not assess the accuracy of the responses). If a question that should have been filled out was left blank, ask the participant if he meant to leave it blank. If the participant has questions about forms 38 or 39, do not interpret the questions or suggest responses. A good response is often "The question means whatever you think it means. Just answer the best you can."

8.1.2.4. Further Recommendations

It is suggested that blood pressure be measured before all other study procedures, except urine collection (for logistical reasons), in order to avoid affecting the BP reading. It is suggested that all self−reporting questionnaires be administered after blood pressure is measured, but before all other study procedures, in order to avoid affecting the participant's responses to the questionnaires. It is suggested that central serum creatinine samples be collected before imaging if applicable and within a 32−hour range, from 4 hours before the start to 4 hours after the completion of the 24−hour urine collection. Freshly−voided spot urine samples may be collected any time before OR after the 24−hour urine collection.

The documents listed below are completed by the participant and will be reviewed by the coordinator prior to the participant leaving the PCC. Any missing or illegible information will be clarified.

- Form 5 - Symptoms Checklist
- Form 12 – Blood Pressure Form
- Form 38 – Quality of Life Questionnaire
- Form 39 – Pain Questionnaire

8.1.3. Flow of Events from Pre-Screening to the Start of ACE +/- ARB Therapy

An overview of the flow of events from pre−screening to the start of first−line therapy has been developed to help study coordinators navigate through the complexities of screening and drug washout. Each step in the process is covered in more detail in subsequent sections.

8.1.3.1. Key Points to Remember During Screening and Washout

1) If participants fail to meet eligibility criteria prior to the initial visit, they are to have the reason(s) for ineligibility explained to them and should also be encouraged to contact a PCP and/or nephrologist.
2) PCCs must receive all necessary medical records before scheduling the initial visit.
3) Screening visits must be scheduled before participants can be registered to the study.
4) Eligibility is based on data collected at the screening visit.
5) Individuals currently on a BP drug for a non−hypertensive indication, including those on a ***small dose*** of beta blocker or calcium channel blocker, will be allowed to enroll in the study. Individuals on a **large dose** of beta blocker or calcium channel blocker must **not** be enrolled. When a participant on a "relatively small dose" of a beta or calcium channel blocker is enrolled, this information is to be recorded on Enrollment Form 10 by checking "yes" for the exclusion and then checking the box to indicate "approved by PI".
6) Participants may be rescreened per protocol, but if the screening visit does not occur within 10 weeks of randomization, it must be repeated.
7) Participants must be enrolled before the start of drug washout or before randomization if no washout is required.
8) To enroll participants, PIs must confirm all eligibility criteria and complete Enrollment Form 10 (signed by PI), which must then be entered within three business days after the start of washout and before randomization.
9) All baseline assessments (except MR imaging) must be completed before randomization, occurring at the baseline visit (B1).
10) Any registered participants who do not go on to randomization, as planned, are considered screening failures. Screening values are to be reviewed for safety; and if the values meet any of the established criteria for safety concerns, participants are to be informed and urged to follow up with their PCP and/or nephrologist.

11) Central serum creatinine results (from two samples) must be received (and be <20% different) before the start of ACE+/−ARB (visit B2).
12) If the two B1 sCr samples are >20% different from each other, redraw samples immediately (maximum. of one repeat collection).
13) Generally, washout medication is to last 14 to 28 days.
14) Out−of−control blood pressure during drug washout may require shortening the washout period to less than 14 days.

8.1.4. Informing Participants and PCPs of Safety Concerns

At the Initial visit, each participant is required to name a primary care physician (PCP), other than a study investigator, and will 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, after randomization, informing the PCP of his/her patient's participation in the study and reports regarding any abnormalities or other concerns.

At the Initial visit, each participant is required to name a primary care physician (PCP), other than a study investigator, and will 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, after randomization, informing the PCP of his/her patient's participation in the study and reports regarding any abnormalities or other concerns.

Randomized participants must be informed of any safety concerns, abnormal laboratory values, and/or abnormal imaging studies, as they occur throughout the study. Participants, in turn, should be encouraged to inform their PCP and/or nephrologist of any such findings. The PCC may also forward information regarding abnormal laboratory values and/or safety concerns to a participant's PCP and/or nephrologist if written authorization from the participant has been received.

8.2. Pre-Screening Visit (PS) – Telephone

Study coordinators will receive inquiries from potential participants by telephone. A toll−free telephone number has been established at each PCC. On receipt of a call from a potential participant, the study coordinator is to conduct a brief pre−screening interview over the telephone, the purpose being to gather basic demographic information and to determine whether the potential participant should be excluded as a result of the pre−screening interview or whether he/she may move forward in the screening process.

Individuals currently on a BP drug for a non−hypertensive indication, including those on a **small dose** of beta blocker or calcium channel blocker, will be allowed to enroll in the study (prior approval from the site PI is required). Individuals on a **large dose** of beta blocker or calcium channel blocker must **not** be enrolled.

PCC personnel may choose to use the optional HALT PKD pre−screening questionnaire to screen potential participants over the phone (Pre−Screening Questionnaire − Optional Tool 91), which may be printed from the HALT PKD website. If the participant has not been excluded from the study by the end of the pre−screening interview, the study coordinator is to instruct the potential participant to arrange that the required medical records *(see Section 8.2.4 − Documentation of Participant ADPKD Diagnosis)* be sent to the PCC for review. If the documentation supports the potential participant's eligibility, the study coordinator should then contact the potential participant to schedule a screening visit. Once the screening visit has been scheduled, the study coordinator may then register the individual to the study. A single, locked copy of records containing the potential participant's personal and contact information must be maintained at the PCC. Note that strict confidentiality of this information must be maintained at all times.

Relatives of individuals with ADPKD who have never been diagnosed are also likely to call the toll−free number for study information. These non−diagnosed individuals should be directed to their primary care physician for further evaluation, as well as for discussion of the risks (insurability, preexisting conditions) and benefits associated with making a new diagnosis of ADPKD.

8.2.1. Forms Required for Pre-Screening Visit

- Form 1 − Monthly Pre−Screening Activity Report
- Form 2 − Participant Contact Information Form
- Form 3 − Registration Form

8.2.2. Monthly Pre-Screening Activity Report

Each PCC is required to track its recruitment activities and fill out and enter Monthly Pre−Screening Activity Report Form 1, at the end of each month. The HALT−PKD Pre−Screening Log (Optional Tool 92) may be used as an aid in tracking pre−screening visits (PS). Total numbers of men and women who begin pre−screening and the method by which participants learned of the study are the items reported. The DCC will generate recruitment reports based on the pre−screening information data−entered each month by the PCCs.

8.2.3. Criteria for Immediate Exclusion During Pre-Screening Interview

Participants must be EXCLUDED if ANY of the following items are applicable to the potential participant being interviewed:

1) <15 or >64 years of age.
2) Absence of ADPKD by ultrasound or other imaging modality such as CT scan 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 m2

   OR

   For participants >49 years of age, GFR >60 ml/min/1.73 m2

Participants without a prior serum creatinine measurement may be scheduled for a screening visit as long as no other exclusion criteria apply.

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.

Participants with borderline ineligibility, based on serum creatinine measurements, may be seen for a screening visit at the discretion of the PI or co−investigator. However, *these participants should be warned that they could, potentially, be found ineligible to participate in the study*.

4) Normotensive (<130/80mm 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.

ESRD is defined as the start of dialysis or kidney transplantation, at the discretion of the participant's primary nephrologist.

8.2.3.1. Converting Serum Creatinine Values to GFR Values

Assignment to Study A or Study B is based on the results of serum creatinine measured at the PCC during the Screening visit. To assist in determining whether a potential participant's serum creatinine value would exclude the individual from the study, the GFR to serum creatinine calculator, or Calculations button at the bottom of the WDES Forms Portal, may be used to estimate GFR using the MDRD four−variable formula. *The new GFR calculator must be used for all PCC and local lab serum creatinine values that are obtained at an institution that uses the IDMS traceable methodology*.

Alternatively, the GFR Table may be used as a quick reference. To use the GFR Table:

1) Determine the person's race (black or non−black) and gender to locate the corresponding column.
2) Determine the person's age (at the time of the initial study visit) to locate the corresponding row.
3) Within the row, locate the appropriate column for the most recent serum creatinine value in order to determine if the participant is potentially eligible for Study A or Study B.

The GFR to serum creatinine calculator, or Calculations button at the bottom of the WDES Forms Portal, is to be used as the official method for determining the appropriate GFR value.

8.2.3.1.1. IDMS Traceable Method

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.

8.2.4. Documentation of Participant ADPKD Diagnosis

If, after going over the inclusion/exclusion criteria, a potential participant appears to be eligible for the study, the participant should be asked to contact the primary care 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 >/=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 above may be scheduled for a screening visit, registered to the study, and assigned a HALT−ID. Total numbers of men and women beginning 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 PKD.

For individuals without a family history of PKD, imaging reports must specifically indicate the presence of at least 20 cysts to be considered definitively diagnostic of PKD. Non−confirming qualifiers, such as "multiple" or "innumerable," cannot be accepted in lieu of a numeric value of 20 or greater. If an imaging report does not specifically state at least 20 cysts, the investigator is required to view the actual films to confirm the diagnosis of PKD.

The screening visit cannot be scheduled until medical records confirming a diagnosis of ADPKD have been received and reviewed by the study coordinator.

8.2.5. Scheduling the Screening Visit

If a potential participant completes the pre−screening interview successfully and the review of his/her medical records reveals no major exclusion criteria, the study coordinator can contact the potential participant to schedule a screening visit. Once the screening visit has been scheduled, the study coordinator should register the potential participant to the study, thereby assigning a HALT−ID to that individual.

8.2.5.1. Instructions for Participants

Participants are to be instructed 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 pre−screening phone interview and the screening visit so the visit may be rescheduled or cancelled, if necessary. In addition, individuals are to be instructed to bring their current medications *and* any medical records and/or imaging reports/films with them to the initial visit, if they were not forwarded to the PCC previously.

Study participants should 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.

Participants will be instructed to drink only to thirst and refrain from eating large protein meals (i.e., >1.3 g/kg/d) and undertaking vigorous exercise (aerobic activities including jogging, aerobic exercise classes, and sports involving at least 30 minutes of running) during the 24−hour period prior to the visit. Participants are to fast (water only) for eight hours before the screening visit.

Complete information on medication and dietary restrictions may be found by referring to Section 8.1.2.2.

Once an appointment for the screening visit is made, the study coordinator should mail an informational packet to the participant that includes written instructions for the visit, as well as consent forms for Screening and Drug Washout and, if applicable, Baseline and Beyond. Each individual PCC is responsible for developing its own informational packet for participants.

8.2.6. Pre-Screening Failure

If a participant is found to be ineligible for the study prior to registration, the reason(s) for the exclusion is to be explained by the study coordinator, who should encourage the participant to follow up with his/her regular physician. The study coordinator may release protected health information (PHI) upon receipt of a written request (authorization) from the participant. In such cases, coordinators can choose to highlight exclusions on a study form (Enrollment Form10 or Pre−Screening Interview Form 91) and fax or mail it to the ineligible participant. Alternatively, coordinators can draft a letter explaining the reason(s) for a participant's exclusion from the study. Pages from the protocol are **not** to be provided to participants or their PCPs.

Monthly, each PCC is to report the total number of participants beginning pre−screening during that month to the DCC via Pre−Screening Activity Report Form 1. For each PCC, the total number of participants registered to the study in a given month will be subtracted from the total number of prescreening visits reported on Form 1 to arrive at an estimate of prescreening failures for the month.

It is important to report prescreening visits only once, for the month in which they occurred.

8.3. Registration

After the screening visit is scheduled for a participant, the study coordinator is to register that participant to the study. Minimal demographic information, as well as the date on which the visit has been scheduled, is to be entered on the Registration Form 3. Once this information is entered, the participant will be assigned a HALT ID.

8.4. Schedule of Assessments for Screening, Baseline and Follow Up Visits

A complete schedule of assessments for screening, baseline and follow−up visits has been developed as a two−part table.

Schedule of Assessments − PS−F5 Visits, refer to Section 7.1.3.1.
Schedule of Assessments − Following F5 Visit, refer to Section 7.1.3.1.

8.4.1. Definitions of Assessments

- **Demographics** –Race, ethnicity, marital and employment status, and level of education is to be collected on Background Questionnaire Form 8, administered at the screening visit.
- **Informed Consent** –The Study Coordinator and/or the investigator must thoroughly review the consent document with the participant, answering any questions, before it is signed by the participant. Participants age 15-17 (Study A) are to review and sign an informed consent form. Depending on the PCC, up to three separate consents may be required: one for screening and washout, one for baseline and beyond, and one for genetic testing that will be collected at the F5 visit (week 16) or after.
- **Renal Disease History** – A complete history of the participant's kidney disease is to be taken at the screening visit.
- **Family History** – Investigators are to gather as much information as possible about the participant's family history of PKD. PCCs are not required to perform full pedigrees, but are to keep track of the relatedness of families to the extent practical for the site for future ancillary studies.
- **Comorbid Conditions** – Comorbid conditions are to be collected as part of the medical history taken at the screening visit.
- **Hypertensive History** – Participants must currently be on medication to control blood pressure, or must demonstrate a BP history of 130/80 mm Hg or higher on three separate occasions prior to the screening visit, in order to meet the HALT PKD eligibility requirements for hypertensive. A thorough history of current medications used to control blood pressure is to be collected at the screening visit.
- **PCC Seated/Standing BP** − Blood pressure is to be measured at the clinical center at every clinic visit. At the screening visit, the BO arm needs to be determined. Blood pressure is to be measured three times while the participant is seated (after five minutes resting and at least 30 seconds between readings). Standing BP is to be measured once, after the participant has been standing for 3 minutes.
- **Complete Physical Exam** – A thorough physical examination is to be performed at the screening visit. The completeness of the exam is to be left to the PIs discretion. Documentation on specific details that are not required on the forms and do not require data entry must be kept in the research and/or clinic chart at the PCC.
- **Symptom – Directed Exam** - At all clinic visits after screening, research staff is to follow any symptoms reported by participants.
- **Background Questionnaire** − Form 8 is to be completed by the study coordinator at the screening visit only. Questions pertain to demographics and lifestyle, including use of caffeine, alcohol and tobacco.
- **Quality of Life Questionnaire** − Form 38 is to be completed by participants at the Baseline visit (B1) and at each annual visit. The SF−36v2 assessment is used to capture the impact of health status on quality of life.
- **HALT PKD Pain Questionnaire** − Form 39 is used to capture the impact of pain on the daily life of the participant, and must be administered after the SF−36v2.
- **MR/MRA** – MR imaging and renal blood flow is to be performed on all participants enrolled to Study A at the baseline visit, month 24 (F24) and month 48 (F48) and month 60 (F60).
- **Interval History** – Participants are to be contacted by telephone during the study titration period and at three months after each clinic visit. Adverse events, concomitant medications, hospitalizations and dose adjustments are monitored between study visits.
- **Home BP Review and Calibration** – Participants are to record their BP measurements at home at regular intervals, with these readings being reviewed by the study coordinator and PI for purposes of dose adjusting and maintaining separation between study treatment arms. At the screening visit, participants are to be issued a home BP monitor and trained how to use it and to record their BP measurements. Participants should be instructed to bring the home BP monitor and documentation of BP readings to every clinic visit. The device is to be calibrated at every clinic visit and the participant's measurement technique is to be observed and evaluated by the study coordinator.
- **Review of Medications** – All concomitant medications must be reviewed at every visit, with changes tracked by recording stop dates and start dates of all medications.

- **Adverse Event History** – At every study visit, participants must be asked about any adverse events experienced since their previous visit. Serious adverse events must be reported to the DCC within 24 hours.
- **Titrate Medication** − Between the baseline visit (B1) and the F5 visit at week 16, study medication is to be gradually increased according to protocol guidelines.
- **Serum Creatinine** – At the screening visit, serum creatinine is to be analyzed at the PCC labs to determine eligibility. At all subsequent visits, serum creatinine is to be shipped to the central laboratory at Cleveland Clinic. At the baseline and F5 visits, two samples need to be collected, one hour apart. Study A and B participants completing a "Quest Visit", (Form 90 Quest Visit or Remote Visit") must utilize the "CSC kit" for the collection of the serum creatinine labs drawn at a hometown or Quest lab. The lab will send the serum creatinine to the CCF lab for central processing.

Refer to 11.3.2.3 for more information.

- **Total Electrolyte Panel** – To be analyzed at the PCC lab; sodium, potassium, chloride, carbon dioxide and urea nitrogen.
- **Partial Electrolyte Panel** − To be analyzed at the PCC or local lab (Quest or hometown): potassium, urea nitrogen, serum creatinine.
- **Additional Blood Tests (PCC)** – Transaminases (AST/SGOT, ALT/GPT), total bilirubin, alkaline phosphatase, albumin, calcium, phosphorus, glucose, complete blood count with platelets. For participants taking Digoxin, levels must be measured per protocol.
- **PCC Random/Spot Urine** – At the screening visit, microalbumin and creatinine are to be collected.

Complete information on medication and dietary restrictions may be found by referring to Section 8.1.2.2.

- **HCG Urine Pregnancy** – All women of child bearing potential are to have a qualitative urine pregnancy test at the screening visit (S).
- **24−Hour Urine Collection** – Participants are required to collect their urine over 24 hours prior to the baseline visit, the F5 visit at week 16, the F12 visit and at each subsequent annual visit. Aliquots are to be prepared for central laboratory analysis at Hillman Cancer Center, Pittsburgh, PA (aldosterone, sodium, potassium, creatinine, microalbumin) and for specimen banking at the NIDDK central repository at Fisher BioServices.
- **Genetic Sample** – Participants who have not already donated a sample to the NIDDK Genetic.
- **Repository -** Are to be invited, at the F5 visit at 16 weeks, to take part in genetic research by providing a sample of blood for immortalization and DNA extraction for use in future studies. Participants have the option to refuse, as well as the option to choose to participate at a visit subsequent to F5. Participants can elect to have their sample destroyed upon written request up to the end of the HALT PKD study.
- **Specimen Banking** –Blood and urine samples are to be shipped to the NIDDK BioRepository at Fisher BioServices.

8.4.2. Reporting B2 and Clinic Visits on HALT PKD Visit Tracking Form 40

The study coordinator must complete and enter HALT PKD Visit Tracking Form 40 for each day on which B2 and clinic visits occur. All participant ID codes and associated visit codes are to be entered on the date of visit. "Date of Visit" is defined as the date on which the first study procedure occurs. HALT PKD Visit Tracking Form 40 must be completed before entering data for the visit. Coordinators are encouraged to follow up with the participant the day following a study visit to confirm that a new dose or medication has begun.

8.5. Screening Visit (S) - Clinic

A standard protocol must be followed for each study visit. On the morning of admission to the GCRC (or other clinical facility where study visits occur), the PI or co−investigator should meet with the participant first in order to summarize the purpose of the study and the commitments required for participation, as well as to give the participant an opportunity to get answers to any questions they may have.

Please refer to Guidelines for PCC Visits, Section 8.1.2 for more information.

8.5.1. Missed Screening Visit

The screening visit cannot be missed, as a participant's eligibility for study participation is determined during the Screening visit. If a participant fails to arrive for a scheduled screening visit, the visit needs to be rescheduled as soon as possible.

Please refer to Section 8.16 − Target Visit Dates and Acceptable Ranges for Visits for information on the protocol for dealing with missed visits.

8.5.2. Forms Required for Screening Visit

- Form 4 − Clinical History Form
- Form 5 − Symptoms Checklist
  - Symptoms Checklist Form 5 Instructions
- Form 6 − Concomitant Medications Form
- Form 7 − Physical Findings−Screening Form
- Form 8 − Background Questionnaire
- Form 9 − Required Lab Results Form
- Form 10−Enrollment Form
- Form 12−Home Blood Pressure Form
- Form 13- Serious Adverse Event Form (if necessary) SAE
- Form 13- Instructions
- Form 14−Screen Failure Form (if necessary)
- Form 36−Home Blood Pressure Calibration Log
- Form 62−Drug Card Assignment Form
  - Drug Card Assignment Form Instructions
- Form 63−Study Medication Form
  - Study Medication Form (63) Instructions

8.5.3. Informed Consent

The appropriate informed consent must be obtained before ANY study procedures may be carried out. (Each PCC is to obtain, according to its own institutional policies, either one informed consent for the Screening visit, Drug Washout, and Study, or two informed consents, one including the Screening visit and Drug Washout and one including the Study only). At the Screening visit, 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, after randomization, informing the PCP of his/her patient's participation in the study and reports regarding any abnormalities or other concerns. Participants for Study A will be asked to sign an addendum to the consent, agreeing to participate in the study past the F48 visit until July 2014.

For more information on the informed consent documents required for the study, please refer to Section 5.2 – Informed Consent for HALT PKD. For more information on consent addendum, see Section 19

Participants for Study B will also be asked to sign an addendum to the consent when they reach endpoint agreeing to yearly contact regarding present health status.

8.5.4. Review of Past Medical Records

Past medical records for every participant, including laboratory results and diagnostic imaging report(s), need to be received by the PCC for review in advance of the screening visit. However, it is likely, on occasion, that some participants' medical records may not be received by the PCC prior to the visit. In such cases, it is imperative that participants bring the medical records with them to the initial visit so they may be reviewed by a study coordinator.

For more information on documentation required in advance of the Screening visit (S1), refer to Section 8.2.4 − Documentation of Participant ADPKD Diagnosis.

8.5.5. Background Questionnaire

Coordinators are to administer Background Questionnaire − Form 8 in which questions regarding race, ethnicity, marital status, and educational status are asked. In addition, questions about lifestyle, such as level and frequency of exercise and use of alcohol, tobacco and caffeine, are also addressed on the background questionnaire.

8.5.6. Medical History

A medical history, including diagnosis of PKD, hypertension, and comorbid conditions, including history of cardiac and renal disease, is to be obtained. Females must be asked about reproductive history and use of contraception.

8.5.6.1. Family History of PKD

Investigators are to gather as much information as possible about the participant's family history of PKD and retain this information at the clinical center for anticipated ancillary studies. PCCs are not required to perform full pedigrees, but are to track, on an ongoing basis, the relatedness of families to the extent practical for the site.

8.5.7. Review of Concomitant Medications

Participants are to be asked to bring all current medications with them to every clinic visit. Start and stop dates for

all current medications are to be recorded on Concomitant Medications Form 6 at every study visit. Individuals currently on a BP drug for a non−hypertensive indication, including those on a ***small dose*** of beta blocker or calcium channel blocker, will be allowed to enroll in the study; and these medications will be tracked on Concomitant Medications Form 6.

8.5.8. Physical Exam

A complete physical exam is to be obtained at the initial visit, with findings recorded on Physical Findings−Screening Form 7. A symptom−guided exam is to be conducted at all subsequent visits. Current symptoms are to be collected at all study visit (Symptoms Checklist Form 5).

8.5.9. Blood Pressure Measurements

8.5.9.1. Clinic BP Measurements

The non−dominant arm (in terms of handedness) is to be used to obtain BP readings unless there is a reproducible (on at least three consecutive measurements) difference of 20 mm Hg or more in systolic BP 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 is to be used. In all other cases, the non−dominant arm is to be used. Once the blood pressure arm has been determined, it should not be changed unless it is absolutely necessary, as all subsequent office and home BPs taken for the duration of the study are to be measured in the arm identified at the initial visit.

All PCCs are to measure BP according to the standardized procedure described below:

Procedure for Measuring Blood Pressure at Screening Visit

- The participant is to be seated quietly in a chair for a minimum of 5 minutes, with feet on the floor and arm supported at heart level. Three measurements are to be taken in the appropriate arm, as described above, with a wait of at least 30 seconds occurring between each measurement. On completion of 3 seated BP measurements, the average of the last two out of three readings should be calculated. The participant is then to stand for 3 minutes with his/her arm supported at heart level. After 3 minutes, 1 blood pressure measurement is to be taken with the participant still standing. If standing BP is more than 20 mm Hg below the average of the last two readings taken when the participant was seated, hypotension may be indicated; and the PI or co−investigator may consider reducing study medication at his/her discretion.

For more information on measuring BP at the PCC, refer to Section 9.1 − Standardized Procedures for BP Management.

8.5.9.2. Home BP Measurements

At the initial visit, the study coordinator is to issue each participant a LifeSource home BP monitoring device (UA767P) and also to instruct each participant on proper use of the device, i.e., when and how often, per protocol, to take home BP measurements. Participants must be instructed to record BP measurements on Home Blood Pressure Form12 and, also, to bring this form with them to all subsequent clinic visits. Home BP monitors are to be calibrated at every clinic visit.

For more information on the measuring and recording of home BP by participants, refer to Section 9.1.2.3 − Procedures for Home BP Measurements.

For more information on calibration of home BP monitors, refer to Section 9.4.1 − Calibration of Home BP Monitors.

8.5.10. Laboratory Measures

All laboratory measures at the Screening visit must be obtained and analyzed at the PCC lab. 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.

8.5.10.1. Lab Measures Obtained Prior to Screening Visit

If results for required blood tests run at the PCC 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. 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.

When results are reported on Required Lab Results Form 9, the "date of visit" will not change, but notes should be included in the comment field that specify dates of collection for the specific tests performed before screening. Even though these free−text fields cannot be used for analysis, they will serve as official documentation that samples were collected prior to screening.

The PCC would be responsible for working out payment arrangements for the lab test, as the DCC is responsible for payment of only routine safety labs obtained at Quest Diagnostics.

8.5.10.2. Screening Serum Creatinine

The serum creatinine value from the Screening visit is to be analyzed at the PCC lab and entered on Required Lab Results Form 9, where it will be automatically equated to GFR using the 4−variable MDRD prediction equation, with the result determining the participant's assignment to either Study A or Study B.

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. Required Lab Results Form 9 has been revised to include a new selection of original MDRD or IDMS traceable method for serum creatinine in order to determine the appropriate calculation for eGFR.

The new conversion calculator was first used by the study on July 16, 2008, but laboratories at the PCCs have recalibrated to the new standard at various times over the course of the study:

- ☐ Cleveland Clinic and Quest Diagnostics Laboratories have used the IDMS traceable method since the start of the study.
- ☐ The Mayo Clinic recalibrated to the new standard on September 26, 2007.
- ☐ Beth Israel Deaconess Medical Center recalibrated to the new standard on January 23, 2008.
- ☐ The University of Kansas Medical Center recalibrated to the new standard on March 11, 2008.
- ☐ Tufts Medical Center recalibrated to the new standard on June 15, 2006.
- ☐ Emory University recalibrated to the new standard on April 8, 2009.
- ☐ The University of Colorado Health Sciences Center recalibrated to the new standard on March 26, 2006.

Participants treated with ACE−I or ARB will still be taking these respective therapies at the time the screening serum creatinine is drawn; thus, the true estimated GFR by MDRD may be, if anything, higher than that measured.

To assist in determining eligibility to Study A or Study B, please refer to Section 8.2.3.1 − Converting GFR Values to Serum Creatinine Values.

For more information on collection and handling of serum creatinine, refer to Section 11.4 − Cleveland Clinic Foundation (CCF) Reference Laboratory − Serum Creatinine Measurements.

8.5.10.3.1. Ineligible Screening GFR Value

If the screening GFR value is lower than the minimum requirement of greater than or equal to 25 ml/min/1.73 m_2, the participant must be contacted immediately and informed that he/she is ineligible for study participation. The participant must also be instructed to resume the antihypertensive agents used prior to drug washout.

8.5.10.3. Other Blood Samples

In addition to serum creatinine, the following blood tests are to be done at the PCC lab, either at the S (or SB1) visit or no more than 8 weeks previous to the S (or SB1) visit: 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.

8.5.10.4. Urine Samples

A random/spot urine sample will be collected at the Screening visit to determine the microalbumin to creatinine ratio.

8.5.10.5.1. Pregnancy Screening

All women of childbearing potential are to be screened for pregnancy by a qualitative urine B−HCG test.

Complete guidelines in reference to pregnancy may be found by referring to Section14.2.2 − HALT PKD Pregnancy Policy.

8.5.11. Combined Screening/Baseline Visit (SB1)

If the participant is not currently on antihypertensive medication, a drug washout period is not required. In such cases, the Screening and Baseline visits may be combined into one visit (SB1). When no washout is required, complete forms 4−10, 15, 16, 18, 19, 20, 21 and 22 for study A, 36−40, and 62−63. Use Form 7 to determine the BP arm, completing questions #1−9, in addition to Form 15. Form 55 will print to give to the participant for use prior to the F5 visit.

For more information, refer to Section 8.7.5 − No Washout Required.

8.5.12. Participant Instructions Given at Screening Visit (S) for Baseline Visit (B1)

8.5.1 2.1. 24 – Hour Urine Collection

24−hour urine is to be collected prior to the Baseline visit, ideally in a GCRC setting. The participant is to be instructed to arrive at the GCRC in the early afternoon on the day prior to the scheduled baseline visit, at which time he/she will begin the 24−hour urine collection.

If there is not a GCRC at the PCC or if the participant cannot spend the night in the GCRC, he/she is to be sent home from the Screening visit with instructions and supplies for beginning the 24−hour urine collection prior to the Baseline visit. Hotel accommodations are to be arranged for participants who live at a distance from the PCC, so that they may collect their urine prior to the visit.

Participants are to be instructed to collect 24−hour urine samples in Section 11.5.2 − Instructions for Participants.

8.5.13. Screen Failure

Screen failure occurs whenever a registered participant does not go on to randomization as planned. Screen failure may occur anytime up to randomization, but not after. Participants may be determined ineligible either by failing to meet eligibility criteria or because of unavoidable delays. Screen Failure Form 14 is to be completed and data−entered within three business days of all screen failures, regardless of a participant's eligibility for rescreening in future. All forms completed at the visit are also to be entered within the usual timeframe.

For information on rescreening guidelines, refer to Section 8.5.14 − Rescreening.

Participants excluded between registration and randomizations are to have the reason(s) for exclusion explained to them and are to be informed of any concerning lab results. Participants should be encouraged to follow up with a primary care physician (PCP) and/or nephrologist. If authorized by the participant in writing, PCCs may directly inform the PCP and/or nephrologist about the participant having been excluded from the study, as well as about any concerning lab results. The study coordinator may release information to the excluded participant in written form upon receipt of a written request (authorization) from such participant to release his/her private health information (PHI). In such cases, coordinators may highlight the exclusions on an appropriate study form (Enrollment Form10 or Pre−screening Interview Form 91) and give it to the participant. Alternatively, coordinators may draft a letter to explain the participant's exclusion from the study; however, pages from the protocol are not to be provided to participants or their PCPs. If screening values exceed established safety criteria, as described in Section 13.4 − Abnormal Lab Values, PCCs are responsible for informing participants and urging them to inform their PCP and/or nephrologist. Participants who fail screening do not need to be followed for the study under intent−to−treat.

Guidelines for informing participants of safety concerns and/or concerning lab values may be found by referring to Sections 8.1.4/11.1/13.4 − Informing Participants of Safety Concerns.

8.5.13.1. Screening Failure - Pregnancy

If a 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 medication must be discontinued immediately and Screen Failure Form 14 (Reason #6) completed and data−entered as soon as possible. Any pregnant participant is to be referred to her primary care physician (PCP) for management of the pregnancy and will not be followed by HALT PKD 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.

Complete guidelines in reference to pregnancy may be found by referring to Section 14.2.2 − HALT PKD Pregnancy Policy

8.5.13.2. Using Screen Failure Form 14

Screen Failure Form 14 must be entered within three business days of site personnel becoming aware that a participant is found to be ineligible for the study, even if the participant will later be eligible for rescreening.

8.5.13.3. Screen Failure vs. Pre−Base line Dropout (PBDO)

Screen Failure

An individual is considered a "screen failure" if he/she either is ineligible or declines participation in the study during washout. Such individuals will have been registered, and may have started washout therapy, but will not be randomized as planned. They may or may not be rescreened in the future.

If a “screen failure” is rescreened, the originally−issued HALT ID code will not be used. After Screen Failure Form 14 has been entered, the participant must be reregistered and given a new HALT ID.

Pre−Baseline Dropout (PBDO)

An individual is considered a "pre−baseline dropout" if he/she has been randomized, but has not completed a baseline visit and never started ACE−I+/−ARB (e.g., for logistical reasons). All participants must be followed, but only if they have completed their baseline visit. An example would be that of a participant who was randomized in advance of the baseline visit, but then found to be ineligible for study participation before the baseline visit occurred. Another example would be that of a Study A participant who was randomized, but was then unable to be imaged, the result being that the baseline visit was not completed.

If a "PBDO" is rescreened, the individual must be reregistered and assigned a new Halt ID.

Modified Participation Form 28, Item L (pre−baseline dropout), must be completed and data entered to capture individuals who have been randomized but who did not go on to the baseline visit.

A randomized participant would be considered a PBDO *only* if he/she has ***not*** completed the baseline visit. A randomized participant ***cannot*** be withdrawn from the study once he/she has completed the baseline visit.

8.5.13.4. Delayed Drug Washout or Randomization

If, after the screening visit, there is a delay of more than 10 weeks before randomization (Visit B1), all screening procedures must be repeated.

8.5.14. Rescreening

The initial PCC visit (S or combined SB1) is to be scheduled only after determining a participant's basic eligibility for the study, as well as whether a washout period is required. Once the initial PCC visit has occurred, it may be determined that the participant is ineligible, due to either failure to meet eligibility criteria or unavoidable delays. In such instances, each participant may be rescreened only one time, unless the reason(s) for ineligibility are listed in below (Numbers 1 and 3).

All registered participants failing to go on to randomization as planned are to be considered screen failures, even if they are eligible for rescreening in the future. Screen Failure Form 14 must be completed and data entered within three business days of all screen failures.

8.5.14.1. Rescreening for Failure to Meet Eligibility Criteria

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 2 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.
        i. Study A: </=60
        ii. Study B: <25 or >60
    b. Albumin−creatinine ratio equal to or greater than 0.5 for study A, or 1.0 for Study B
    c. Fasting serum glucose equal to or greater than 126 mg/dl and random non−fasting serum glucose equal to or greater than 200 mg/dl.
2) Women of child−bearing potential who test positive by qualitative B−HCG urine pregnancy test may be rescreened *per the protocol exclusion criteria* listed below:
    a) Women who have had a pregnancy of more than 12 weeks duration (past the first trimester) must wait a minimum of 6 months postpartum, miscarriage or abortion before rescreening and must not be lactating at the time of rescreening.
    b) For a pregnancy of 12 or fewer weeks duration, a minimum of 2 months post miscarriage or abortion is required.
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 intervals of 4 months or greater.
    b) In cases of hyperkalemia while on ACE−I and/or ARB therapy, participants may be rescreened, for potassium levels >5.5, at intervals of 4 months or greater.

8.6. Enrollment

All participants must be enrolled after the Screening visit (S) and *before* the start of drug washout (B0), with Required Lab Results Form 9 and Enrollment Form 10 then data entered within 3 business days. Enrollment verifies that the investigator attests that the participant has met all inclusion/exclusion criteria and is being followed for adverse events. To enroll a participant, a paper copy of Enrollment Form10 must be completed and signed by the PI. Only those participants who go on to be randomized will be followed under the intent−to−treat policy. All others are to be considered screen failures, as described above in Section 8.5.14, even if they have already been enrolled but are not eligible for randomization for any reason or may be eligible for rescreening later.

Enrollment occurs at the PCC, as described above, before the start of washout drug, and is not to be confused with data−entry of Enrollment Form10, which is to occur within three business days of the start of washout drug.

Individuals currently on a BP drug for a non−hypertensive indication, including those on a ***small dose o***f beta blocker or calcium channel blocker, will be allowed to enroll in the study. Individuals on a **large dose** of beta blocker or calcium channel blocker must **not** be enrolled. When a participant on a "relatively small dose" of a beta or calcium channel blocker is enrolled, this information is to be recorded on Enrollment Form10 by checking "yes" for the exclusion and then checking the box to indicate "approved by PI".

8.7. Drug Washout (B0)

The purpose of the drug washout period is to allow a baseline serum creatinine and urine albumin−to−creatinine ratio to be measured in the absence of ACE−I, ARB or other antihypertensive agents (e.g., vasodilators such as hydralazine, minoxidil and dihydropyridines), that may influence these values independent of renal function. Therefore, participants on antihypertensive agents at the time of enrollment to the study are to discontinue current antihypertensive therapy and begin a drug washout period of at least 2 weeks and no more than 4 weeks. Participants will begin taking labetalol 100 mg po BID or, for participants with a contraindication to beta−blocker therapy, Clonidine at a starting dose of 0.1 mg po BID. Medications may need to be discontinued gradually, per the clinical judgment of the investigator, for those participants taking more than one BP medication at the time washout begins, as this is considered standard clinical practice.

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.

The drug washout period is followed by a Baseline (B1) visit at the PCC for randomization and continues until ACE+/−ARB therapy begins. After the Baseline visit, study drugs will be dispensed. Drug washout medications are to be tapered off and discontinued as study drugs are initiated (at the B2 visit) and increased according to the stepped protocol for study medications (either A or B) to which the participant has been assigned.

If, for some reason, the drug washout period is interrupted (i.e., the participant starts ACE−I or ARB), the drug washout may be restarted so long as the participant can be randomized within 10 weeks of the Screening visit.

8.7.1. Drug Washout Immediately Following Screening Visit

If all required laboratory results are available from the PCC lab before the end of the Screening (S) visit, including GFR of >60 ml/min/1.73 m_2 for a potential participant of Study A or GFR between 25 and 60 ml/min/1.73 m_2 for a potential participant of Study B, and the participant is willing, drug washout can begin immediately following the Screening visit (S=B0). The study coordinator is to review the data from the Screening Visit to confirm that the participant is eligible for the study and that all required procedures have been completed. The coordinator may then inform the participant of his/her eligibility for Study A or B and enroll the participant, which must occur prior to the start of drug washout. Enrollment Form10 must be completed and signed by the investigator before the start of drug washout, and is to be data−entered within 3 business days after enrollment. Study Medication Form 63 must also be completed at the S visit and data−entered within 3 business days. Washout drugs are to be dispensed at the Screening visit.

8.7.1.1. Drug Washout Subsequent to Screening Visit

If additional information is still required by the end of the Screening visit or the potential participant wishes to discuss participation with his/her family, the study coordinator should follow up with the participant by telephone to confirm his/her eligibility for HALT PKD (B0 visit would take place several days after S). If the participant elects to continue after being informed of his/her eligibility, the drug washout can begin with the B0 visit. Consent for drug washout should already have been obtained, in person, during the Screening visit as part of the Screening Consent Form. Participants should also have been issued washout medication and an electronic BP measuring device and trained in BP measurement at the Screening visit.

The study coordinator is to review the data from the Screening Visit prior to placing the B0 visit telephone call to the participant. The coordinator is to confirm that the participant is eligible for the study and that all required procedures

have been completed. Once the study coordinator has reviewed the data, she should phone the participant and first inform him/her of eligibility for Study A or B, then discuss current symptoms and medications (Forms 5 and 6). The study coordinator can then enroll the participant, which must occur prior to the start of drug washout. Enrollment Form10 must be completed and signed by the investigator before the B0 Visit and is to be data−entered within 3 business days after enrollment. Study Medication Form 63 must also be completed and data−entered within 3 business days of having dispensed washout drugs at the S visit.

8.7.2. Blood Pressure Control During Drug Washout

Participants are to be instructed to measure BP at a minimum frequency of every other day during the drug washout period. If blood pressure is >160/100 mm Hg, 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 their study coordinator or PI in case an immediate visit to the PCC for randomization needs to be arranged. If the participant is unable to be assessed at the PCC within 24 hours, BP should be managed with increased labetalol/Clonidine and/or other therapies (other than ACE−I or ARB), as directed by the PI, with close follow−up over the telephone until the next study visit.

For participants on more than one antihypertensive medication prior to drug washout, the PI is to decide, on a case−by−case basis, whether higher doses of labetalol (or Clonidine, if there is a contraindication to labetalol) are needed. If labetalol alone does not control BP in these participants, Clonidine therapy may be needed in addition to the labetalol. Clonidine should be tapered off 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.

8.7.3. Instructions to Participants for Drug Washout

Participants are to be instructed to discontinue existing antihypertensive therapies and begin the drug washout period, which will last from 2−4 weeks. 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. During the drug washout period, participants are to take labetalol, 100 mg po BID, or Clonidine, at a starting dose of 0.1 mg po BID, for participants who have a contraindication to beta−blockers. 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 labetatol 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.

Participants with well controlled BP with relatively little medication. . .

* may be tapered off existing medication, but **not** put on labetalol or Clonidine during drug washout, per the discretion of the PI. However, such participants must be closely monitored by the study coordinator.

Participants taking either labetalol or Clonidine as their sole BP therapy. . .

* do not require a drug washout.

Participants taking a beta−blocker, other than labetalol, as their sole BP therapy. . .

* must be switched to labetalol for the washout period.

Participants taking Clonidine in combination with other BP therapies . . .

* must discontinue the other BP medications and continue taking Clonidine alone, but labetalol or other therapies may be added during washout, if necessary. Clonidine should be tapered off 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.

Participants are to be instructed to measure blood pressure at a minimum frequency of every other day during the drug washout period. In addition, participants must be informed that, if blood pressure readings are >160/100 mm Hg or symptoms of hypertension develop (e.g. headache, blurred vision), or if there are intolerable side−effects of the washout medications, they are to contact the study coordinator or PI to arrange an immediate visit to the PCC for randomization.

8.7.4. Safety Labs

Safety labs are not required during the drug washout period. However, should the investigator, at his or her discretion, order additional safety labs, or additional test results become known to the PCC, serum creatinine and potassium values are to be data−entered within two weeks of sample collection via Required Safety Lab Results Form 51.

8.7.5. No Washout Required

If participants are not currently on antihypertensive medications at the time of the Screening visit, they do not need a drug washout. In addition, a drug washout is not needed for participants taking either labetalol or Clonidine as their sole blood pressure therapy. In such cases, the Screening visit (S) may be combined with the Baseline visit (B1) to

form the SB1 visit.

For more information on a combined S/B1 visit, refer to Section 8.5.13 − Combined Screening/Baseline Visit (SB1).

8.7.6. Early Randomization

Ideally, randomization occurs at the Baseline visit (B1) after all study procedures, except MR imaging, have been completed. However, in some cases it will be necessary to shorten the drug washout period to less than two weeks by moving up the B1 visit. If BP is out of control during the drug washout, or if there are intolerable side−effects of the washout medications, and the participant is able to return to the PCC for a physical exam, the B1 visit needs to be scheduled immediately.

For information on the protocol for controlling BP during drug washout, refer to Table 9−3 − Blood Pressure Control over the Course of the Study.

For more information on immediate randomization, refer to Section 8.14 − Unplanned Study Visits.
For more information on randomization procedures, refer to Section 8.9 − Randomization.

8.8. Baseline Visit (B1)

The Baseline visit (B1) takes place at the PCC once all screening criteria have been met and the drug washout period, if required, has continued for at least two weeks. To begin the B1 visit, study coordinators and investigators are to provide information and answer questions relating to the process of informed consent, randomization, interventions, logistics of subsequent study visits and risks/benefits of participation in the study.

At Baseline and throughout the study, PCCs must inform participants of any concerning lab values (per Table 10−4) or abnormalities found on MR scans and encourage them to follow up with the physician identified as their PCP at the Screening visit. When a participant is subsequently randomized, the HALT PKD investigator is to send an initial letter to the named PCP to inform him/her of the participant's enrollment in HALT PKD.

8.8.1. Forms Required for Baseline Visit

- Form 5 − Symptoms Checklist
  - ◊ Symptoms Checklist Form 5 Instructions
- Form 6 − Concomitant Medications Form
- Form 9 − Required Lab Results Form
- Form 12 − Home Blood Pressure Form
- Form 13 − Serious Adverse Event Form (if necessary)
  - ◊ SAE Form13 Instructions
- Form 15 − Current Physical Findings Form
- Form 16 - Urine Sample Collection Form
- Form 18 − Archived Blood Sample Collection Form
- Form 19 − Central Creatinine Collection Form
- Form 20 − Randomization Form
- Form 21 − MRI (Renal) Session Information Form (Study A)
- Form 22 − Renal Blood Flow (MRA) Form (Study A)
- Form 36 − Home Blood Pressure Calibration Log
- Form 37 − 24−Hour Urine Collection Checklist
- Form 38 − Quality of Life Questionnaire
- Form 39 − Pain Questionnaire
- Form 62 − Drug Card Assignment Form
  - ◊ Drug Card Assignment Form

Instructions * Form 63 − Study Medication Form
  - ◊ Study Medication Form (63) Instructions

8.8.2. Informed Consent

For those sites that require two, separate informed consents, one for Screening and Drug Washout and one for Baseline and beyond, the informed consent for the Baseline visit and beyond must be obtained before any study procedures can be performed.

The participant will have indicated in the consent document, signed at the Screening visit, whether HALT PKD is authorized to communicate with his/her named PCP. If participants have granted authorization, PCCs may directly

inform PCPs of any abnormalities or concerns.

8.8.3. SF−36v2 and Pain Questionnaire (Health −Related Quality of Life)

Baseline health status is to be assessed at the B1 visit using the Medical Outcomes Study Short Form 36 Questionnaire (SF−36v2), a self−reporting questionnaire that assesses physical, mental and social aspects of health−related quality of life. The separate HALT PKD Pain Questionnaire (Form 39) is to also be administered to capture the impact of pain, progressive kidney disease, and adherence to interventions (e.g., low blood pressure) on mental and physical components of health.

Participants are to complete the Quality of Life Questionnaire Form 38 (SF−36v2) prior to completing Pain Questionnaire Form 39.

8.8.4. Interval History

An interval history is to be obtained. Participants need to be asked if they have had any change in symptoms since their last study visit and if they have seen any medical professionals. Women of childbearing potential need to be asked if there have been any changes in reproductive history or use of contraceptives since the last study visit.

8.8.5. Symptom−Directed Physical Exam

A symptom−directed physical exam is to be performed.

8.8.6. Blood Pressure Measurements

8.8.6.1. Clinic BP Readings

Participants' blood pressures are to be measured at the PCC, three times while seated and once while standing. Instructions to be followed for measuring BP are as follows:

The participant is to be seated quietly in a chair for a minimum of 5 minutes, with feet on the floor and arm supported at heart level. Three measurements are to be taken in the appropriate arm, as described above, with a wait of at least 30 seconds occurring between each measurement. 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 the last two readings will be repeated. On completion of 3 seated BP measurements, the average of the last two out of three readings should be calculated. The participant is then to stand for 3 minutes with his/her arm supported at heart level. After 3 minutes, 1 blood pressure measurement is to be taken with the participant still standing. If standing blood pressure is more than 20 mm Hg below the average of the last two readings taken when the participant was seated, hypotension may be indicated; and the PI or co−investigator may consider reducing study medication at his/her discretion.

For more information on measuring BP at the PCC, refer to Section 9.1 − Standardized Procedures for BP Management.

8.8.6.2. Review Home BP Readings from Drug Washout

The participant is to bring the Home Blood Pressure Form 12, on which all home BP measurements taken every other day during the drug washout period have been recorded, to the Baseline visit for review by the study coordinator and PI.

For more information on the measuring and recording of home BP by participants, refer to Section 9.1.2.3 − Procedures for Home BP Measurements.

8.8.6.2.1. Calibration and Technique Monitoring

The Home BP monitor is to be calibrated and the participant's measurement technique observed per protocol.

For more information on calibration of home BP monitors, refer to Section 9.4.1 − Calibration of Home BP Monitors.

8.8.7. Review of Medications

Participants need to be instructed to bring all current medications with them to every clinic visit, including Screening and Baseline. Medication start and stop dates are to be collected at every visit and recorded on Concomitant Medications Form 6. Coordinators are to verify that participants are in compliance with taking study medications as instructed.

8.8.8. Baseline Serum Creatinine

The average of two serum creatinine measurements, drawn a minimum of one hour apart and sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for analysis, are to be used to establish the baseline serum creatinine measurement.

If possible, it would be optimal to draw the two serum creatinine measurements for Study A participants before they begin their imaging exams.

Participants must be instructed to fast between venipunctures. Only these liquids, coffee, milk, juice, and soft drinks, are permissible between draws. On receipt of the results from Cleveland Clinic, the study coordinator is to confirm the consistency of the two serum creatinine measurements − a difference of 20% or less between the two measurements is considered an acceptable level of agreement. If the two measurements differ by greater than 20%, arrangements must be made for drawing a second set of serum creatinine samples, which are then to be sent to Cleveland Clinic for repeat analysis. For individuals who live far from the PCC, repeat blood samples may be drawn at a local laboratory and shipped by overnight mail to the central laboratory.

If there is still a difference of >20% in the results from a second set of samples, washout therapy should be discontinued and all medications returned to the PCC by the participant. The participant cannot receive the treatment regimen, but is to be followed under intent−to−treat.

This above−described procedure for collecting two serum creatinine measurements is to be repeated at the F5 visit to provide a baseline measure after maximizing ACE−I (lisinopril) and ARB (telmisartan or placebo).

For more information on collection and handling of serum creatinine samples, refer to Section 11.4 − Cleveland Clinic Foundation (CCF) Reference Laboratory − Serum Creatinine Measurements.

8.8.9. Urinary Aldosterone

To gauge the intensity of blockade of the RAAS, urinary aldosterone from the Baseline visit (B1), is to be measured by forwarding aliquots from participants' 24−hour urine collections to a central laboratory (Diagnostic Laboratory Facility at Harvard University) for analysis. Urinary aldosterone will also be measured 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 has been established. The 24−hour urine samples will be collected at GCRCs for the majority of participants. 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 subsequent visit. All voids over the course of the next 24 hours, including the first void on the morning of the PCC visit, are to be collected in the jug.

The 24−hour urine sample is to be sent for analysis only if the collection meets the criteria for adequate collection. If the 24−hour urine sample falls within the 75−125% range of predicted creatinine excretion, based on Walser formulas, based on actual body weight, it will be considered an adequate collection *(Walser−1987)* and used for determination of aldosterone excretion rate. Samples should not be repeated if they fall outside the range. If a sample falls within the 50−150% range of predicted, based on Walser formulas, based on actual body weight, it is to be considered adequate to be used for determination of aldosterone to creatinine ratios.


Each aliquot to be analyzed for urinary aldosterone must contain a preservative (boric acid).

8.8.10. Other Laboratory Measures

8.8.10.1. Blood Samples

Blood is to be drawn and tested for potassium, BUN, and creatinine at the PCC lab. If the participant is taking Digoxin, these test results must be available before the start of study drug.

8.8.10.2. Urine Samples


Aliquots from participants' 24−hour urine collections are to be sent to the central lab (DLF at Hillman Cancer Center) for analysis of sodium, potassium, creatinine, and microalbumin. Aliquots of urine chemistries must **not** contain a preservative.

8.8.10.3. Digoxin Level

If a participant is on Digoxin, the level must be checked at the baseline visit, and the results must be reviewed prior to the start of study medication.

8.8.11. Specimen Banking

Blood and urine specimens are to be obtained from participants and sent to the NIDDK Biorepository for use in future studies. Samples include serum, plasma, freshly voided urine, and 24−hour urine.


If serum/plasma samples are hemolyzed, or otherwise lost or destroyed, they should be redrawn if the participant lives locally to the PCC and sent to Fisher BioServices via FedEx. The decision to redraw blood is left up to the sites. If a sample is to be redrawn, the site must notify the DCC in advance so a new set of accession numbers can be generated.

8.8.12. Hyperkalemia

Hyperkalemia is likely to be encountered in Study B participants and even some Study A participants. Standard measures will be used to control potassium, including dietary modifications and/or use of furosemide and/or use of exchange resins (sodium polystyrene sulfonate). Because it may be difficult to obtain sodium polystyrene sulfonate on an urgent basis in some locations, all participants in Study B must be sent home from the baseline visit with 3, 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 must also be given 3, 15g doses of sodium polystyrene sulfonate at the baseline visit to be saved for later use, if needed.

8.8.13. MR/MRA/Cardiac MR (Study A)

Participants enrolled to Study A are to undergo MR (renal volume measurement), MRA (renal blood flow measurement), and Cardiac MR (left ventricular mass measurement) after they are randomized at the Baseline (B1) visit.

For further information on MR/MRA/cardiac MR studies, refer to Section 12 − Magnetic Resonance Imaging (Study A)

* MRI Session (Renal) Information Form 21 is to be completed by the radiology technologist.
* Renal Blood Flow (MRA) Form 22 is to be completed by either the study coordinator or radiology technologist.

8.8.13.1. MR/MRA/Cardiac MR Results

MR scans are to be read and interpreted at the PCC. However, the PCC is not responsible for work−up/diagnosis, follow−up, or treatment of any abnormalities revealed by these imaging studies. Rather, if an abnormality is found on a scan (e.g., an unusual mass) the radiologist must notify the principal investigator, who, in turn, must immediately notify the participant. If the participant grants written authorization, the participant's PCP and/or nephrologist may also be notified by the PCC.

8.8.14. Baseline Failure

For participants registered to the study, screen failure may take place anytime up to randomization (but not after). When this happens, the reason(s) for exclusion from the study will be explained to them. Participants may request this information in writing for their own records or for forwarding to their primary care provider (PCP). In such cases, coordinators may highlight exclusions on a study form (e.g., Enrollment Form 10) and give it to the participant. Alternatively, coordinators may draft a letter explaining the participant's exclusion from the study, but pages from the protocol should not be provided to participants or to their PCPs. If the lab values resulting in screen failure present safety concerns or reveal abnormalities, PCCs are responsible for informing participants and urging them to inform their PCP and/or nephrologist.

If a participant fails to meet eligibility criteria at or before randomization, Screen Failure Form14 must be completed and entered within three business days of site personnel becoming aware of the failure. Participants failing to meet eligibility criteria before randomization or who are deemed by the investigator to be unfit for randomization are considered to be screening failures, even if they will later be eligible for rescreening.

Guidelines pertaining to safety concerns and/or abnormalities and policies for informing participants of such may be found by referring to Sections 8.14/11.1.8/13.4 − Informing Participants of Safety Concerns.

8.8.15. Missed Baseline Visit

Refer to Section 8.16 − Target Visit Dates and Acceptable Ranges for Visits for more information on the protocol for a missed baseline visit.

8.9. Randomization

Participants requiring a drug washout period must return to the study center for the randomization visit (B1). Randomization must occur within 10 weeks of the Screening Visit (S), or screening procedures will need to be repeated. For participants who do not require a drug washout, the Screening visit (S) and Baseline visit (B1) may be combined into one visit (SB1). To randomize a participant, the study coordinator must enter Randomization Form 20. Assignment to Study A or Study B is based on the result of serum creatinine measured at the PCC during the screening visit. Participants whose baseline level of renal function (GFR) falls outside the accepted level of renal function of the study to which they have been enrolled are not to be excluded in accordance with the intent−to−treat principle.

To assist in determining eligibility to Study A or Study B, refer to Section 8.2.3.1 − Converting GFR Values to Serum Creatinine Values.

8.9.1. Study A

Participants with a Glomerular Filtration Rate (GFR) >60 ml/min/1.73 m_2 are to be randomized to Study A.

8.9.2. Study B

Participants whose Glomerular Filtration Rate (GFR) falls between 25−60 ml/min/1.73 m_2 are to be randomized to Study B.

8.9.3. PCP Notification of Enrollment

At the Screening visit, each participant will have named a physician as their primary care physician (PCP). 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 such authorization was granted, the HALT PKD investigator is to send an initial letter to the named PCP to inform him/her of the participant's enrollment in HALT PKD. A Physician Information brochure must be enclosed with the initial letter.

8.9.4. 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), should be randomized and start study medication at the lowest dose, with follow−up as outlined in the study protocol.

8.9.5. Pregnancy

Complete guidelines in reference to pregnancy may be found may be found by referring to Section 14.2.2 − HALT PKD Pregnancy Policy. Guidelines for randomization in cases of pregnancy are included within this policy and also included below.

8.9.5.1. Pregnancy Prior to Randomization

If a participant becomes pregnant prior to the baseline visit, she must *not* be randomized, but should be considered a screen failure, even if she has already been enrolled and/or intends to terminate the pregnancy. Study medication must be discontinued immediately and a Screen Failure Form 14 (Reason #6) data−entered as soon as possible. Any pregnant participant is to be referred to her primary care physician (PCP) for management of the pregnancy and is *not* to be followed by HALT PKD 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.

8.9.5.2. Pregnancy After Randomization

If the participant becomes pregnant after randomization and is *currently* pregnant at the time study staff learn of the pregnancy, study drugs must be stopped immediately (enter Study Medication Form 63 and complete the Modified Participation Form 28 as soon as possible). The participant is to be referred to her PCP for management of both the pregnancy and hypertension. Should the woman and her doctor decide to unmask study medication (ARB versus placebo), the study arm assignment is to be unmasked once written permission from the PI is obtained. All pregnancies must be reported on Symptoms Checklist Form 5 (5B). Modifications to study drugs and follow−up are described below. Follow−up is to remain the same, irrespective of whether study arm assignment remains masked or not.

Required Modifications for Pregnant or Lactating Participants:

1) Study medications (ACE−I/ARB or ACE−I/placebo) must be discontinued immediately.
2) All other study medications must be discontinued and care transferred to the PCP.
3) Pregnant or lactating participants should 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 must *not* be imaged. Home BP is not required.
5) Participants may re−enter the study and return to full participation without being rescreened or re-consented, 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.
6) Complete Modified Participation Form 28.
7) The Serious Adverse Event Form 13 will be submitted on all modified pregnant participants in the event of hospitalization, including the delivery of the infant.
8) Coordinators should re-modify participant back to full participation as soon as breastfeeding is stopped.

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

8.9.5.3. Planned or Spontaneous Abortion After Randomization

If a participant becomes pregnant after randomization, but has had a planned or spontaneous abortion by the time study staff learn of it, study medication is not to be discontinued nor follow−up modified. The event (abortion) must be reported on Symptoms Checklist Form 5 (other event).

8.9.6. Emergency Randomization− (N/A − no longer in use)

Ideally, randomization occurs at the Baseline visit (B1) after all study procedures, except MR imaging, have been completed. However, in some cases, technical problems may occur, making it impossible to randomize participants in the usual manner. In such cases, PCCs are to follow the guidelines below for emergency randomization.

8.9.6.1. Web Data Entry System (WDES) Inaccessible to PCC

If the WDES is functioning properly but the PCC is not able to access it, the following steps are to occur:

1) The study coordinator must alert the Research Program Coordinator, either by phone or by e−mail that an emergency randomization is required.
2) The PCC is to complete Randomization Form 20 and fax it to the attention of the Research Program Coordinator at the Data Coordinating Center. The fax number is (412) 647-0632. If the Research Program Coordinator is not available, the form should be faxed to the attention of the Project Manager at the same fax number. Required Lab Results Form 9 and Enrollment Form10 should also be faxed to the DCC if they were not previously entered. All forms must be signed and dated by the PI prior to faxing them to the DCC.
3) On receipt of the above−described form(s), the DCC is to immediately enter the form(s) necessary for randomization. As soon as this step has been completed, the DCC is to inform the PCC of either the participant's assigned treatment arm and medication bottle number (successful randomization) or the reason for the participant's ineligibility (unsuccessful randomization).
4) The DCC is to then promptly fax confirmation of the participant's randomization and treatment arm to the PCC.

8.9.6.2. WDES Not Functioning Properly – N/A-no longer in use

If there is a problem with the WDES, the following steps are to occur:

1) The study coordinator must then alert the Research Program Coordinator, either by phone or by e−mail, that an emergency randomization is required.
2) The PCC is to complete Randomization Form 20 and fax it to the attention of the Research Program Coordinator at the Data Coordinating Center. The fax number is (412) 586−9672. If the Research Program Coordinator is not available, the form should be faxed to the attention of the Project Manager at the same fax number. Required Lab Results Form 9 and Enrollment Form10 should also be faxed to the DCC if they were not previously entered. All forms must be signed and dated by the PI prior to faxing them to the DCC.
3) The DCC should then immediately confirm (manually) that the participant is eligible for enrollment and/or randomization. The DCC is to contact the form completer if there are any questions.
4) The DCC is to maintain an emergency randomization list for each site and will refer to the list for the appropriate site to obtain the next available medication bottle number for the participant.
5) The DCC is to immediately inform the site of the assigned medication bottle number and then promptly send written verification to the site by fax or email.

8.9.6.3. Emergency Randomization Needed Outside Normal Business Hours – N/A

If it is absolutely necessary to randomize a participant outside of normal business hours, the following steps are to occur:

1) The PCC is to call Gigi Flynn at home (314) 647−1109.
2) If there is no answer after fifteen minutes, call Robin Woltman at home (314) 993−0232.
3) If there is no answer after fifteen minutes, call Phil Miller on his cell phone (314) 757−4135.
4) The DCC staff member is to immediately confirm, by manually completing the necessary form(s), whether the participant is eligible for enrollment and/or randomization.
5) The DCC staff member is to then refer to the appropriate emergency randomization list for the site to obtain the next available medication bottle number for the participant and then inform the site of the assigned medication bottle number.
6) On the next business day, the DCC staff member needs to send written verification to the site of the medication bottle number that was emergently assigned to the participant.

8.9.6.4. Emergency Randomization Drug Card Assignment

Each PCC will create two sets of drug cards (e.g., sets number one and two) and set them aside for emergency randomizations in future. The DCC will tell each PCC which drug cards numbers to include in each drug−card set. When an emergency randomization occurs, the DCC will tell the PCC which of the two sets to assign to the participant. When

an emergency drug card set is assigned, a new set will be created (e.g., set number 3) so that two sets are always on hand.

8.9.7. Informing Participants of Abnormal Lab Values

At Baseline and throughout the study, PCCs will inform participants of any concerning lab values or abnormalities found on MR scans and encourage them to follow up with their primary care physician and/or nephrologist. If authorized by the participant in writing, PCCs may inform physicians of these abnormalities directly.

Guidelines pertaining to safety concerns and/or abnormalities and policies for informing participants of such may be found by referring to Sections 8.1.4/11.1.8/13.4 − Informing Participants of Safety Concerns.

8.10. Study Medication

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 has discontinued masked medication or withdrawn consent to continue in the study.

Study drugs and additional antihypertensive agents are to be distributed to participants at the Baseline visit (B1). These medications must be added in a stepped fashion, beginning at the B2 visit, according to the Stepped Protocols for Addition of Antihypertensive Agents. Study drug(s) are to be maximized as tolerated to ensure the participant's blood pressure does not fall below the lower limit of the targeted range. Study coordinators are to review home blood pressure records and adverse events from the prior two−week period with the participant during each telephone visit to guide subsequent therapy.

For further information on dispensing study drugs, refer to Section 10.3.3 − Masked Study Drugs−Dispensing Telmisartan/Placebo.

8.11. Start of ACE +/− ARB Therapy (Visit B2)

Participants must not begin taking masked study medications (ACE +/− ARB therapy) until results of the two baseline serum creatinine measurements, confirming a difference of 20% or less, are received from the central laboratory. Once the appropriate serum creatinine results have been received at the PCC, the study coordinator is to contact the participant by phone to instruct him/her to begin taking study medications (B2 visit). The participant is also to be instructed to begin tapering off, and subsequently discontinuing, the labetalol (or Clonidine) being taken for drug washout. The coordinator must confirm the date on which the participant began taking masked study medication by completing Therapy Confirmation Form 56 at the F5 visit.

For information on the procedure to follow in the event of a difference of greater than 20% between the two baseline serum creatinine measurements, refer to Section 8.8.8 − Baseline Serum Creatinine.

8.12. Follow− Up Visits (F#) – Telephone

8.12.1. Forms Required for Follow−up Visits – Telephone

- Form 5 − Symptoms Checklist
  - ◊ Symptoms Checklist Form 5 Instructions
- Form 6 − Concomitant Medications Form
- Form 9 − Required Lab Results Form
- Form 12 − Home Blood Pressure Form
- Form 51 − Required Safety Lab Results
- Form 62 − Drug Card Assignment Form
  - ◊ Drug Card Assignment Form Instructions
- Form 63 − Study Medication Form
  - ◊ Study Medication Form (63) Instructions
- Form 56 − Therapy Confirmation Form

8.12.2. Study Drug Titration Period (B2 up to F5 Visit)

Study medications are to be initiated at the B2 visit, with dose increments occurring every two weeks until the maximal dose has been achieved. To verify and report the actual start/stop dates of washout drugs and ACE+/−ARB therapy, Therapy Confirmation Form 56 must be completed at the F5 visit.

Increment study drugs according to the Stepped Protocols for Addition of Antihypertensive Agents.

Serum potassium, creatinine, and BUN must be measured, at the PCC or at a local laboratory, one week after each specified dose increment. Results from outside laboratories must be faxed or communicated electronically to the PCC and reviewed by study coordinators, along with home blood pressure records and adverse events reported by the participant during follow−up telephone visits to take place after each two−week period. The follow−up telephone visits serve as a guide for subsequent therapy.

At the first dose increment, the participant is to be instructed to increase the dose of study drug per the stepped protocol. Only 40 mg drug cards of telmisartan or placebo will be dispensed for the titration period, with participants titrating to the 80 mg strength being instructed to take 2, 40 mg tablets. Adhering to this schedule, the study drug is expected to be at maximum dose, and BP stabilized, 9 weeks after randomization. Participants are to be instructed to take study medication in the morning and monitor blood pressure at least every four days during the study drug titration period.

8.12.2.1. Safety Labs during Titration Period

Participants are to be instructed that serum potassium, creatinine, and BUN must be measured, either at the PCC or a local lab, one week after specified dose increments. Results from outside laboratories should be faxed or communicated electronically to the PCC. Safety samples must be collected no later than 14 days after each dose increment, and the PI must review results prior to the next dose increase. For individuals currently taking Digoxin, those levels must also be checked one week after each specified dose increment, with dose adjustments made, if necessary, per the discretion of the PI. Safety labs are **not** required if the dose is not increased.

☞ Safety labs are not required if the dose of study medication is not increased.

For information on incrementing study medication doses and corresponding safety labs, refer to the cheat sheet on Safety Labs and Dose Increments.

Study A

For participants enrolled in Study A, safety samples need to be drawn after every second dose increment, expected to occur at weeks 3 and 8 (L2 and L4).

Study B

For participants enrolled in Study B, safety samples need to be drawn after every dose increment, expected to occur at weeks 1, 3, 5, and 8 (L1−L4).

Safety samples must be collected, at minimum, as specified above. However, depending on the participant's baseline potassium and kidney function and how quickly the dose is escalated, additional safety samples may be collected more frequently than the minimum required at the discretion of the investigator.

☞ At any time during the trial, if the investigator orders additional safety labs, or additional test results become known to the PCC, serum creatinine and potassium values are to be data−entered within two weeks of sample collection via Required Safety Lab Results Form 51 as an X visit.

8.12.2.2. Safety Labs when GFR <30

Whenever a participant's GFR (based on central serum creatinine results) drops below 30 (not expected during titration), the participant will have more frequent follow−up visits with his or her 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, and the results are to be data entered within two weeks via Required Safety Lab Results Form 51.

Safety labs are reviewed monthly by the Quality Control Committee. The DCC implemented changes on the QC report in June, 2012, flagging participants that missed their three month safety labs. The site coordinators are asked to follow up with the participants and obtain the outstanding safety labs.

8.12.2.3. Shortened Titration of Study Medications for Difficult−to−Control BP

For participants with difficult−to−control blood pressure, study medications (ACE+/−ARB/placebo) may be started at a dose step higher than the first, at the discretion of the investigator. 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.

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 for participants 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.

8.12.2.4. Drug Interaction of Telmisartan and Digoxin

Co-administration of Telmisartan and Digoxin, both metabolized by the liver, can lead to an increase in the peak concentration of Digoxin by up to 50%. Thus, Digoxin levels are to be checked at baseline and with potassium and BUN/creatinine between titration of ACE−I and telmisartan/placebo in the first 8 weeks of the study. Dose adjustments for Digoxin are to be made, as necessary, by the PI. Digoxin levels should stabilize once a steady dose of telmisartan is reached, such being anticipated by the final titration step, as confirmed by the L4 safety lab. If levels continue to fluxuate, continued testing should be arranged. Digoxin levels need to be followed every 6 months and should be rechecked within 1 week of making a dose adjustment in telmisartan/placebo.

8.12.3. Post Study Drug Stabilization Period (F5 Visit and After)

After study drugs have stabilized (after the first 16 weeks), study coordinators are to follow up with participants by telephone at three−month intervals between clinic visits.

8.12.3.1. Blood Pressure Monitoring between F5 and F12 PCC Visits

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

8.12.4. Interval History

Study coordinators are to take an interval history during each telephone follow−up visit, to include review of unscheduled medical encounters, hospitalizations, and start of dialysis or transplantation. Per the Symptoms Checklist (Form 5), female participants are to be asked if any periods have been missed.

8.12.4.1. Review of Unscheduled Medical Encounters

Study coordinators are to ask whether participants have seen any medical professionals since the last study visit. Women of childbearing potential are to be asked if there have been any changes in reproductive status or in use of contraceptives since the last study visit.

8.12.4.2. Hospitalizations

Study coordinators must report all hospital admissions, regardless of relatedness to study participation, to the DCC as SAEs within 24 hours of being notified that a hospitalization has occurred. A discharge summary is to be requested and kept on file at the site.

8.12.4.2.1. Hospitalization Adjudication

A copy of the discharge summary must be submitted to the DCC for the purpose of hospital adjudication. Coordinators will de-identify the entire document reviewing each page of the discharge summary to assure all identifiers are removed. The HALT PKD ID and SAE number should be documented on each page of the discharge summary. Copies are to be sent securely and may be scanned, faxed or emailed to the DCC, provided participant confidentially during transmission is maintained.

8.12.4.2.2. Hospitalization For Kidney Transplant

The admission for transplant *does not* require the submission of a Serious Adverse Event form, the transplant is considered an anticipated study endpoint. Hospitalization for the purposes of a kidney transplant requires:

- ◊ Form 30 Hospitalization Form
- ◊ Submission of a discharge summary for the transplant submitted to the DCC.
- ◊ In all transplant cases, the identifier on the discharge summary will be the HALT PKD ID and “999”.

8.12.4.3. Start of Dialysis/Transplantation

Study coordinators must report kidney dialysis and transplantation both considered end stage renal disease, to the DCC within 24 hours of being informed of such occurrences. Kidney dialysis and transplantation are both reported on:

- ◊ End Stage Renal Disease Form 32
- ◊ Post Closeout Follow up (Study B) Form 35

Refer to: 14.1.1. Post Closeout Participants

- ◊ Transplants will be reported on Form 30 (no SAE is to be completed), refer to 8.12.4.2.2

The ESRD Medical Evidence Report (CMS 2728 which is required by the Department of Health & Human Services, will be completed by the admitting hospital dialysis/transplant staff and submitted to the DHHS.

ESRD is defined as the start of dialysis or kidney transplantation, at the discretion of the subject's primary nephrologist.

End−Stage Renal Disease Form 32 and Post−Closeout Follow−Up (Study B) Form 35 refer to 14.11 Post close out Participants. Transplants will be reported on Form 30 – Hospitalization only. No SAE is to be completed, refer to 8.12.4.2 Hospitalizations. An additional form, ESRD Medical Evidence Report (CMS 2728), which is required by the Department of Health & Human Services, must also be completed by the admitting hospital dialysis/transplant staff and submitted to the DHHS.

8.12.4.4. Episodes of Acute Dialysis

Some participants admitted to the hospital are diagnosed with an acute kidney injury and begin dialysis.

- If the acute kidney injury resolves and renal function is restored, the participant will not be viewed as reaching ESRD.
- If the participant is discharged and dialysis is maintained, the date of the initial onset of the acute episode during hospitalization will be used to document the date of ESRD.
- Coordinators will document any incidence of known acute kidney injury incurred during the hospitalization in the comments of the SAE Form 13.

8.12.4.5. Placement of Hemodialysis Access

Some participants are hospitalized for procedures to place hemodialysis catheters of AV fistulas/shunts in preparation for the start of dialysis.

- If CSC and eGFR values are not available, the date of the first dialysis treatment will be used as the date for the ESRD determinations.
- The date of surgical intervention for dialysis access will not be utilized as the ESRD date.

8.12.5. Review of Medications

Start and stop dates for all concomitant medications are to be collected at every visit. Study coordinators are to verify that participants are in compliance, per protocol, with regard to study medication.

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. It should be noted that study medication may not necessarily have to be stopped. All BP drugs taken for non−BP indications are to be recorded on Concomitant Medications Form 6 and data−entered. The data system will be set up to flag whether these medications were preexisting or started after the start of washout.

8.12.6. Adverse Events

Adverse events must be ascertained during every telephone visit by reviewing and completing Symptoms Checklist Form 5 with participants. Adverse event reporting may require completion of additional forms (e.g., Required Safety Lab Results Form 51, Serious Adverse Event Form 13).

Safety labs are not required after the titration period. However, should the investigator, at his or her discretion, order additional safety labs, or additional test results become known to the PCC, serum creatinine and potassium values are to be data−entered within two weeks of sample collection via Safety Lab Results Form 51.

For more information on "out−of−control" BP, refer to Section 9.2.3.1 − Dose Adjustments for Out−of−Control BP.

8.12.7. Review of Home Blood Pressure Measurements

Participants are to be instructed to continue to monitor blood pressure readings at home at least once a month after targeted BP control has been achieved. Study coordinators are to review records with the participant via telephone visits every three months through the end of the study. Frequency of home BP monitoring and study visits can be increased, at the PI's discretion, for individuals with "out−of−control" BP at any point in the study.

Non-Compliance of Home Blood Pressures – The decision to modify a participant due to home blood pressures not being provided at the time of the PCC visit is the decision of the Principal Investigator at each site. If the PI decides the safety of the participant is compromised, he/she will make the decision to modify the participant. The PI will review whether or not other BP readings are available for their participant as well as the trends in BP readings to date.

8.12.8. Changes in Study Medications

Additional antihypertensive agents may be added, as needed, according to the appropriate stepped protocol for Study A or Study B

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 has discontinued masked medication or withdrawn consent to continue in the study.

8.12.9. Quest Visit - Telephone Visit - Remote Visits

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, also known as a "telephone visit" or "remote visits", may be conducted by phone within +/− (1) month of the target visit date and will be accepted in lieu of the PCC visit. Only one Quest visit (in lieu of a PCC visit) is permissible a year.

Centrally Serum Creatinines's must be obtained for the "Quest Visit/Remote Visit". The DCC renegotiated the Quest Diagnostics contract in August of 2012. Now, participants may utilize a Quest Diagnostic Facilities for drawing the centrally processed serum creatinine labs.

The following rules apply to the Quest Visit:

- The visit must take place within +/- 1 month of the target visit date and will be accepted in lieu of the PCC visit.
- Only one Quest Visit (in lieu of a PCC visit) is permissible each year.
- Quest Visits are calculated based on the occurrence within a *twelve month period* and not calculated based on the *calendar* year.
- Participants may use a Quest or Hometown facilities for lab draws
- The serum Creatinine must be processed centrally at CCF—coordinators will provide CSC kits to the participant for the CSC draw.
- The CSC lab must be centrifuged within an hour of the draw and shipped within 24 hours to CCF for the purposes of central processing.
- Refer to the following MOP entries for CSC guidance:
  - 11.3.1.1 Approved uses for Quest labs-Quest Visit in Lieu of PCC Visit
  - 11.3.3 Hometown Laboratories
  - 11.3.3.4 Obtaining Serum Samples for Central Analysis of Creatinine
- Once a Quest Visit is completed, it is imperative that the participant attend their next PCC visit.
- In order for study drug to be dispensed, participants need to complete Q six month follow up.
- As of August 2012, Form 29 Protocol Violation Form is required for any participant completing a Quest Visit without submitting a CSC sample.
- The Quest Visit should take place on during the 6-month visit (i.e.: F42, F54) to avoid missing the yearly 24 hour urine collection and MRI procedure.
- For Study A participants, imaging scans should occur as near as possible to the Months 24, 48, and 60 visits within +/− six months of the target visit date. Refer to section 8.13.13 MRI/MRA/Cardiac MR (Study A)
- The Quest/remote visits are to be used in extreme circumstances, are an exception, are to be used only when attendance to a PCC appointment is unavoidable and reserved for those cases in which a routine clinic visit would be an undue burden for a participant.
- 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

For more information on Quest visits in lieu of PCC visits, refer to Section 8.14 − Quest Visits in Lieu of PCC Visits.

8.12.10. Missed Follow−Up Visits - Telephone

Refer to Section 8.16 − Target Visit Dates and Acceptable Ranges for Visits for information on the protocol for dealing with missed follow−up visits (telephone).

8.13. Follow− Up Visits (F#) – Clinic

Follow−up clinic visits during the first year of HALT PKD are to take place at the PCC at 16 weeks (F5) and 12 months (F12) after the start of ACE +/− ARB therapy (B2). After the first year, follow−up clinic visits at the PCC are to take place every six months through the end of the study in order to monitor/manage blood pressure, provide study drugs to participants, record outcomes, and maintain participant interest in the study.

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 may be conducted by phone within +/− 3 months of the target visit date and will be accepted in lieu of the PCC visit. Only one Quest visit (in lieu of a PCC visit) is permissible a year.

8.13.1. Forms Required for Follow−Up Visits - Clinic

- Form 5 − Symptoms Checklist
  - Symptoms Checklist Form 5 Instructions
- Form 6 − Concomitant Medications Form
- Form 9 − Required Lab Results Form
- Form 12 − Home Blood Pressure Form
- Form 13 − Serious Adverse Event Form (if necessary)

- SAE Form 13 Instructions
- Form 15 − Current Physical Findings Form
- Form 35 – Post Closeout Follow Up
  - *Form Required Yearly (Study B)*
- Form 36 − Home Blood Pressure Calibration Log
- Form 37 − 24−Hour Urine Collection Checklist
- Form 38 − Quality of Life Questionnaire
- Form 39 − Pain Questionnaire
- Form 62 − Drug Card Assignment Form
  - Drug Card Assignment Form Instructions
- Form 63 − Study Medication Form
  - Study Medication Form (63) Instructions

8.13.2. Interval History

Study coordinators are to take an interval history at each in−clinic follow−up visit, to include review of unscheduled medical encounters, hospitalizations, and start of dialysis or transplantation. Per the Symptoms Checklist (Form 5), female participants are to be asked if any periods have been missed.

8.13.2.1. Review Unscheduled Medical Encounters

Study coordinators are to ask whether participants have seen any medical professionals since the last study visit. Women of childbearing potential are to be asked if there have been any changes in reproductive status or in use of contraceptives since the last study visit.

8.13.2.2. Hospitalizations

Study coordinators must report all hospital admissions, regardless of relatedness to study participation, to the DCC as SAEs within 24 hours of being notified that a hospitalization has occurred. A discharge summary is to be requested and kept on file. In addition, a copy of the discharge summary will be collected by the PCC. The study coordinators 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.

8.13.2.3. Start of Dialysis/Transplantation

Study coordinators must report kidney dialysis and transplantation; both considered end stage renal disease, to the DCC within 24 hours of being informed of such occurrences. Kidney dialysis and transplantation are both reported on End−Stage Renal Disease Form 32. An additional form, ESRD Medical Evidence Report (CMS 2728), which is required by the Department of Health & Human Services, must also be completed.

ESRD is defined as the start of dialysis or kidney transplantation, at the discretion of the subject's primary nephrologist.

8.13.3. Quality of Life and Pain Questionnaires

Health status is to be assessed annually using the Medical Outcomes Study Short−Form 36 Questionnaire (SF−36v2), a self−reporting questionnaire that assesses physical, mental and social aspects of health−related quality of life. The separate HALT PKD Pain Questionnaire is to be administered to capture the impact of pain, progressive kidney disease, and adherence to interventions (e.g., low blood pressure) on mental and physical components of health.

Participants are to be instructed to complete Quality of Life Questionnaire Form 38 (SF−36v2) prior to completing Pain Questionnaire Form 39.

8.13.4. Review of Medications

At every visit, participants must be instructed to bring all concomitant medications with them to clinic visits. Medication start and stop dates are to be collected at every visit and recorded on Concomitant Medications Form 6. Coordinators are to verify that participants are in compliance with taking study medications as instructed. 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. It should be noted that study medication may not necessarily have to be stopped. All BP drugs taken for non−BP indications are to be recorded on Concomitant Medications Form 6 and data−entered. The data system will be set up to flag whether these medications were preexisting or started after the start of washout.

8.13.5. Adverse Events

Adverse events must be ascertained during every in−clinic visit through use of Symptoms Checklist Form 5. Adverse event reporting may require that additional forms be completed (e.g., Required Safety Lab Results Form 51, Serious Adverse Event Form 13).

Safety labs are not required after the titration period. However, should the investigator, at his or her discretion, order additional safety labs, or additional test results become known to the PCC, serum creatinine and potassium values are to be data−entered within two weeks of sample collection via Required Safety Lab Results Form 51.

Refer to Sections 8.15.3 and 8.15.4 for complete information on reporting adverse events and serious adverse events.

8.13.6. Blood Pressure Measurements

8.13.6.1. Clinic BP Measurements

During each follow−up visit, the study coordinator is to measure each participant's blood pressure three times while seated and once while standing, with the results being recorded on Form 15 − Current Physical Findings.

The protocol for obtaining these BP measurements is listed below:

* The participant is to be seated quietly in a chair for a minimum of 5 minutes, with feet on the floor and arm supported at heart level. Three measurements are to be taken in the appropriate arm, as described above, with a wait of at least 30 seconds occurring between each measurement. On completion of 3 seated BP measurements, the average of the last two out of three readings should be calculated.
* The participant is then to stand for 3 minutes with his/her arm supported at heart level. After 3 minutes, 1 blood pressure measurement is to be taken with the participant still standing. If standing blood pressure is more than 20 mm Hg below the average of the last two readings taken when the participant was seated, hypotension may be indicated; and the PI or co−investigator may consider reducing study medication at his/her discretion.

For more information on measuring BP at the PCC, refer to Section 9.1 − Standardized Procedures for BP Management.

8.13.6.2. Home BP Measurements

The participant is to bring two sets of self−taken home BP measurements to each follow−up visit at the PCC for review by the study coordinator and PI.

1) The first set of measurements (for BP control) is to be taken at least once a month (every four days during titration) and recorded in the participant's BP Diary. Three readings per sitting are required.
2) The second set of measurements (for BP separation), is to be taken twice daily for seven consecutive days (14 readings, 10 readings being the minimum required) within the month before the clinic visit. Three readings per sitting are required. These readings are to be recorded on Home Blood Pressure Form 12.

The second set of values (from Home Blood Pressure Form 12 must be data−entered in the Web Data Entry System (WDES) at the time of the visit. The system will automatically calculate the average of the last 2 out of 3 readings for 14 readings (a minimum of 10 readings is required).

For more information on the measuring and recording of home BP by participants, refer to Section 9.1.2.3 − Procedures for Home BP Measurements.

For more information on calibration of Home BP Monitors, refer to Section 9.4.1. − Calibration of Home BP Monitors.

8.13.7. Symptom−Directed Exam

A symptom−directed physical exam is to be performed by a PI or co−investigator at each follow−up visit.

8.13.8. Changes in Study Medications

Additional antihypertensive agents may be added, as needed, according to the appropriate stepped protocol for Study A or Study B.

8.13.9. Serum Creatinine

Two serum creatinine samples are to be drawn at the F5 visit and shipped to Cleveland Clinic the same day. Participants must be instructed to fast (water is permissible) between venipunctures. On receipt of the results from Cleveland Clinic, the study coordinator is to confirm the consistency of the two serum creatinine measurements − a difference of 20% or less between the two measurements is considered an acceptable level of agreement. If the two

measurements differ by greater than 20%, arrangements must be made for drawing a second set of serum creatinine samples, which must be sent to Cleveland Clinic for repeat analysis within two weeks. For individuals who live far from the PCC, repeat blood samples may be drawn at a local laboratory and shipped by overnight mail to the central laboratory. Only one serum creatinine sample will be collected at subsequent 6−month and 12−month follow−up clinic visits. All samples must be sent to the Cleveland Clinic Foundation Reference Laboratory for measurement of GFR within two weeks.

8.13.9.1. Central Serum Creatinine Management

A centrally processed serum creatinine (CSC) is to be utilized for the following:

- Quest Visits (Remote Visit) Refer to 8.12.9. Quest Visits
- Confirmatory samples drawn at a Hometown Lab--Refer to 11.3.3 Hometown Lab and 14.2.4 Study B Endpoints.
- Modified Participants that agree to follow-up at a PCP every 6-12 months

NOTE: Quest Diagnostic Labs may draw endpoint confirmatory samples because the lab uses the IDMS traceable method

Centrally Processed Serum Creatinine Kits - The University of Pittsburgh DCC will provide CSC Styrofoam kits to sites for distribution to participants. The participant takes the CSC kit to the lab on the day of the blood draw. The lab will complete the lab draw, centrifuge the serum creatinine and ship the sample within 24 hours of the draw to the Cleveland Clinic Lab for processing.

For more information, refer to Section 11.3.3 – Hometown labs or 11.3.3.4 Obtaining Serum Samples for Central Analysis of Creatinine

8.13.9.2. Central Serum Creatinine Measurements for International Participants

Coordinators are to encourage HALT PKD participants residing outside of the United States to utilize a hospital outpatient lab for HALT PKD blood draws. Participants should identify a lab that utilizes an IDMS traceable method of processing serum creatinine. If possible, a note from the lab confirming use of the IDMS traceable method may be obtained, although obtaining this documentation is not mandatory.

International Lab Options Include:

- ◊ local hospital outpatient lab.
- ◊ military hospital (for enlisted participants or family members of military).

International Participant Form 9 Completion:

- ◊ International lab will fax results directly to the PCC.
- ◊ “Other” is selected to indicate Lab Used (document name of facility)
- ◊ In the Form 9 comments section:
- ◊ if applicable, indicate “IDMS traceable method used.”
- ◊ include terms indicating: “international participant”, the country of residence, the type and location of the lab (i.e military hospital, local hospital, outpatient clinic etc.).

Coordinators will complete an Unexpected Event Form and submit it to the DCC.

8.13.10. Urinary Aldosterone

Urinary aldosterone is to be measured at the F5 visit and at annual visits by forwarding aliquots from each participant's 24−hour urine collection to the central laboratory at CCF.

For more information on collection and handling of 24−hour urine specimens, refer to Section 11.5 – Central Processing Facility for 24−Hour Urine Measurements. Participants are to be instructed to collect 24−hour urine samples per the instructions in Section 11.5.2 − Instructions for Participants.

8.13.11. Other Laboratory Measures

8.13.11.1. Blood Samples

Serum electrolytes and CBC with platelets (PCC lab) are to be drawn at every six−month follow−up visit. At annual visits, random glucose, serum albumin, calcium and phosphorus will be run at the PCC.

8.13.11.2. Urine Samples

Aliquots from each participant's 24−hour urine collection are to be sent to the central lab (Hillman Cancer Center) for analysis of sodium, potassium, creatinine, and microalbumin. Aliquots of urine chemistries must *not* contain a preservative. Qualitative urine pregnancy testing is to be carried out in women if there is a missed menstrual cycle or other reason to suspect pregnancy; thus, study coordinators are to ask female participants about missed periods at every PCC visit, as well as during telephone follow−up visits.

8.13.12. Specimen Banking

Blood and urine specimens are to be obtained annually and sent to the NIDDK Bio-repository at Fisher BioServices for use in future studies. Samples include serum, plasma, freshly voided urine, and 24−hour urine. At the F5 visit, urine samples will be collected (serum and plasma samples will not be collected at this visit).

If serum/plasma samples are hemolyzed, or otherwise lost or destroyed, they should be redrawn, if the participant lives locally to the PCC, and sent to Fisher BioServices via FedEx.

For further information on biosample collection, handling and shipping, refer to Section 11.6.2 − Biosample Handling − Blood and Section 11.6.3 − Biosample Handling − Urine.

8.13.12.1. Genetic Sample

At the F5 visit, all participants enrolled in HALT−PKD, from whom a genetic sample is not already archived in the NIDDK Repository (e.g., CRISP participants), should be invited to contribute to the HALT−PKD Genetic Repository at Rutgers by providing a blood specimen for EBV transformation.

Genetic samples are not to be obtained from participants who do not agree to cell immortalization. A written informed consent, specifically addressing the drawing of genetic samples for use in future studies, must be ***explained*** to and ***signed*** by participants ***before*** any genetic samples may be drawn. It is suggested that the genetic sample informed consent document be separate from that of the overall study informed consent document.

For further information on genetic sample collection, handling and shipping, refer to Section 11.6.1 − NIDDK Genetic Repository.

8.13.13. MRI/MRA/Cardiac MR (Study A)

Participants enrolled to Study A are to undergo MR (renal volume measurement), MRA (renal blood flow measurement), and Cardiac MR (left ventricular mass measurement) at the 24, 48 and 60 month follow−up visits. Participants are to be instructed to hold morning doses of all medications until images have been acquired to reduce the hemodynamic effects of medications on renal blood flow measurement.

* The MRI may be obtained six months *before or after* the target F24, F48, F60 visit date. (Example: F48 may be obtained at F42 or F54 PCC visit).
* The subsequent MRI scan date will not be altered to accommodate a delayed scan.
* MRIs requiring rescan must be completed within six months of original scan.
* Participants attending the PCC visit and missing their MRI or missed rescans constitute a protocol violation.

For further information on MR/MRA/cardiac MR studies, refer to Section 12 − Magnetic Resonance Imaging (Study A).

8.13.14. Missed Follow−Up Visits - Clinic

Please refer to Section 8.16 − Target Visit Dates and Acceptable Ranges for Visits for information on the protocol for dealing with missed follow−up visits (clinic).

8.14. Quest Visit in Lieu of PCC Visit (if 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 (“remote visit”) may be conducted by phone within +/− one month of the target visit date, and will be accepted in lieu of the PCC visit. All possible required data should be collected from the participant, and all required labs should be collected at a local hometown or Quest Laboratory.

For Study A participants, imaging scans should occur as near as possible to Months 24 and 48, within +/− 1 year of the target visit date.

The Following Rules Apply to the Quest Visit:

- The visit must take place within +/− **(1)** month of the target visit date and will be accepted in lieu of the PCC visit.
- Only one Quest visit (in lieu of a PCC visit) is permissible a year
- Quest Visits are calculated based on the occurrence within a *twelve month period* and not calculated based on the *calendar* year
- All labs, such as, sodium, potassium and digoxin levels may be drawn and processed by Quest. The serum creatinine must be centrifuged within an hour of the draw and shipped within 24 hours to the Cleveland Clinic Laboratory for the purpose of central processing. Separate lab requisitions are provided by Quest; one for serum
  creatinine and a second requisition for all other labs
- Once a Quest Visit is completed, it is imperative that the participant attend their next PCC visit
- In order for study drug to be dispensed, participants need to complete Q six month follow up

- Centrally processed serum creatinine (CSC) samples must be obtained for all participants completing remote visits
  - Refer to 11.3.3 Hometown Labs and section 11.3.3.4
  - Obtaining Serum Samples for Central Analysis of Creatinine
- As of August 2012, a Form29, Protocol Violation Form is required for any participant completing a Quest visit without submitting a CSC sample
- The Quest Visit should take place on during the 6-month visit (i.e.: F42, F54) to avoid missing the 24 hour urine collection and MRI procedure (Study A)
- For Study A participants, imaging scans should occur as near as possible to the Months 24, 48, and 60 visits within +/− six months of the target visit date. Refer to section 8.13.13 MRI/MRA/Cardiac MR (Study A)
- The Quest/remote visits are to be used in extreme circumstances, are an exception, are to be used only when attendance to a PCC appointment is unavoidable and reserved for those cases in which a routine clinic visit would be an undue burden for a participant
- 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
- The PCC is responsible for working out payment arrangements for standard lab tests (i.e. sodium, potassium, BUN, Digoxin, etc.)
- The DCC is responsible for the cost of the following sample analysis:
  - Routine safety labs obtained at Quest Diagnostics
  - Centrally processed serum creatinine drawn at Quest Diagnostics or a Hometown lab and processed at CCF.
- It is recommended that separate lab requisitions are generated for standard labs (i.e. sodium, potassium, BUN, Digoxin, etc.) and the centrally processed serum creatinine to facilitate billing.

8.15. Unplanned Study Visits

8.15.1. Immediate Randomization

During the Drug Washout period, participants are to be instructed to obtain home blood pressure measurements at a minimum frequency of every other day. If blood pressure is >160/100 mm Hg, symptoms of hypertension develop (e.g., headache, blurred vision), or there are intolerable side effects of washout medications, participants must contact the study coordinator or PI for an immediate visit to the PCC for randomization.

If a participant cannot be assessed at the PCC within 24 hours, his/her blood pressure should be managed with increased labetalol (Clonidine for participants with contraindication to beta−blocker therapy) and/or other therapies (not ACE−I/ARB/calcium channel blocker), as directed by the PI. These participants must be followed closely by telephone until the next scheduled study visit, at which time he/she is to be randomized per protocol.

For more information on emergency randomization procedures, refer to Section 8.7.6 − Early Randomization.
For more information on randomization procedures, refer to Section 8.9 − Randomization.

8.16. Treatment Changes

8.16.1. Out−of−Control Blood Pressure

The frequency of home blood pressure monitoring and study visits can be increased, at the PI's discretion, for participants whose blood pressure is determined to be "out−of−control" at any point in the study.

For more information on "out−of−control" BP, refer to Section 9.2.3.1 − Dose Adjustment for Out−of−Control BP.

8.16.2 . Out−of−Range Blood Pressure (Separation)

The frequency of home blood pressure monitoring and study visits can be increased, at the PI's discretion, for participants whose blood pressure is determined to be "out− of−range" at any point in the study. During the Blood Pressure committee teleconferences, a report of blood pressure “range of separation” and flagged blood pressure values are reviewed. The DCC communicates concerning blood pressure trends to the site investigator and coordinators. Participant tolerance of drug therapy is discussed and, if appropriate, changes in pharmacotherapy management will be implemented.

For more information on BP Targets and Acceptable Ranges, refer to Section 9.2.1 − BP Targets and Acceptable Ranges.

8.16.3. Adverse Events

Adverse symptoms or drug effects must be recorded and data−entered throughout the study through use of Symptoms Checklist Form 5. Adverse event reporting may also require that additional forms be completed (e.g., Required Safety Lab Results Form 51, Serious Adverse Event Form13, and Study Medication Form 63).

For more information on managing adverse symptoms of drug effects, refer to Table 10−4 − Management of Adverse Effects of Medications.

8.16.4. Serious Adverse Events

Serious Adverse Events (SAE) must be recorded and data−entered throughout the study through use of the Serious Adverse Events Form 13. Concomitant Medications Form 6 and Study Medication Form 63 must be current in the database, including the most recent study visit or date of action prior to the date of onset.

For complete information on SAEs, refer to Section 13.8 − SAE Definition and Guidelines.

8.17. Target Visit Dates, Acceptable Visit Ranges, and Missed Visits

At the time of the B2 visit (start of ACE +/− ARB therapy); a study calendar will be generated for each participant listing the target dates for each study visit. The first table below (Table 8.1 − Acceptable Ranges and Missed Visits) outlines the acceptable ranges within which each visit is to occur. Visits not occurring within the acceptable range are considered out of range. Missed visits are those that are expected but are never completed. Please refer to Table 13.1 (Major Protocol Violations) to determine the appropriate actions to take when study visits or required procedures do not occur within defined, acceptable ranges.

Table 8−1. Acceptable Ranges and Missed Visits

Visit	Acceptable Range (after which the visit is "missed")
S (Screening)	Unmissable Visit.
B0 (−2−4 Weeks)	Unmissable visit. Two−to−four week washout is required if taking BP medication.
B1 (Baseline)	If >8 weeks after S visit for drug washout, redo screening and randomize within 10 weeks. If >10 weeks after S visit for randomization, redo screening.
B2 (Time 0)	Unmissable visit. Masked medication must begin as soon as possible.
L1 (Week 1)	Unmissable lab,must be drawn 7−14 days after dose increase.
F1 (Week 2)	Unmissable phone visit, +/− 5 business days.
L2 (Week 3)	Unmissable lab,must be drawn 7−14 days after dose increase.
F2 (Week 4)	Unmissable phone visit, +/− 5 business days.
L3 (Week 5)	Unmissable lab,must be drawn 7−14 days after dose increase.
F3 (Week 6)	Unmissable phone visit, +/− 5 business days.
L4 (Week 8)	Unmissable lab,must be drawn 7−14 days after dose increase.
F4 (Week 9)	Unmissable phone visit, +/− 5 business days.
F5 (Week 16)	Clinic Visit, +/− 2 weeks − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 8 weeks of the visit target date, a query will be generated.*
F7	Routine phone visit, +/− 1 month
F10	Routine phone visit, +/− 1 month
F12 (Annual)	Routine clinic visit, +/− 1 month − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated.*
F15 (3 Month)	Routine phone visit, +/− 1 month and all 3 month phone visits.
F18 (6 Month)	Routine clinic visit, +/− 1 month and all 6 month PCC visits − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated.*
F21 (3 Month)	Routine phone visit, +/− 1 month
F24 (Annual)	Routine clinic visit, +/− 1 month (queries after 6 weeks) − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated.* *MRI must be done between F18 and F30 inclusive

F48 (Annual)	Routine clinic visit, +/− 1 month and all annual PCC visits − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated.* *MRI must be done between F42 and F54 inclusive
F60 (Annual) (Study A & B)	Routine clinic visit, +/− 1 month − *If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated.* *MRI must be done between F54 and F66 inclusive
F90 (Annual)	Routine clinic visit+/− 1 month (queries after 6 weeks) − If home BP readings are unavailable at the time of the clinic visit, they may be collected within the following month. If not entered within 10 weeks of the visit target date, a query will be generated. Letters to local PCP and Nephrologist should be dictated at this visit to begin the transition back to local MD care
F96 (Annual)	Routine clinic visit, +/− 1 month (queries after 6 weeks) – Visit to occur prior to the June 30, 2014 time point. Study Closeout Protocol is to be initiated and study drug taper arranged. Communication with PCP and local nephrologist begin at the F90 visit
Post−TX Follow−Up	Normally visits are q 6 months. If > +/− 3 months, add comment to calendar section of data−entry system. Range = 6 months (queries after 7 months) − *For participants agreeing to continue measuring home BP: If readings are unavailable at the time of the clinic visit, they may be collected within the following month.*
X (Visit)	Unmissable, data−enter all additional safety lab results (sCr and K).
XF (Visit)	Required safety labs (GFR<30), +/− 1 month of TVD for 3−month follow−up visit.

Target Visit Dates

A target visit date (TVD) will be established for each study visit. The TVD for the Baseline visit (B1) will be the date entered on Enrollment Form 10. For visits after baseline, TVDs will be based on the start of masked medication (visit B2).

Acceptable Ranges and Missed Visits

Each target visit date will have an acceptable visit range (AVR) associated with it, based on the table above. If a visit does not occur within its AVR, the visit is considered either missed or out of range.

Visit is Missed/Out−of−Range

Any study visit which does not occur within its acceptable visit range will be considered either missed or lost from the analysis, or out of range. For missed visits (those that never occur), enter Missed Visit Form 25 (within two weeks after the last date of the acceptable visit range). For out−of−range visits (those that occur but not within the acceptable range), it is not necessary to enter Form 25. However, note that it is a protocol violation if any required titration visit (F1−F5, including L1−L4) is either out of range or missed (enter Protocol Violation Form 29 within two weeks after the last date of the acceptable visit range). In most cases, queries will not be generated until two weeks, or more, after the end of the acceptable range.

 For more information about missed and out−of−range visits, refer to the cheat sheet in section 18.5.

For more information on missed and out−of range visits, refer to the cheat sheet in Section 18.5: Target Visit Dates, Acceptable Visit Ranges, and Missed Visits.

For more information on missed and out of range visits during the titration period, refer to the cheat sheet in Section 18.5: Missed and Out of Range Visits during Titration.

Notes on visit ranges and missed visits

1) Visits S and B0 are "unmissable" visits. Use Screen Failure Form14.
2) Baseline Visit (B1): Use Screen Failure Form 14, or visit may have to be delayed, creating a second Screening Visit. (S).
    a. A repeat Screening Visit (S) is required if >8 weeks after the S visit for drug washout and >10 weeks after the S visit for randomization.
3) All ranges are based on visit target dates.
4) Safety Labs: Unmissable, Range = 7−14 days after dose increase.
5) Phone visits during titration: Unmissable, Range = +/− 5 business days.
6) F5/week 16, first follow−up clinic visit, Range = +/− 2 weeks
7) Routine phone visits, Range = +/− 1 month.

8) Routine clinic visits, Range = +/− 1 month.

For Study A Only − F24: Unmissable, Range = Visit and MRI must be done between Months 22 and 26 inclusive.

For Study A Only − F48: Unmissable, Range = Visit and MRI must be done between Months 46 and 50 inclusive.

For Study A Only − F60: Unmissable, Range = Visit and MRI must be done between Months 58 and 62 inclusive.

8.18. Transfer of Participant Care

If a patient desires to transfer from one PCC to another for any reason, the following steps should be taken

1) The study coordinator at the current PCC is to complete all data entry prior to the transfer, and should contact the study coordinator at the destination PCC to request a transfer of participant care.
2) If the transfer is accepted by the PI and study coordinator at the destination PCC, the participant's research chart and any medical records referable to the HALT PKD study are to be sent to the destination PCC (after the patient has signed a medical release form).
3) The DCC is to be informed, via telephone, fax, or email that a transfer is in progress
4) Participant Transfer Form 27 is to be completed by both PCCs, in a two−step process, and faxed to the DCC and data−entered by the DCC before the first visit at the destination PCC
5) Prior to completing the data entry, the study coordinator at the destination PCC is to consent the participant using the appropriate informed consent form. To facilitate uninterrupted patient care, it is recommended that the consent form be sent to the participant by mail. A telephone discussion then can follow with either the PI or study coordinator to answer any questions and explain the differences in consent format between the different centers. The signed form is then to be returned to the destination PCC.

When data entry is completed, the participant will be assigned a new participant ID code. The initial letter will reflect the destination clinic, but the 7 random digits will remain the same.

8.19. Modified Participation

Over the length of the study, cases will occur in which endpoints are reached, participants withdraw from the study, or participation needs to be modified. Per the intent−to−treat principle, every effort must be made to follow each participant enrolled until the end of the study or death. For each Study A participant, the "end of the study" is defined as the F48 visit, or its "target visit date" if that visit is not completed. For Study B participants, the "end of the study" is defined as the F48 visit however; participants are being asked to continue in the study until the end of September, 2010. Table 14−1− Follow−Up after Primary Endpoints, Early Withdrawal or Modified Participation outlines procedures to be followed when a change in the level of participation occurs.

In order to continue on study medications, participants must agree to be followed at the PCC at least every six months. If participants do not agree to six−month follow−up visits at the PCC, study medications must be discontinued and participants asked to choose the intensity and frequency of follow−up to which they will consent. The coordinator must complete Modified Participation Form 28 to document the reason(s) for modified participation and the level of follow−up chosen by the participant. Study requirements for each level of follow−up may be found by referring to the Modified Follow−Up Due cheat sheet.

It is *strongly* recommended that the study coordinator obtain the participant's consent for modified follow−up (please see note below).

A Modified Participation Checklist has been developed that clearly indicates the options for modified participation from which participants may choose. *This checklist also serves to document the specific option for modified participation to which the participant has consented.*

* An IRB−approved consent form for modified participation may be required for some PCCs, and each study coordinator should check with her IRB to make this determination

For further information on modified participation, refer to Section 14.2 − Early Termination of Study Drugs or Follow−Up

Further information on modified participation may also be found in Section 8.5 − Study Cheat Sheets.

8.19.1. No Contact Policy

Occasionally sites have participants who, for whatever reason, do not contact the PCC for extended periods, despite coordinators' best efforts to reach them. For these situations, the study has adopted the policy that once a single visit has been missed, participants are given a period of 6 months of non−contact before considering them to have withdrawn their consent. Refer to section 14.2.2.1.

* Coordinators will make regular attempts to contact participants, at least biweekly, during the first month, either by phone, email, or U. S. Postal Service, and at least monthly during subsequent months.
* Toward the end of the six month period of no contact, thThe coordinator will send a certified letter to the

participant in a final attempt to contact and schedule a visit.

* If no response from the subject is received within 6 months of repeated efforts to contact them, the participant will be considered be “lost to follow up” and to have withdrawn consent to participate in the study.
* Modified Participation Form28 should then be completed, selecting the options 3a. “Participant has withdrawn consent, not otherwise specified” and 5d. "refuses all follow−up".
* The terms “lost to follow up” should be documented in the Form28 comments detailing the site’s attempts to contact the participant.
* The Form28 question 3M “Other” is not used to document a “lost to follow-up” participant.
* Once the participant has been modified as withdrawn, the coordinator should make no further attempts to contact the participant.
    * When filling out Form28 Q4 “drug stop dates” on the “lost to follow up” participants the drug use information is commonly unknown.
        * To document the drug stop date on withdrawn participants:
            - Use the most conservative date
            - Calculate the last known date which the participant was known to be using study drugs based on the amount of drug supplied at the last PCC visit.

8.19.2 . Reappearance of “Lost to Follow-up Participants

Occasionally, participants that have been modified due to “lost to follow-up” contact the site coordinator or re-appear showing a renewed interest to continue in the study. In May 2012, the HALT PKD Steering Committee approved the following management: Refer to Section 14.2.2.2.

- Any “lost to follow up” participant that contacts the PCC or re-appears requesting resumption of study involvement may re-modify back into study.
- Re-modification can only occur if the participant reappears *within one year from the date of initial “lost-to-follow-up” modification.*
- If re-modified, the PCC may reintroduce study medication as outlined on Table 13.

8.19.3. Study A and B Participants that Extend then Withdrawal

In the event a participant consents to study extension and later decides they no longer wish to continue in the study, the site coordinator will:

If no additional participation is desired, the participant is considered to have withdrawn from study participation.

- Offer the participant the option to modify study involvement to a lesser degree of participation
    - Complete Form 28 and identify level of participant follow-up desired
    - Complete Form 28 and indicate 3a. “Withdrawn”.

Note: A post closeout form is not applicable for those participants agreeing to the extension and then withdrawing prior to June 30, 2014. Refer to section 14.2.2.3.

Chapter 9. Blood Pressure (BP) Management

9.1. Standardized Procedures for BP Management

Maintaining separation between the standard and low blood pressure (BP) groups in HALT PKD is critical for studying the effects of BP control on cystic progression to be studied (Study A). Blood pressure will be monitored at home and at the PCC throughout the study. Home BP readings are to be used to guide medication increments/additions. The rationale behind using home BP readings for this purpose is that PCC BP readings are likely to be systematically higher and it may be logistically difficult to obtain more frequent PCC readings because of long distances some participants must travel to attend study visits.

Following the Baseline 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. If BP remains above target after three steps, the participant must be reassessed at the PCC.

Table 9−1. Overview of PCC and Home Blood Pressure Measurements

	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.

9.1.1. Participating Clinical Centers (PCC)

Standardized procedures, as outlined in the following subsections, are to be used to measure blood pressure at PCC study visits. Study coordinators are to train participants to use the same procedures at home as those used at the clinical centers, and an instruction sheet on proper placement of the BP device is to be distributed to study participants.

The participant's home BP measurement technique is to be evaluated at each clinic visit, with any necessary retraining documented by the study coordinator and kept on file at the PCC.

9.1.1.1. Arm for BP Measurements

The non−dominant arm (in terms of handedness) is to 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 BP of 20 mm Hg or more between both arms, the arm with the *higher* BP is to be used. In all other cases, the non−dominant arm will be used. Both office and home BPs are to be measured in the same arm

9.1.1.2. Sitting BP

After sitting quietly for at least 5 minutes, with feet on the floor, arm resting at heart level, 3 BP readings are to be obtained at least 30 seconds apart. Dose adjustments are to be made based on home BP readings. If home BP readings indicate that BP is controlled, but BPs taken at the PCC are above or below target, participants should be instructed to repeat the BP measurements at home the following day (refer to white−coat hypertension in section 9.1.3). A record of the BP values taken after the PCC visit are to be kept in the research chart but no data entry is required.

If the mean of the last 2 out of 3 readings in a single sitting is above the targeted range for either the systolic or diastolic readings for the respective study group, BP 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 are not to 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.

For more information on the minimum number of home BP readings to be obtained prior to a PCC visit and on when they should be repeated, please refer to Section 9.1.2.4 − Frequency of Home BP Measurements.

9.1.1.3. Standing BP

To ensure the safety of study participants, standing BPs are to be obtained at every PCC visit and compared with sitting BPs. The study coordinator is to take sitting BPs, as noted above in Section 9.1.1.2, with the average of the last two sitting systolic BPs used as the sitting systolic BP. The participant should then be asked to stand up, and the coordinator is to take the participant's BP again after 3 minutes. If the standing systolic BP drops by 20 mm Hg or more from the sitting systolic BP, consideration should be given to reducing study drugs, irrespective of symptoms

9.1.2. Home BP

Home BP readings are to be used to guide medication increments/additions, as BP readings taken at the PCC 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. To ensure BP control, home BP results are to be collected from participants at every study visit to monitor blood pressure. To ensure the desired goal of separation is achieved, home BP results (recorded over seven consecutive days in the month immediately prior to the visit) are to be collected from participants at or before each PCC visit and data−entered to allow the DCC to identify and track participants with 'out−of−range' BPs on a case−by−case basis. The official blood pressure, calculated at the time of data entry, will be used to dose adjust at PCC visits.

9.1.2.1. Home BP Monitor and Cuffs

Home BP is to be measured in a standardized fashion using an auto inflation electronic blood pressure device (LifeSource UA767P). These devices may be ordered with either small (UA767PVS), medium (UA767PV), or large cuffs (UA−767PVL), with selection of the appropriately−sized cuff being made based on arm circumference. The width of the bladder should be 40% and the length 80% of arm circumference. Each LifeSource BP cuff is marked with the proper fit range to indicate whether it is the appropriate size cuff for the participant's arm. A marker on the cuff also indicates where the brachial artery should be when placing the cuff.

The appropriate upper arm circumference for each size cuff has been listed below:

- Small – Upper arm circumference: 6.3-9.4 inches (16-24cm)
- Medium – Upper arm circumference: 9.4-14.2 inches (24-36 cm)
- Large – Upper arm circumference: 14.2 – 17.7 inches(36-45 cm)

Home BP monitors will be ordered and paid for centrally by the DCC. The DCC will order an initial supply of BP monitors and cuffs for delivery to each site prior to the beginning of the recruitment period. The BP devices will be shipped directly from the vendor to the PCC.

Study coordinators must place subsequent orders by contacting the DCC Program Manager, Patty Smith and placing an order. The request should include the quantity of devices to be ordered, cuff size, and justification as to why more devices are required. Shipping charges are incurred on orders less than $750, so please plan orders such that the study can avoid shipping charges. Once the order is submitted, the DCC will contact the PCC, if there are any questions, and will place the order, after which BV Medical will invoice the DCC.

The PCCs are responsible for supplying each participant with four AA batteries (1.5 volts each) to power his/her home BP unit.

Returns and exchanges may be handled by calling Lauren Liacone at BV Medical and requesting an R.A.# (return authorization number). Lauren's telephone number is 888−822−8293. Sites may want to consider exchanging just the cuff from each unit, as this is less expensive from a shipping standpoint.

- *BP Cuff Distributor*: Contact information for BV Medical is as follows: BV Medical 28 W 206 Commercial Avenue Arrington, IL 60010 Attn: Jim Resser (888) 822-8293
- *BP Cuff Manufacturer*: Lifesource – Steve Yesitis (Customer Service Manager) (800) 726-7099 (x-134)

9.1.2.2. Assignment of BP Monitor to Participants

At the Screening Visit (S), each participant is to be issued an auto inflation, electronic BP monitoring device (LifeSource UA767P) and instructed on how to use it. An instruction sheet on how to place the BP device properly is to be distributed to all study participants. Participants deemed ineligible to participate in the study prior to the B1 visit should be contacted by telephone and given instructions for mailing the machine back to the PCC.

9.1.2.3. Procedures for Home BP Measurements

At the Screening Visit (S) the study coordinator is to train the participant to take his/her own BP measurements at home. Participants should be instructed to sit quietly for at least 5 minutes, with the arm resting at heart level, and then obtain 3 BP readings at least 30 seconds apart. The average of 2nd and 3rd readings in a sitting will be the official reading for that sitting. If there is an unacceptable level of variability between the last two readings (>10 mm Hg difference in systolic or diastolic), participants are to record a 4th and 5th reading for that sitting and the average of the last 4 readings (2−5) will be the official reading for that sitting.

The participant should not take his/her BP immediately after awakening in the morning, due to BP surge. Rather, the participant should obtain BP measurements at least 30 minutes after awakening but before eating breakfast. Participants are also to be instructed to abstain from smoking and consuming caffeine for 30 minutes prior to taking BP measurements.

9.1.2.4. Frequency of Home BP Measurements

The frequency of BP measurements will differ at different stages of the study and should be obtained as noted below:

- ***During Washout Period***
  - *At least every other day*
- ***During Titration Period***
  - *At least every four days*
- ***Steady State for Duration of Study***
  - *At least monthly*

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

Each participant is to be given a BP log and instructed to record BP readings and the dates and times when the BP measurements were taken

After the BP target has been reached, anticipated by F4, participants are to measure BP at home twice daily for 7 consecutive days (i.e., 14 readings x 3 readings each sitting) during the month prior to a PCC visit. The official BP reading for the visit is defined as the average of the readings from the 7 consecutive days (the last 2 of 3, or the last 4 of 5) and is to be computed for each participant at the appropriate PCC visit. Blood pressure 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 10 home BP readings prior to the PCC visit, he/she must be asked to obtain and record home BP readings over 1 week (7 consecutive days) 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 is considered non−compliant if, in the month *after* the PCC visit, he/she does not obtain the minimum number (10) of readings over the course of 1 week.

If fewer than 10 home BP readings are recorded, home BP measurements must be repeated over 7 days within the month immediately following the PC visit, with dose adjustments made accordingly. Anytime home BP's are repeated for all seven days after the PCC visit, those measurements must be data-entered

PCCs can expect to receive phone calls from participants reporting extraneous BP readings during the follow up phase of the study. When treated subjects, who are otherwise asymptomatic and doing well, call their PCC with questions and random BP readings, which are not required for the study, no action should be taken by the PCC regarding changes in blood pressure medication.

9.1.2.5. Training

For more information on the required frequency of taking home BP measurements, to Table 9−6 − Blood Pressure Control over the Course of the Study

Participants are to be trained to measure BP at home using the same methods as those used at PCCs. Cuff placement must be emphasized − the bladder should be over the brachial artery (watch for medially−placed cuffs). The bladder of the home BP device is calibrated and will indicate to the participant whether it is too large or too small when it is put on. Additionally, a marker on the cuff will indicate to the participant where the brachial artery should be. An instruction sheet on proper placement of the BP device must be given to every participant.

9.1.2.6. Instructions for Participants

All HALT PKD participants must be trained and certified to measure and record their own blood pressure at home. Techniques and frequencies are included in the blood pressure training manual. A copy of the Participant Guide to Home Blood Pressure is to be given to each participant. Certification consists of a written test (10 of 12 questions must be answered correctly) and demonstration of technique per the calibration of home BP units. Specific instructions to be followed by participants in measuring home BP are listed below

1) Blood pressure is to be taken 30 minutes after waking in the morning, but before breakfast, and is to be taken before the evening meal.
2) Do not smoke or ingest caffeine for 30 minutes before measuring blood pressure
3) Sit quietly in a chair with back support. Arm should be bared and supported on a surface at heart level. Do not cross your legs or ankles. Relax and avoid talking while measuring your blood pressure.
4) Remove any constricting clothing and place cuff on bare arm.
5) Position the lower edge of cuff 1 inch above the bend of the elbow
6) Position the tube to the center of the arm in line with the middle finger
7) Rest for five minutes before measuring BP.
8) Press the start button.
9) Systolic (top number) and diastolic (bottom number) readings will be displayed
10) Record blood pressure as systolic pressure and diastolic pressure in home BP log
11) Wait at least 30 seconds and press the start button again.
12) Record the second systolic and diastolic pressure readings in home BP log.
13) Wait at least 30 seconds and for a third time press the start button.
14) Record the third systolic and diastolic pressure readings in home BP log.
15) If there is a difference of more than 10 mm Hg (systolic or diastolic) between the second and third readings within a single sitting, you will need to record a fourth and fifth reading at that sitting.
16) Record all BP readings for each sitting in the home BP log.
17) After stabilization, to determine whether or not to call the study coordinator based on BP level, calculate the average of the last 2 of 3 BP readings (or the last 4 of 5 readings if applicable). If either the systolic or diastolic average is out of the targeted range, call the study coordinator.

9.1.2.7. Home BP Data Collection Forms

During the washout period, participants are to record their blood pressure readings (taken at least every other day) on the Home Blood Pressure Form 12, which will later be entered into the database. In addition to recording home BP measurements, participants are also to be instructed to record the dates and times that the measurements were taken on Form 65. Participants should be instructed to bring the Home Blood Pressure Form12 with them to the baseline visit to allow the study coordinator to go over it with them. If necessary, the study coordinator can review the Home Blood Pressure Form12 with the participant by telephone prior to the baseline visit. Also at the baseline visit, study coordinators are to supply participants with two different forms (as described below) on which both routine and consecutive home blood pressure measurements are to be recorded.

Each participant must keep a blood pressure diary for recording routine blood pressure measurements subsequent to the baseline visit (at least every four days during titration, then at least weekly or monthly after stabilization). The study coordinator will review the BP diary with the participant, by telephone, every other week during titration and every three months after stabilization. The BP diary will be reviewed at the PCC if a three−month review coincides with a clinic visit. Participants with out−of−control BP are to be followed more frequently per study protocol. Each PCC will determine the method its participants use to record routine BP measurements and may elect to supply its participants with an empty notebook in which to record routine BP readings

☞ Routine home BP measurements that participants report to the PCC by phone are to be transcribed on to a form of the coordinator's choosing and stored in the participant's research chart. The Home Blood Pressure Form 12 may be used for this purpose.

☞ Home Blood Pressure Form12 is to be used for recording the consecutive home BP measurements (used for BP separation) taken twice daily over seven consecutive days within the month before a PCC visit (beginning with the F5 visit).

In addition to recording home BP measurements on the Home Blood Pressure Form12, participants should also be instructed to record the dates and times when the BP readings were taken. Ten is the minimum number of BP readings considered acceptable. The readings from the Home Blood Pressure Form12 must be entered into the database at or before each PCC visit.

For more information on the required frequency of taking home BP measurements, refer to Table 9−6 − Blood Pressure Control over the Course of the Study.

9.1.3. Discrepancy between Home and Office BP Readings

Study coordinators are to observe participants taking their own BP measurements during clinic visits. These participant−obtained measurements must then be compared with the BP measurements taken by the study coordinator during clinic visits. The following four situations may arise as a result of this procedure

- ◊ ***Improper Technique***
  - ⟐ Improper technique is implied when, using the same device, there is significant disagreement (per PI discretion) in the BP measurements between those taken at home by the participant and those taken in the clinic by the study coordinator. In this situation, the participant must be retrained and asked to obtain and record home BP readings over 1 week (7 consecutive days) within the month immediately *after* the PCC visit. The study coordinator is to follow up with the participant, with dose adjustments being made based on the average of the home BP measurements obtained *after* the PCC visit. These BP measurements must be data−entered.
- ◊ ***Home BP Monitor not Calibrated***
  - ⟐ If the home BP monitor is not calibrated, the participant is to be provided with a new BP monitor and asked to obtain and record home BP readings over 1 week (7 consecutive days) within the month immediately *after* the PCC visit. The study coordinator is to follow up with the participant, with dose adjustments being made based on the average of the home BP measurements obtained *after* the PCC visit. These BP measurements must be data−entered
- ◊ ***White−Coat Hypertension***
  - ⟐ If BP is controlled at home but higher than home readings and the targeted range when taken by the nurse in the clinic, the calibration of the home monitor needs to be checked. If this is not the explanation for discrepancies in readings, the participant's technique for taking BP with the home monitor needs to be reviewed. If self−measured BP in the clinic, using the participant's home monitor, is higher than the participant's 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. White coat hypertension is confirmed if the 24−hour ABP should show blood pressure readings similar to those reported by the participant using the home monitor and systematically lower than those taken in clinic. Results from 24−hour ABP monitoring must be retained in the participant's research chart. As an alternative to

24−hour ABP monitoring, the PI may ask the participant to obtain additional BP readings at home over the course of the following week, with the study coordinator following up to verify that BP is under control and in the targeted range

- If home BP readings taken the day after the PCC visit are in the range of those taken over the 7 days before the PCC visit, the participant is to be dosed accordingly, **OR**
- If a home BP readings taken the day after the PCC visit are in the range of those taken at the PCC visit , the participant is to be dosed accordingly and asked to repeat home BP readings over 7 days in the month after the PCC visit. These BP measurements must be data−entered

Home BP readings are considered the official BP reading in such participants, and titration of antihypertensives must be made on the basis of home readings and not office readings

- ***Non-Compliance***
  - Blood pressure controlled at home but high when taken by the nurse or self−measured in the clinic could be an indication of non−compliance. The PI may choose to verify cases of suspected non−compliance via 24−hour ABP monitoring. Results from 24−hour ABP monitoring must be retained in the participant's research chart. The participant may also be asked to obtain additional BP readings at home, with the study coordinator following up to verify that the participant is obtaining the requested readings and to verify that BP is under control and in the targeted range.

A participant suspected of being non−compliant is to continue taking home BP readings, with dose adjustments being made on the basis of those home readings. However, from the point that a participant is deemed non-compliant, the official BP readings used to gauge adequacy of control and titration of medications must be based on those obtained at the PCC.

If a participant is determined to be non-compliant, such non-compliance must be documented as a protocol violation. The decision to modify a participant due to home blood pressures not being provided at the time of the PCC visit is the decision of the Principal Investigator at each site. If the PI decides the safety of the participant is compromised, he/she will make the decision to modify the participant. The PI will review whether or not the other BP readings are available for their participant as well as the trends in BP readings to date.

9.2. BP Control

9.2.1. BP Targets and Acceptable Ranges

The range of blood pressure readings that will be accepted for the standard and low BP targets and ranges for Study A are as follows:

Table 9−2. Blood Pressure Targets and Acceptable Ranges for Study A

Study A	Target (mm Hg)	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

The BP target and range for Study B is as follows:

Table 9−3. Blood Pressure Target for Study B

Study B	Target (mm Hg)	Accepted Range (mm Hg)	
		Systolic	Diastolic
Standard BP Study Arm (All Study B)	</=130/80	110−130	80

9.2.2. Dose Adjustments

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.*

Half−step dosing is allowed for all open−label drugs, as deemed necessary by investigators. refer to Table 10−3: Protocol for Increase & Decrease of ACE+/−ARB

Therapy for Studies A & B in Section 10.3.6.1 − Protocol for Increases/Decreases in ACE−I+/−ARB Therapy

Refer to the cheat sheets, "Increase/Decrease Table" and "Suggested Dosing Guidelines" for further information on making dose adjustments.

9.2.2.1. Dose Adjustments in Study A

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

Table 9−4. Suggested Guidelines for Dosing in Study A − Standard BP Group

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 9−5. Suggested Guidelines for Dosing in Study A − Low BP Group

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 hypertension	Increase dose
95-100 mm Hg	>60 mm Hg	Maintain same dose

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 the BP is within the desired range

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.

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 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 also has 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

9.2.2.2. Dose Adjustments in Study B

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 will likely be rare.

9.2.3. BP Control over Course of Study

As summarized in Table 9.6 below, blood pressure will be measured *at least every other day* during the washout period, *at least every four days* during the titration period and *at least monthly* through the duration of the study. Table 9.6 also 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 targeted goals. If BP is below the accepted range, the prior step in the ordered Stepped Protocols for Addition of Antihypertensive Agents (Study A) is to be followed. If BP is too high, the subsequent step of the ordered protocol is to be followed

Table 9−6. 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	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 4 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
>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 above table 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	**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
Symptoms of hypotension: lightheadedness, fatigue, malaise **Symptoms of hypertension*:*** headache, blurred vision, malaise, fatigue						

9.2.3.1. Dose Adjustment for Out-of-Control BP

Drug Washout and Titration: During both the drug washout and titration periods, 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 should be instructed to increase the dose of labetalol (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. If the participant is unable to be assessed at the PCC within 24 hours, blood pressure will be managed with increased labetalol/Clonidine and/or other therapies other (other than ACE−I or ARB), to be directed by the PI with close follow−up over the telephone until the next study visit. For out of control BP during the titration period, participants should be instructed to call the PCC, so medication can be increased ahead of the next scheduled titration. During the titration phase (B1 to F4), if BP remains *above* the *targeted goal* but *less* than 140/90 mm Hg, doses will be titrated at two−week intervals until the BP target is reached or the study drugs are maximized

F4 to End of Study: 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 2 readings (>10 mm Hg difference in systolic or diastolic), participants are to record a 4th and 5th reading for that sitting and the average of the last 4 readings (2−5) will be the official reading for that sitting. 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.

9.2.3.2. Control During Study Drug Maximization

Study medications are to be initiated at the B2 visit, with the dose incremented every 2 weeks until the maximal dose is achieved − unless the participant is symptomatic of hypotension OR blood pressure is below the accepted, targeted range (standard BP group: 120−130/70−80 mm Hg or low BP group: 95−110/60−75 mm Hg [Study A]; and 110−130 mm Hg systolic/80 mm Hg diastolic [Study B]). At two−week intervals, the study coordinator is to contact the participant by telephone to review home blood pressure records from the prior two−week interval. If the participant is *not* symptomatic of hypotension AND blood pressure is *not* below the accepted, targeted range, as described above, the study coordinator may instruct the participant to increase the study drug. Adhering to this schedule, the study drug can be expected to be at maximum dose 8 weeks after randomization. Study coordinators need to instruct participants to monitor blood pressure *at least every four days* during the study drug titration period

9.2.4. 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:

- ⟐ lisinopril will be reduced by half (from 5 mg to 2.5 mg). If hypotension persists
- ⟐ lisinopril will be stopped. If hypotension persists
- ⟐ blinded study medication (telmisartan or placebo) will be stopped

For the first step (i), the participant should be instructed to cut the lisinopril tablet in half; or if the participant is unable to do this, 2.5 mg tablets may be sent by overnight mail

Management of Hypotensive Participants Whose BP Increases. It is assumed that BP in these hypotensive participants will increase over the course of the 4−6 year study. In such cases medications may be restarted, according to the below, assuming there are no contraindications

- ◊ If both lisinopril and blinded study medication (telmisartan or placebo) were stopped, blinded study medication should be restarted, according to the stepped medication protocol, if the participant's BP subsequently increases.
  - ⟐ If, after restarting blinded study medication, the participant's BP is still too high, lisinopril may also be restarted.
- ◊ If only lisinopril was stopped, it may be restarted if the participant's BP subsequently increases

9.3. Long−Term Management of BP

Participants are to be instructed to continue monitoring their BP at least once a month after targeted control has been achieved. Also, participants should be informed that the study coordinator will contact them by telephone every three months for the duration of the study to review their home BP log (Home Blood Pressure Form 12). Additional antihypertensive agents are to be added from the stepped protocols, as needed. The frequency of home BP monitoring and/or study visits may be increased, at the physician's discretion, for individuals whose BP is deemed out−of−control at any point in the study.

9.3.1. Lifestyle Measures for Improvement of BP

Coordinators should regularly counsel participants regarding lifestyle measures that improve BP control, as per guidelines of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure *(JNC−VII−2003)*. Participants should be instructed to reduce salt intake to less than 2.1 g (100 mmol)/day, and participants with a BMI >27 kg/m_2 should be provided with dietary instructions that promote weight loss. Participants should also be encouraged to participate in some form of exercise for at least 30 minutes on most days of the week.

9.3.2. Discontinuation of ACE−I +/−ARB

For information pertaining to the tapering of study drugs at withdrawal or closeout, refer to 10.3.6.2

9.4. Quality Control

9.4.1. 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.

Ascertainment of BP using A&D Calibration Test Meter (CTM) Connected to Home Monitor:

a) Unplug the cuff from the Home BP monitor
b) Plug the long end of the black hose from the CTM into the Home BP unit
c) Plug the cuff of the Home BP unit into the short end of the black hose
d) Place the blood pressure cuff onto the participant's arm
e) Press the start button of the CTM
f) Press the start button of the Home BP unit.
g) Let both devices perform the blood pressure measurement automatically
h) The measurement results will be presented automatically on the LCD display of each device. Compare the results. If the difference exceeds 2 mm Hg (systolic or diastolic), wait at least 30 seconds and re-measure.
i) If there is again a difference of 4 mm Hg or greater, the investigator may choose to replace the Home BP device and repeat the process.

If "Cuff Err" is displayed on the CTM, the inflation level was not high enough. You will need to inflate the Home BP unit to a higher level manually. For UA−767P with the last reading recall feature, PRESS AND HOLD the start button until reaching the desired pressure level (this replaces step 6 above).

Optional: Pressure reading using a Digimano 1000 [Model 2000 PS] (Netech, Hicksville, New York) monitor with Y−tube to connect cuff may be used per PI discretion:

1. Replace the CTM with the Digimano and allow the Digimano to warm up for at least two minutes before use.
2. Inflate the cuff on a dummy arm (Styrofoam cylinder or comparable object) and then observe the decline across instruments. If there is a difference of greater than 3 mm Hg between the two devices, repeat.
3. If there is again a difference of 3 mm Hg or greater, the investigator may choose to replace the Home BP device and repeat the calibration process.
4. The old device is to be returned to the vendor for recalibration or is to be discarded.

In September of 2012, Steve Yesitis and the LifeSource staff engineer indicated “the purpose of CTM (calibrated test meter) is to verify the accuracy of another UA-767P monitor. To reassure the monitor is working correctly and still accurate, we created the CTM which can be used to accomplish this goal. Basically, CTM is another blood pressure which is taking blood pressure measurement simultaneously with another device. We call this device, DUT (device under test). At the end of the measurement, if the DUT reports the result within the required window, we can conclude the DUT is behaving the same way as the CTM. That concludes the DUT is still accurate”.

9.4.1.1. Annual Calibration of Digimano

If the Digimano is to be used for optional calibration, it must be sent to the vendor, Netech, once each year to ensure it remains calibrated. The address for Netech is as follows:

◊ Netech Corporation 60 Bethpage Drive Hicksville, NY 11801 Telephone: 800−547−6557 Fax: 516−433−7458. Calibration information for the Digimano is to be maintained locally at each PCC and will be audited during site visits.

9.4.2. Calibration of PCC BP Monitor

Each PCC will use an auto−inflation electronic device (e.g., Dinamap) to obtain BP measurements from participants at office visits. During each clinic visit, BP measurements are to also be obtained using the participant's home BP monitor, which will itself be calibrated using the Calibration Test Meter (CTM), as described above in Section 9.4.1.

Although home BP is not actually calibrated to the Dinamap, these measurements, taken at nearly the same time, are considered adequate to allow for quality control of the correlation between the two devices. Measurements taken with the home BP monitor and calibration device do not need to be submitted to the DCC, but should be recorded locally (Form 36) and made available for audit.

Clinical sites are to calibrate the Dinamap device per each institution's policy. If the Dinamap measurements are found to be systematically different than those obtained with home BP devices, the Dinamap should be calibrated. It is recommended that the Dinamap be calibrated, at least, annually, or more frequently if the Dinamap is in heavy use or if the Dinamap is dropped.

9.4.3. PCC Staff

9.4.3.1. Training/Retraining

Study coordinators are trained according to the Blood Pressure Manual for HALT PKD. Training and certification cover the following topics: Clinical Site BP (PCC), Home BP, Training the Participant, BP

Targets/Control, Frequency, and Dose Modifications. The observer (trainee) must be trained and certified in the standardized procedures described in the BP training manual. The trainer must have been previously trained and certified in these procedures. In preparation for manual BP training, the observer (trainee) should study blood pressure technique prior to testing using the training CD, "Off the Cuff," produced by Blue Cross Blue Shield and endorsed by the Minnesota Medical Association, American Heart Association and the Minnesota Nurses Association. The CD takes approximately 2 hours to complete. The accuracy of the blood pressure measurement is to be verified by the trainer using a double stethoscope. The observer's reading needs to be within 4 points of the trainer's reading (systolic and diastolic).

9.4.3.2. Certification/Recertification

Study coordinators must be certified prior to initiation of the study and then recertified annually. Other personnel performing blood pressure measurements must be fully trained by a certified study coordinator per the Manual of Procedures. Certification consists of a written examination and two successful demonstrations of specific techniques while being observed by the trainer. The observer (and the trainer) must undergo annual competency testing in order to maintain certification. Annual recertification consists of a written examination and a single successful demonstration of techniques while being observed by a trainer.

9.4.3.3. Performance Evaluation

Method to be determined at a later date.

Chapter 10. Study Drugs

10.1. Supply of Study Drugs

Masked study medications (telmisartan [ARB] and placebo) are being provided to HALT PKD by the company Boehringer−Ingelheim Pharmaceuticals, Inc., with each individual PCC being responsible for procuring its own open−label antihypertensive agents (washout medication and those listed in the stepped protocols for addition of antihypertensive agents). HALT PKD is responsible for arranging packaging, labeling and distribution of masked study medications and has chosen the company Aptuit (formerly Quintiles Clinical Supplies) to provide these services. Aptuit will ship supplies of masked study medications (telmisartan and placebo) to each PCC at six−month intervals. The masked study medications are to be stored on−site, either at the research pharmacy or in a secure (locked) room within the site's HALT PKD office or clinic, and then distributed to participants per the procedures outlined in Section 10.3.3 − Masked Study Drug−Dispensing Telmisartan/Placebo.

10.2. Stepped Protocols for Addition of Antihypertensive Agents

10.2.1. Study A

Table 10−1. Protocol for Addition of Antihypertensive Agents in Study A

Steps	Treatment	Control
	Combination ACE-I/ARB	**Combination ACE-I/PLACEBO**
1-4	Lisinopril 5mg/Telemisartan 40mg Lisinopril 10mg/Telemisartan 40mg Lisinopril 20mg/Telemisartan 80mg	Lisinopril 5mg/Placebo 40mg Lisinopril 10mg/Placebo 40mg Lisinopril 20mg/Placebo 80mg Lisinopril 40mg/Placebo 80mg
5	Hydrochlorothiazide 12.5 mg qd*	Hydrochlorothiazide 12.5 mg qd*
6-8	Metoprolol 50mg BID Metoprolol 100mg BID Metoprolol 200 mg BID	Metoprolol 50mg BID Metoprolol 100mg BID Metoprolol 200 mg BID
9 & On	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

10.2.2. Study B

**For pediatric participants weighing <40 kg, hydrochlorothiazide should be reduced.*

Table 10−2. Protocol for Addition of Antihypertensive Agents in Study B

Steps	Treatment	Control
	Combination ACE-I/ARB	**Combination ACE-I/PLACEBO**
1-4	Lisinopril 5mg/Telemisartan 40mg Lisinopril 10mg/Telemisartan 40mg Lisinopril 20mg/Telemisartan 80mg Lisinopril 40mg/Telemisartan 80mg	Lisinopril 5mg/Placebo 40mg Lisinopril 10mg/Placebo 40mg Lisinopril 20mg/Placebo 80mg Lisinopril 40mg/Placebo 80mg
5-6	Furosemide 20mg BID Furosemide 40mg BID	Furosemide 20mg BID Furosemide 40mg BID
7-9	Metoprolol 50mg BID Metoprolol 100mg BID Metoprolol 200 mg BID	Metoprolol 50mg BID Metoprolol 100mg BID Metoprolol 200 mg BID
10 & On	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

Please refer to Section 10.3.6.1 − Protocol for Increases/Decreases in ACE−I+/−ARB Therapy for further information on increasing and decreasing medications.

You may also refer to the cheat sheets, entitled "Increase/Decrease Table" and "Suggested Dosing Guidelines" for further information

10.3. Study Drugs

Investigators, study coordinators and participants are blinded to the identity of the ARB (telmisartan)/placebo study drug in both Studies A and B. The dispensing pharmacy is also blinded to the identity of the ARB (telmisartan)/placebo in both studies. All other study medications are open−label drugs for approved uses.

Pediatric participants weighing >/=40 kg should receive adult doses of study medications. For pediatric participants weighing <40 kg, the only agent that needs to be reduced is hydrochlorothiazide, which is an open−label therapy.

10.3.1. Masked Study Drugs (Telmisartan/Placebo): Packaging, Labeling, Storage, Distribution

Masked study drugs will be packaged, labeled, stored and distributed by the company Aptuit, located in New Jersey. The study medications will be packaged in 32−count, double−foil, blistered drug cards containing either 40 mg tablets or 80 mg tablets of either telmisartan or placebo. Telmisartan and placebo drug cards will be intermixed and packaged in boxes (referred to as shippers) containing 100 cards of either 40 mg or 80 mg tablets. Each shipper measures 17 1/4" x 12" x 10 1/4" and contains 2 rows of 50 drug cards.

A double−panel label (each panel identical to the other), either in yellow (40 mg) or white (80 mg), will be affixed to each 32−count card. The unique drug card number will be imprinted on both panels, as will the name of the study and the dose strength of the study medication. Each double−panel label will also include dedicated space for writing in the participant's HALT−ID number and date on which the card is dispensed, and this information must be filled in on both panels at the time of dispensation. When a drug card is dispensed to a participant, one part of the label is to remain affixed to the card, while the other part is to be torn off, affixed to Drug Card Assignment Form 62, and then filed in the participant's research chart.

Once masked study drugs are packaged, they will be stored at Aptuit under controlled conditions, and Aptuit will ship supplies of masked drugs to PCCs at six−month intervals, as outlined below:

1. At six−month intervals each PCC must determine how much study medication (i.e., number of 32−count drug cards of 40 and 80 mg telmisartan and placebo) is needed for the upcoming six months and then communicate its needs to the DCC.
    - *It is imperative that the PCCs request new supplies of masked study medications at least 4−5 days before they are needed in order to give both the DCC and Aptuit adequate time to handle the request. Additional charges will be incurred by the study anytime Aptuit receives a request with a lead time of less than 2 days.*
2. Based on the information received from each PCC as to the quantity of study medication needed for the next six−month period, the DCC will communicate to Aptuit a specific range of drug card numbers it must send to each specific PCC.

PCCs are to store all study drugs according to institutional policies and manufacturers' guidelines. Masked study medication is to be stored within the acceptable temperature range of 59−86 degrees Fahrenheit. Damaged and extra drugs are to be destroyed according to local procedures after the DCC has been notified.

3. Aptuit will then ship boxes (each measuring 17 1/4" x 12" x 10 1/4") containing the specifically−assigned drug cards to the specific PCC to which the cards have been assigned.
4. The DCC maintains electronic records of the drug card numbers specifically assigned to each PCC. Based on these electronic records, the DCC will know what drug card numbers can be assigned to participants at each site.
5. When study medication needs to be dispensed to a participant, the study coordinator must generate Drug Card Assignment Form 62 in order to assign specific drug card numbers to that participant. The study coordinator is to then dispense the specifically−assigned drug cards to the specific participant, according to the policies in place at the specific site.

Drug Card Assignment Form 62 may be generated at the time of visit or date of action (whenever a change in medication occurs between study visits); or it may be generated prior to the visit, if necessary. Ideally, the form would be generated no more than one day before a visit; but if necessary, it can be generated up to one week before a visit.

If Drug Card Assignment Form 62 is generated in error or if Form 62 is generated for a visit that does not occur, please refer to Section 16.2.6.1 – Generating Masked Drug Card Numbers (last paragraph) and follow the procedures for resetting the status of drug cards

6. Sites will fax to the DCC a copy of the packaging slip for *each* order received from Aptuit.
7. As noted above, the participant's HALT−ID number and the date on which the card is dispensed must be filled in on both panels of the double−panel label at the time of dispensation. One part of the label must remain affixed to the card, while the other part must be torn off, affixed to Drug Card Assignment Form 62, and subsequently filed in the participant's research chart.

For more information on completing Drug Card Assignment Form 62, please refer to Drug Card Assignment Form Instructions.

EXPIRED DRUG: Aptuit will destroy expired drugs. Notify the DCC if you choose to have Aptuit destroy expired masked study medications.

10.3.1.1 – Drug Card Validation Prior to Dispensing Study Drug

In order to reduce the likelihood of dosing errors, a uniform procedure is to be followed when study drug cards or open label medications are to be dispensed to a participant.

The recommended procedure is designed to confirm drug cards numbers, prescribed dosage, participant subject ID and, for those drugs that will be shipped, confirmation of the participant's mailing address. A copy of all study prescriptions submitted to the pharmacy will be kept on file within the source document.

Refer to 10.3.4.3. Instructions for Participants, 10.3.4.3.1. Dosing Verification Procedure

Telmisartan/Placebo Drug Cards

* Prior to the drug cards being dispensed, all drug cards will go through a validation process where the coordinator and a qualified PCC staff person will complete a double check of all drug cards. It is recommended that the qualified staff include: HALT PKD coordinators and data entry staff or nursing staff employed at the site's research clinic.
* To prevent the inadvertent switching of participant drug cards, coordinators will review one participant's drug supply at a time—one set of drug cards on the bench/counter during the review.
* The coordinator will remove the drug cards from the pharmacy bag and confirm the investigator's prescribed order. The study drug dosage will be confirmed on each assigned drug card.
* The coordinator will read aloud the drug card number from the ticket attached to the card while the other staff person confirms that the number is the same as listed on the Form 62.
* The coordinator will read aloud the participant's subject ID number; the ID will be confirmed by the second staff person.
* The coordinator will then repeat this step with the second ticket. The second staff person will then confirm the number is correct before placing it on the Form 62. These steps will be repeated for each drug card dispensed to

the participant.

* If the drug cards are to be mailed, a review of the participant address will be completed confirming the most current and validating the address inscribed on the FedEx label.
* When the review is complete and the cards have been validated, the HALT PKD coordinator and the individual assisting in this process will sign the bottom of the Form 62.
* PCCs with Research Pharmacies distributing study drug to participants.
    - Pharmacy staff will confirm study drug card numbers, subject ID, and drug dose with the investigator's prescription. Once the double verification is completed the two pharmacy staff members will sign the bottom of Form 62.

Open Label Medications (Lisinopril and All Other Hypertensive Prescriptions)

* Coordinators will compare the investigator's prescription to the information listed on the drug bottle label.
* Two staff members will confirm the participant's name and ordered drug.
* Prescriptions that specify the dose and frequency will have those values confirmed. (Some prescriptions state "take as directed by HALT PKD staff".)
* The coordinator and staff member completing the verification will initial the lower right hand corner of each prescription.
* Coordinators will review all new medication directions with the participant.

10.3.2. Open-Label Study Drug (Lisinopril): Packaging and Shipping

The pharmaceutical company Merck is supplying HALT PKD with ACE−I (lisinopril) for the study. The 5, 10, 20 and 40 mg strengths were originally supplied to the study in 100−count bottles. However, as of October 2006, Merck will supply 5, 10, and 20 mg lisinopril in 90−count bottles. Merck has discontinued the 40 mg strength, so participants at that dose will need to take 2, 20 mg tablets. Lisinopril will be shipped to each site on an annual basis, and the HALT PKD Project Manager, will make the appropriate arrangements for this with Merck.

A packing slip will be enclosed in each box of lisinopril shipped by Merck. On receipt of a shipment, the study coordinator must fill in the packing slip with the lot numbers and expiration dates for the lisinopril in each box received. This information is found on the labels affixed to the bottles. In most cases all of the lisinopril in a box will have come from the same lot and will have the same expiration date. All packing slips must be faxed to the Project Manager (412) 586-9672 at the DCC. Merck Quarterly Reports

The HALT PKD Status Update Reports, or "Merck Quarterly Reports", were submitted to Merck by Emory University from 2006- February 2012. In August 2012, the DCC assumed the responsibility of completing the online submission of quarterly reports. The reports will be submitted electronically prior to the following target dates:

- **2012**
    - November 6
- **2013**
    - February 4
    - May 5
    - November 1
- **2014**
    - January 30
    - April 30
    - July 29
- **Final Report**
    - October 27

As of August 2012, the HALT PKD contact at MERCK is Lynn Bentz; Scientific Leadership & Research Manager, Global Center for Scientific Affairs | Office of the Chief Medical Officer, 351 N Sumneytown Pike, North Wales, PA 19454 (Mailstop 2CD-30); Phone: (267) 305-1716; Fax: (267) 305-6534, Email: lynn.bentz@merck.com

On July 3, 2012, the DCC received a letter of continued drug support from Bruce Brundage, Scientific Leadershop & Research Coordinator. The continued support was provided in response to the extension of the HALT PKD study until July 2014. He can be reached at (267) 305-2993, Email: bruce brundage@merck.com.

10.3.3. Masked Study Drug: Dispensing Telmisartan/Placebo

At the Baseline Visit (B1) each participant is to be dispensed 8, 40 mg drug cards, which should last until the next study visit (F5) at 4 months, regardless of the rate of dose escalation. The study coordinator will be notified by the DCC, electronically, of the specific drug cards to pull and dispense to a specific participant. Participants must be instructed **not** to begin taking ACE−I or masked study medications until the B2 visit. The B2 visit cannot take place until the results of the 2 serum creatinine samples drawn at the baseline visit (B1) become available from the central lab and it has been verified that the 2 samples fall within the defined range of <20% difference from each other. If the 2 samples do not fall within <20% difference from each other, they must be repeated.

To minimize waste, participants are to be instructed to use all tablets on a drug card before going on to the next card, even in the case of a dose increase. Thus, if a participant titrates up from a 40 mg dose of telmisartan or placebo to an 80 mg dose, but still has 40 mg tablets remaining in a drug card, the participant is to be instructed to take 2, 40 mg tablets until the 40 mg drug card is depleted. Once the 40 mg card has been depleted, the participant can begin taking tablets from the assigned 80 mg drug card. In the event of a dose reduction, however, the participant must be instructed to begin taking tablets from the 40 mg drug card immediately, even if all the tablets on an 80 mg card have not yet been taken.

Participants must be instructed to bring all of their drug cards with them to every PCC visit, including depleted cards, as the number of new drug cards assigned to the participant depends on the quantity needed after determining how much study medication remains from the previous visit. The study coordinator needs to confirm that the participant has brought all previously−dispensed drug cards along to the clinic visit and then, according to industry standards, destroy any depleted drug cards.

10.3.4. Initiation and Titration of Study Medications

Whenever study medication is dispensed to a participant (study visit or date of action), the study coordinator must complete Study Medication Form 63 and data−enter it within 3 business days. Form 63 is applicable to washout medications, ACE−I+/−ARB therapy, and open−label medications. The study coordinator must complete and data−enter Drug Card Assignment Form 62 to have telmisartan/placebo drug cards assigned (see Section 10.3.1).

10.3.4.1. Titration of Telmisartan/Placebo

Study medications for the titration period are to be prescribed to the participant at the B1 visit and initiated at the B2 visit. Only 40 mg drug cards of telmisartan or placebo are to be dispensed for the titration period, with participants titrating to the 80 mg strength being instructed to take 2, 40 mg tablets. The dose is to be incremented every two weeks until the maximal dose is achieved, unless the participant is symptomatic of hypotension OR blood pressure falls below the accepted level for the study (Study A: standard BP group 120/70 mm Hg or low BP group 95/60 mm Hg [Study A]; and 110−130 mm Hg systolic/80 mm Hg diastolic [Study B]). Adhering to the stepped protocols for addition of antihypertensive agents, blood pressure is expected to reach stabilization at the maximum dose by 8 weeks after randomization.

10.3.4.2. Lisinopril Titration Kits

Only the 5 mg and 20 mg strengths will be used during the titration period. Participants who titrate up from 5 mg to 10 mg should be instructed to take 2, 5 mg tablets. Similarly, participants titrating from 20 mg to 40 mg should be instructed to take 2, 20 mg tablets.

Each participant's titration kit should contain the following:

Lisinopril − 5 mg

3, 100−count bottles (90−count bottles once 100−count bottles run out.)

Lisinopril − 20 mg

2, 100−count bottles (90−count bottles once 100−count bottles run out.)

It is recognized that unopened bottles of lisinopril may need to be discarded when a participant titrates up to a higher dose. This is due to regulations that state that once a drug has been dispensed to a patient, it cannot be returned to inventory, even if it has not been opened. As the study has no way of knowing which participants will titrate to what doses, it was decided that each participant's titration kit will include the maximum amounts that may be needed.

Lower doses of study medications need to be available at each PCC for dispensation to participants who are intolerant of the starting dose.

For specific information on lower doses of study medications, please refer to Section 9.2.4 – Management of Hypotension.

10.3.4.3. Instructions for Participants

Participants must be instructed to take study medication in the morning and monitor blood pressure at least every four days during the study drug titration period. At two−week intervals, the study coordinator is to contact participants by telephone to review home blood pressure records from the prior two−week interval. As long as blood pressure has not fallen below the accepted range and symptoms of hypotension are not present, participants are to be instructed to increase the dose of study drug per the stepped protocol. For participants whose blood pressure is out of control or above the target for titration (>150/100 mm Hg) or who experience symptoms of hypertension, study medications may be incremented ahead of schedule, according to the appropriate stepped protocol (Study A or Study B). Again, participants titrating up to 80 mg tablets of telmisartan or placebo are to be instructed to take 2, 40 mg tablets during the titration period.

10.3.4.3.1. Dosing Verification Procedure

In order to reduce the likelihood of dosing errors, a uniform procedure is to be followed at every clinic and telephone visit in which either a new study medication is prescribed or the dose of an existing medication is changed. This procedure will assist the coordinator in determining whether the participant understands how much study medication is to be taken, and how often each study medication is to be taken.

Whenever participants are prescribed a new study medication, or the dose for an existing medication is changed, the study coordinator is to have the participant write down the name of the drug, the dose, and the frequency at which it is to be taken. The participant must then be asked to repeat the dosing instructions back to the study coordinator, just prior to the end of his/her visit, so the participant's understanding of his/her instructions can be verified. If the medication information is repeated incorrectly, the coordinator needs to clarify the instructions and then ask the participant to repeat the information back again. This procedure applies to all clinic and telephone visits.

10.3.4.4. Safety Samples

Serum potassium, creatinine, and BUN must be measured at the PCC, or at a local laboratory, one week after each specified dose increment. Results from outside laboratories must be faxed or communicated electronically to the PCC. For individuals currently taking Digoxin, levels must also be checked one week after each specified dose increment, with dose adjustments made, if necessary, per the discretion of the PI. Safety labs are **not** required if the dose is not increased.

Study A participants must have safety samples drawn after *every second dose increment*, expected at weeks 3 and 8 (L2 and L4). For Study B participants safety samples must be drawn after *every dose increment*, expected at weeks 1, 3, 5, and 8 (L1−L4). Safety samples must be collected no later than 14 days after the dose increment, and the investigator must review the 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, as well as on how quickly the dose is escalated, safety samples may be collected more frequently than the minimum required, per the discretion of the investigator.

10.3.4.5. Titration Blood Pressure Target

The target BP during the titration period (B2 to stabilization) is </=150/100 mm Hg. If BP remains above the accepted range for the study, but </=150/100 mm Hg, doses will be titrated at 2−week intervals until the target BP is reached or study drugs are maximized. It is anticipated that BP will be stabilized by the F4 visit, i.e., steadily controlled within the accepted range at the maximum dose tolerated for Study A (Standard BP: 120−130/70−80 mm Hg; Low BP: 95−110/60−75 mm Hg) or Study B (110−130/80 mm Hg). It should be noted that the titration period will continue until the F5 visit at Month 4 when the participant is seen at the PCC.

Doses should not be increased if: 1) BP falls below the lowest level within the accepted range for Study A (standard BP group 120/70 mm Hg; low BP group 95/60 mm Hg); or 2) the participant is symptomatic of hypotension (Studies A and B).

10.3.4.6. Shortened Titration of Study Medications for Participants with Difficult to Control Blood Pressure

For individuals with difficult−to−control blood pressure, study medications (ACE+/−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.

10.3.4.7. Drug Interaction of Telmisartan ; if Card Numbers are Generated in Error and Digoxin

Co administration of Telmisartan and Digoxin, both metabolized by the liver, can lead to an increase in the peak concentration of Digoxin by up to 50%. Thus, any participant taking Digoxin must have his/her Digoxin levels checked at baseline and according to the same schedule as that for obtaining the other safety labs (potassium, BUN, creatinine) during the eight−week titration period. Dose adjustments for Digoxin are to be made, if needed, per the investigator.

Digoxin levels should stabilize once a steady dose of telmisartan has been reached, anticipated by the final titration step. The L4 safety lab results should confirm stabilization of Digoxin levels, but continued testing will need to be arranged if levels continue to fluctuate. Once the titration period has ended, participants on Digoxin must have their levels checked every 6 months. In addition, whenever a participant's dose of telmisartan/placebo changes over the course of the study, Digoxin levels must be checked within one week of the dose adjustment.

10.3.5. Steady State

When a participant's blood pressure reaches the accepted range for the assigned study, he/she is considered to be in steady state. Participants taking an 80 mg dose of telmisartan or placebo in steady state should no longer take 2, 40 mg tablets, unless it is necessary to finish up any remaining tablets in a previously−assigned 40 mg drug card. During steady state, the DCC will assign 80 mg drug cards for participants taking that dose. Participants must be instructed to bring all study medications, including depleted drug cards, with them for each PCC visit.

10.3.6. Dose Modifications

Study drugs and additional antihypertensive agents are to be added in a stepped fashion according to the protocols for addition of antihypertensive agents shown in Section 10.2.1 (Study A) and Section 10.2.2 (Study B). Home blood pressure records from the prior two−week period are to be reviewed at each telephone visit, along with symptoms and lab results, to guide subsequent therapy. If blood pressure remains above the target after the study drug has been maximized (8 weeks), open−label therapies should then be added according to the appropriate stepped 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 a beta−blocker is contraindicated).

Please refer to Section 9.2.2 − Dose Adjustments for specific information on dose modifications in Study A and Study B.

10.3.6.1. Protocol for Increases/Decreases in ACE−I+/−ARB Therapy

Dose Increases

Increase drugs by a single whole step (e.g., 1 to 2).

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 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 also has 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.

Dose Decreases

Half−step reductions are allowed for all open−label drugs, as deemed necessary by investigators.

- ◊ Decrease open−label drugs by a whole step (e.g., 3 to 2) or a half step (e.g., 3 to 3a).
- ◊ If open−label drugs are being taken, decrease the drug most recently added.
- ◊ Do not reduce ACE+/−ARB therapy until all open−label drugs have been discontinued, unless the open−label drug is required for a non−BP indication.

Table 10−3. Protocol for Increase & Decrease of ACE+/−ARB Therapy for Studies A & B

Step	Treatment	Control
	Combination ACE-I/ARB	**Combination ACE-I/PLACEBO**
1	**Lisinopril 5mg/Telmisartan 40mg** 1-A. Lisinopril 2.5mg/Telmisartan, 40mg 1-B. Lisinopril 0mg/Telmisartan 40mg 1-C. Lisinopril 0mg/Telmisartan 0mg	**Lisinopril 5mg/Telmisartan 40mg** 1-A. Lisinopril 2.5mg/Placebo 40mg 1-B. Lisinopril 0mg/Placebo 40mg 1-C. Lisinopril 0mg/Placebo 0mg
2	**Lisinopril 10mg/Telmisartan 40mg** 2-A. Lisinopril 7.5mg /Telmisartan 40mg	**Lisinopril 10mg/Placebo 40mg** 2-A. Lisinopril 7.5mg /Placebo 40mg
3	**Lisinopril 20mg/Telmisartan 80mg** 3-A. Lisinopril 15mg /Telmisartan 80mg 3-B. Lisinopril 10mg /Telmisartan 80mg	**Lisinopril 20mg/Placebo 80mg** 3-A. Lisinopril 15mg /Placebo 80mg 3-B. Lisinopril 10mg /Placebo 80mg
4	**Lisinopril 40mg/Telmisartan 80mg** 4-A. Lisinopril 30mg /Telmisartan 80mg	**Lisinopril 40mg/Placebo 80mg** 4-A. Lisinopril 30mg /Placebo 80mg

Please refer to Section 9.2.2 − Dose Adjustments for further guidelines on increasing and decreasing medications.

You may also refer to the cheat sheets, entitled "Increase/Decrease Table" and "Suggested Dosing Guidelines" for further information.

10.3.6.2. Discontinuation of Study Drugs

Once the criteria to stop study drugs has been established (i.e. Study B endpoint or study closeout), the investigator will begin to taper the participant off of the telmisartan/placebo. The Investigator will determine the taper blood pressure goals for the participant and a reasonable level of BP surveillance. Conventional antihypertensive medications will be prescribed to control the participant's blood pressures during the taper. Study Coordinators will convey the changes in pharmacotherapy to the participant and provide instructions on how to monitor blood pressures (BP) during the tapering

The investigator may identify alternative therapies to manage blood pressures during the taper process. Investigators are encouraged to use their own discretion and prescribe appropriate antihypertensive medications based on the needs of the participant.

Drug Taper Protocol Recommended by the HALT PKD Blood Pressure Committee:

- The Investigator will provide the following orders to site coordinators:
    - Time point to begin study drug taper
    - Prescribed changes in antihypertensive medications (documenting medications, dose, and frequency etc.).
    - Target blood pressure goals and frequency of BP surveillance for participant during the tapering process.
    - Dictate a letter to the local physician (PCP/nephrologist) detailing the initiation of study drug taper and pharmacotherapy plan

All orders related to the drug taper are recorded in the participant's research chart with all other source documents. Investigator's name, date, medication changes, and the participant's reported blood pressure response will be recorded.

The Coordinators will:

- explain all changes in medication management to the participant
- provide a hard copy prescription to the participant or call in any changes to their local pharmacy.
- provide detailed instructions on blood pressure monitoring and the frequency of reporting the results to the PCC.
- convey the participant's reported blood pressure response to the new drug regime to the investigator and communicate any dose modifications back to the participant.
- assist the participant's with the transition of care to the local PCP/Nephrologist.
- Send the investigator's dictated letter regarding study drug taper to the local physician.

- Retain copies of all communication with the participant and local physician (PCP /nephrologist) in the research chart source document.

- It is recommended that participants begin their study drug taper on a Sunday. This permits investigators a full week to monitor blood pressure response to medication changes and recommend any necessary dose adjustments.
- The BP committee recommends participants take their BP three times per day, relaying results to coordinators every other day until target goals are achieved. It is up to the discretion of the investigator to establish the frequency and intensity of BP monitoring.
- The suggested BP target range for participants is ≤ 130/80.
- Participants will be directed to contact their study coordinator if blood pressure readings exceed 130/80 during the taper period.
- Once the participant's study drug is stopped, and BP readings are maintained within the identified goals established by the investigator, the participant's care may be transitioned to the local PCP/nephrologist.
- Documentation of email communication or phone conversations between coordinator and participant will be included in the research record.
- To facilitate the transition of care back to local physicians, the PI will dictate a letter summarizing the participant's status within the HALT PKD study. The letter should include the current pharmacotherapy plan. A copy of the PI letter to the local physician will be retained in the research record.
- Coordinators will educate participants in the importance of monitoring their blood pressures monthly on a life-long basis and will encourage the participant to convey any readings of concern to their local physician.
- All study drug cards and unused study medications must be returned to the site coordinator.
- Documentation of drug destruction will be maintained.

Tapering of Telmisartan/Placebo

- 80mg of Telmisartan/Placebo
  - At the onset of study drug taper, those participants on 80mg of telmisartan/placebo will decrease their dose to 40mg once daily.
  - Blood pressures will be reported and conventional antihypertensive therapies will be prescribed until the target goals for the participant are achieved.
  - Once blood pressure control is established, the 40mg dose will be discontinued. At the discretion of the investigator, blood pressures monitoring will continue and medications dose adjustments refined until target goals for participant are reached.
- 40mg of Telmisartan/Placebo
  - At the onset of study drug taper, those participants on 40mg of telmisartan/placebo will discontinue the study drug altogether.
  - Blood pressures will be reported and conventional antihypertensive therapies will be prescribed until the target goals for the participant are achieved.
  - At the discretion of the investigator blood pressures monitoring will continue and medications dose adjustments refined until target goals for participant are reached.

10.3.7. Procedure for Unmasking Study Drugs

Participants are to be unmasked only in cases of such severe medical concern that unmasking is determined to be warranted by the PI, and unmasking cannot take place without the permission of the PI. For each PCC, only the PI and persons named by him or her will be given access to unmasking information. To unmask a participant's treatment arm assignment, the PI or his or her designee must complete Unmasking Drug Form 26 and submit it to the DCC via data−entry.

For complete information on modified participation in HALT PKD, please refer to Section 8.18 − Modified Participation.

10.3.7.1. Pregnancy

In the event that a participant becomes pregnant while on study, medications must be discontinued immediately and the pregnant woman referred to her primary care physician for management of the pregnancy and hypertension. ACE−I is harmful to the fetus in the second and third trimesters; but with B−hCG screening in women at baseline and in women who miss regular menstrual cycles, all pregnant participants should be identified within the first trimester, minimizing teratogenicity.

Should the woman and her doctor decide to unmask study medications (ARB versus placebo), the study arm assignment is to be unmasked upon receipt of written permission from the PI. All pregnancies must be reported on the Symptoms Checklist (Form 5 − 5b).

For complete procedures regarding pregnancy in HALT PKD, please refer to Section 8.9.5 − Pregnancy.

10.3.7.2. Emergency Unmasking

In the event that a PI deems unmasking necessary but the web data entry system (WDES) is either not accessible or not functional, persons authorized to unmask treatment arms should call Charity Moore (412) 246-6961; Kaleab Abebe (412) 246-6931. If neither are available, please call Patty Smith (412) 692-2490.

If it is after hours and a true emergency, Call Charity Moore at (803) 240-6777, Kaleab Abebe (412) 973-7018.

10.4. Open−Label Study Drugs

All study drugs, with the exception of ARB/placebo, are open−label medications (see Section 10.2.1 [Study A] and Section 10.2.2 [Study B]). If blood pressure remains or rises above target after study drugs are maximized (8 weeks), open−label therapies are to be added according to the appropriate study 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).

Pediatric participants weighing >/=40 kg should receive adult doses of study medications. For pediatric participants weighing <40 kg, the only agent that needs to be reduced is hydrochlorothiazide, which is an open−label therapy.

Half−step dosing is allowed for all open−label drugs, as deemed necessary by investigators. Please refer to Table 10−3: Protocol for Increase & Decrease of ACE+/−ARB Therapy for Studies A & B in Section 10.3.6.1 − Protocol for Increases/Decreases in ACE−I+/−ARB Therapy.

10.4.1. Dispensing Open−Label Study Drugs

Each PCC will develop its own protocol for dispensing open−label drugs to its participants. Most sites will utilize the services of their research pharmacy for dispensing open−label drugs. However, some sites will obtain their own open−label drugs and store them on−site in a secure (locked) room, with the study coordinator being responsible for dispensing the drugs to participants.

10.4.2. BP Drugs taken for Non−BP Indications

Individuals currently on a BP drug for a non−hypertensive indication, including those on a ***small dose*** of beta blocker or calcium channel blocker, will be allowed to enroll in the study. Individuals on a **large dose** of beta blocker or calcium channel blocker must **not** be enrolled. When a participant on a "relatively small dose" of a beta or calcium channel blocker is enrolled, this information is to be recorded on Enrollment Form 10 by checking "yes" for the exclusion and then checking the box to indicate "approved by PI".

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.

All BP drugs taken for non−BP indications are to be recorded on Concomitant Medications Form 6 and data−entered. The WDES will be set up to flag whether these medications were preexisting or were started after the start of washout.

The Quality Control Committee will follow cases of BP drugs being taken for non−BP indications, though it should be noted that study medication may not necessarily have to be stopped. A computer routine will be set up to flag whether these medications were preexisting or began after the start of washout, and this information will be communicated to the QC Committee in its monthly report.

10.5. Management of Side Effects

Table 10−4 below outlines procedures for managing anticipated adverse effects from study drugs. Specifically, investigators are to manage hyperkalemia and increases in serum creatinine per these procedures, which reflect current standards for clinical care. 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, unless they are due to an overt and clearly reversible issue as determined by the study investigator.

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 10−4. Standard measures will be used to control potassium, including dietary modifications and/or use of furosemide and/or use of exchange resins (sodium polystyrene sulfonate). Diet would always be the first step, but the PI has the option (but not the requirement) to use more than

one measure. If necessary, the participant may be sent to a local ER, to be decided by the PI.

The rapid time frame for treatment is related to turnaround time for repeat testing. If a participant is local, potassium could be repeated quickly. However, if the participant is not local, repeat testing could take too long.

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 unnecessary, at the discretion of the PI, in cases, such as participants who 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.

Table 10−4. Management of Adverse Effects of Medications

Event	Definition	Response	No Response to Prior
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.
Hyperkalemia (PCC to manage)	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 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.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.

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).

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.

10.6. Pill Counts

Participants are to be instructed to bring their study medications, including all depleted drug cards (masked study medication), with them to every PCC visit for the purpose of tracking compliance. The number of new drug cards assigned to the participant is dependent on the quantity of new medication needed after determining how many tablets remain on the card(s) dispensed at the last visit. In addition, each PCC is responsible for tracking quantities of open−label study medications to ensure that participants are taking their medications as directed.

10.7. Destruction of Study Medications

Damaged and extra study drugs are to be destroyed according to local procedures after the DCC has been notified. Empty drug cards (i.e., all tablets on card have been taken) returned by participants may also be destroyed according to local procedures.

Chapter 11. Laboratory Procedures

11.1. Overview of Samples

Blood and urine samples are to be collected, processed and analyzed at participating clinical sites (PCCs), Quest Labs, local (hometown) labs, and central laboratories (Cleveland Clinic Foundation [CCF] Additional samples are to be collected and shipped to NIDDK Repositories at Rutgers University and Fisher BioServices. Details regarding collection, handling and shipment of each sample type are provided in subsequent sections.

11.1.1. Required Lab Assessments

Below is a list of all samples being collected for the study:

1. **Serum Creatinine** − PCC lab runs at the Screening visit; send all others to CCF. Collect two samples, one hour apart, at Baseline and F5 visits. Collect one sample at subsequent visits. Quest labs may be utilized to draw confirmatory samples for endpoint determination.

Please refer to Section 8.13.9.1 - Central Serum Creatinine Management, Section 11.3.3 – Hometown Labs and Section 11.3.3.4 – Obtaining Serum Samples for Central Analysis of Creatinine for details.

2. **CBC** − Complete blood count with platelets.
3. **Total Electrolyte Panel** − Sodium, potassium, chloride, total carbon dioxide, BUN.
4. **Partial Electrolyte Panel** − Safety Labs run at the PCC or a local lab during titration (potassium, BUN, creatinine), or at any other time per PI discretion or if GFR <30 (potassium and creatinine).
5. **Transaminases** − AST/SGOT and ALT/SGPT.
6. **Other Blood Tests** − Total bilirubin, alkaline phosphatase, albumin, calcium, phosphorus, glucose.
7. **Digoxin Levels**, required for any participant taking Digoxin.
8. **Urine Tests** − Random/spot urine (microalbumin, creatinine), B−HCG qualitative urine pregnancy test.
9. **24−Hour Urine Samples** − Send aliquots to CCF central lab for aldosterone, sodium, potassium, creatinine and microalbumin measurements. CCF will receive aliquots of 24 hour urine specimens and analyze samoles for urine aldosterone and the following urine chemistries: Sodium, potassium, creatinine and microalbumin.

10. **Genetic Sample** − Send whole blood to Genetic Repository (Rutgers).
11. **Specimen Banking** − Send serum, plasma and urine (freshly voided and 24−hour collection) to Biorepository (Fisher BioServices).

11.1.1.1. Definitions and Schedules of Assessments

A complete definition of assessments and a two−part schedule for collecting assessments at screening, baseline and follow−up visits, have been developed and are listed below.

- Definitions of Assessments
- Schedule of Assessments − PS−F5 Visits
- Schedule of Assessments − Following F5 Visit

11.1.1.2. Additional Safety Lab Visits

Safety samples must be collected at minimum intervals as specified above. However, depending on the participant's baseline potassium and kidney function and how quickly the dose is escalated, additional safety samples may be collected more frequently than the minimum required at the discretion of the investigator. At any time during the trial, if the investigator orders additional safety labs, or additional test results become known to the PCC, serum creatinine and potassium values are to be data-entered as an X visit, via Required Safety Lab Results Form 51, within two weeks of sample collection.

Whenever a participant's GFR (based on central serum creatinine results) drops below 30 mls/min/1.73m$_2$, participants should have more frequent follow−up visits with their primary nephrologist than every 6 months (the HALT study visit frequency). For these participants, the study requires additional safety testing (serum creatinine and potassium) at 3−month intervals, and the results are to be data−entered as an XF visit, via Required Safety Lab Results Form 51, within two weeks.

Participants taking Digoxin must have these levels tested at the B1 visit, with required safety labs, every six months thereafter, and 1 week after changes in ARB/plabeco.

11.1.2. Supplies for Sample Collection and Shipment − N/A−no longer in use

PCCs are to provide all materials necessary for venipuncture and urine collection. For samples being sent to NIDDK Repositories, collection tubes for all blood samples and cryovials and specimen boxes for urine samples will be supplied by NIDDK. PCCs are responsible for obtaining storage tubes for samples shipped to central labs (CCF and DLF), as well as for obtaining shipping materials for samples sent to BMCF. NIDDK will provide the necessary shipping materials for samples being sent to Rutgers and Fisher BioServices. *Each study coordinator must create an account on the FedEx website in order to create airbills online and then print them. One central account number is being used for both CCF and BMCF (the DCC is the payer). A separate central account number is being used for each Repository (NIDDK is the payer).*

Any necessary FedEx supplies should be ordered online by the study coordinator. FedEx airbills do not need to be ordered, as they will be completed online and printed. However, plastic pouches will need to be ordered through FedEx Ship Manager, as printed airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

11.1.3. Sample Collection

All samples are to be collected per specific instructions outlined in the sections below. A random 10% of all central serum creatinine, urine aldosterone, and urine chemistry samples each require an additional sample for quality control. All samples for central lab analysis require that an additional back−up sample, taken from the original collection sample, be stored at the PCC until test results are available. Whenever possible, 24−hour urine samples are to be collected at a GCRC. If no GCRC is available, participants should be instructed to collect their urine per written instructions provided them by the PCC. Form 37 (24−Hour Urine Checklist) is to be completed for every 24−hour urine sample collected and is to be stored in the participant's research chart.

11.1.4. Labeling

Coordinators are to print labels and shipping manifests, along with the necessary data collection forms, prior to each PCC visit. Each sample has a unique 8−digit accession number assigned to it and numeric/barcode labels will be generated for it. One label is to be placed on the sample tube and a duplicate label is to be placed on the sample collection form. For central lab samples, accession numbers with the suffix "A" are to be attached to the original sample (to be sent to the lab), and suffix "B" labels are to be placed on back−up samples (stored at the PCC until results are available). For repository samples, there is no distinction between labels.

Labels should, ideally, be generated the day before a visit or date of action and no more than 1 week, at most, before a visit or date of action.

11.1.4.1. Instructions for Printing Labels from the Web Data Entry System (WDES)

1. Properly place the appropriate label sheet(s) in a laser printer.
2. From the Forms Portal, select "Forms Generation."
3. Select the HALT PKD ID, HALT PKD VISIT and the EFFECTIVE DATE at the top of the page.
4. Select generate forms packet
5. Select print labels.

11.1.4.2. Using Appropriate Labels for Sample Tubes and Collection Forms

Refer to the sample label key to determine how each label is be used. Note that the key does not show labels for quality control samples, (required for 3% of all samples sent to a central lab). All labels for each sample are printed together. The first in the series is to be affixed to the sample collection form. For samples sent to central labs (serum creatinine, urine chemistry and aldosterone), there is no suffix attached to the accession number on the first label. For repository samples, the suffix is the same for all labels. Subsequent labels within a series are to be affixed to the actual sample tubes. For central lab samples, accession numbers with the suffix "A" are to be attached to the original sample (to be sent to the lab), and suffix "B" labels are to be placed on back−up samples (to be stored at the site until results are available). For repository samples, there is no distinction between labels.

11.1.4.3. Proper Placement of Labels on Forms and Tubes

Make sure that each label placed on the collection form is for the appropriate sample. Do not mix up labels for serum and plasma, for example. When placing labels on sample tubes, align the barcode along the length of the tube and be sure to leave space through which the sample level may be seen along the entire length of the tube. This is especially important for genetic samples. Write the date of collection on each sample tube. Do not write any personally identifying information on the tube.

For additional information on labels, please refer to the following cheat sheets: Labels for Sample Collection and Sample Label Key (color−coded).

11.1.5. Data Entry

Study coordinators at each PCC are to enter HALT PKD Visit Schedule Form 40 prior to entering visit data. For each date, list all participant ID codes and corresponding visit codes. The "date of the visit" is defined as the date of the first study procedure or participant contact.

Required Lab Results Form 9 is to be entered within three business days of sample collection at the L1−L4 visits (safety labs), and within two weeks of sample collection at all subsequent PCC visits. PCCs are to forward their ranges of normal lab values to the DCC annually and forward any updates as they occur. The ranges will be entered into the database and will automatically determine which values entered on Required Lab Results Form 9 are considered abnormal at that institution. Whenever an abnormal value is entered, the "abnormal" box should be checked in order to avoid a query. As of September 2012, the DCC will be completing internal reviews evaluating the timeliness of data entry of all forms generated during the participant's visit. Forms not entered within the two week timeframe are considered a protocol violation.

Sample Collection Forms 16−19 are to be entered within two weeks of sample collection at all PCC visits.

- Form16 − Urine Sample Collection Form
- Form17 −Genetic Sample Collection Form
- Form18 − Archived Blood Sample Collection Form
- Form19 − Central Serum Creatinine Collection Form

At any time during the study, Required Safety Lab Results Form 51 is to be entered within two weeks of additional safety labs (serum potassium and creatinine) being collected. Safety lab results should be entered in any of the following three situations:

- Additional safety labs are ordered per the PI's discretion.
- Additional safety labs are required at three−month intervals because the participant's GFR dropped below 30.
- The PCC becomes aware of creatinine or potassium lab results at any time during the study.
- Digoxin levels are required (e.g., if there is a dose modification of masked drug in a participant taking digoxin).

11.1.6. Sample Storage and Shipment

Samples are to be either shipped to the appropriate lab or repository on the day of collection (e.g., central serum creatinine collected at B1 and F5 visits and all NIDDK blood samples) or stored at the collection site (frozen at −20 degrees Celsius or colder) and batch−shipped to the appropriate lab or repository (within four months for all samples, except for serum creatinine samples, which are to be shipped every two weeks). Samples designated for the NIDDK Biosample Repository at Fisher BioServices are to be stored in specimen boxes provided by the Repository. PCCs may wish to purchase similar specimen boxes in which to store the urine samples, but this is not required.

Information on all samples destined for central labs or repositories is to be manually entered onto shipping manifests, which are to be stored in sample log books at the PCC. A shipping manifest must accompany every sample shipment from the PCC. To facilitate rapid verification at PCCs, central labs and repositories, samples should be stored in such a way as to reflect the order in which they have been listed on shipping manifests. Shipping manifests are to be stored chronologically, stapled in sequential order, and numbered "page__of " within a shipment. Coordinators are encouraged to list cell locations on shipping manifests for further clarification.

- Shipping Manifest − Cleveland Clinic Central Lab
- Shipping Manifest − Repository−Genetic Sample
- Shipping Manifest − Repository−Serum/Plasma Samples
- Shipping Manifest − Repository−Urine Samples

Central labs and repositories will confirm receipt of each sample shipment via e−mail to the appropriate PCC. Any problems with shipments will be reported to the PCC via secure website.

Copies of all shipping manifests must remain at the site for auditing purposes.

For shipping manifest requirements specific to Repository−Serum/Plasma Samples and Repository −Urine Samples, please refer to Section 11.6.2.6 − Serum/Plasma Shipping Manifests and Section 11.6.3.6 − Urine Shipping Manifests

11.1.6.1. FedEx Ship Manager − N/A−no longer in use

The FedEx online system is being used to ship all HALT PKD samples to central labs and repositories. Using the online system, the study coordinator can create and print airbills quickly and easily. In addition, airbills can be set up to e−mail the recipient (i.e., central labs and repositories) when a shipment is sent, email the coordinator when a shipment has been delivered, and also email the shipment and delivery information to the DCC.

To view a demo of the Fedex Ship Manager, go to the FedEx Demo page and click on "CLICK HERE TO VIEW DEMO"

Opening a FedEx Ship Manager Account − N/A−no longer in use. *To use the free FedEx Ship Manager, each coordinator must open an account by navigating to the FedEx home page (http://www.fedex.com/us) in a browser and then clicking on "open an account" at left.*

- It is not possible for the coordinators to set up their accounts using the DCC FedEx account number due to the PCCs and the DCC having addresses in different cities. Thus, each coordinator will need to set up an account by using either her own institutional FedEx number or by creating a new account. If there is already an account set up for the institution, it is recommended that this account be used, as this will allow the coordinator, if desired, to use the FedEx Ship Manager to utilize the service for sending items unrelated to HALT PKD.

Including Required Information for HALT PKD − FedEx Manager can no longer be accessed using the DCC (UPitt) FedEx account #. It is *imperative* that the following three items be included in the "Billing Details" section of each airbill. This enables FedEx to bill the Division of Biostatistics and enables Biostatistics to differentiate FedEx invoices for HALT PKD from those associated with other projects.

1. Field: "Bill transportation to" − Select "Third Party"
2. Field: "Recipient/third party account #"−
   a) For Central Lab samples (CCF and BMCF): Enter the DCC's FedEx account number: *165309723*
   b) For NIDDK Biosample Repository: Enter Fisher BioServices' FedEx account number: 282009021 − *N/A−no longer in use.*
   c) For NIDDK Genetics Repository: Enter Rutger's FedEx account number: 276870645−*N/A−no longer in use.*

3. Field:" *Double Data Entry"* − Enter "HALT PKD."

It is also *imperative* that the following notification information be included in the "FedEx Ship Alert" section of each airbill.

1. **Recipient:** The e−mail address for the applicable central lab or repository must be entered and the "Shipment Notification" box checked. This alerts the lab or repository that a shipment is on its way; and if the shipment is not received within the appropriate timeframe, the lab or repository will know to begin tracking the shipment.
2. **Sender:** Each coordinator should enter her own e−mail address and check the "Delivery Notification" box. This will confirm to the coordinator that a shipment has been delivered. If the coordinator does not receive the confirmation within the appropriate timeframe, she will know she know to begin tracking the shipment.
3. **Other:** The e−mail address for the DCC must be entered and both the "Shipment Notification" and "Delivery Notification" boxes checked. This will assist the DCC in verifying that billing is correct and will also allow the DCC to assist the PCCs, labs and repositories in tracking shipments.

Managing the FedEx Ship Manager Account − N/A−no longer in use.

My FedEx Home

- ◊ Once your account has been created and you are logged in, you should be on your "My FedEx Home" page. From this page you will be able to manage your FedEx Ship Manager account, as well as track the current status of all of your shipments. Click on the "Preferences" link to define the options you want to display on your personal FedEx page.

Fast Ship Profiles

- ◊ Each coordinator should prepare fast ship profiles for each entity to which shipments will be sent, as all shipment information, including billing details, service type, packaging, weight, and e−mail notifications, is saved in each Fast Ship Profile. Thus, the coordinator needs to enter shipping information for the central labs and the repositories only once, at the time of the first shipment. Shipping profiles are then saved for use in subsequent shipments and may be edited as needed.
- ◊ A Fast Ship Profile can easily be created at the time the coordinator is preparing her first shipment of samples to a particular lab or repository. Once the appropriate "Recipient" information has been entered, simply check the boxes next to "Save in/update my address book" and "Add to my Fast Ship profiles."

☞ PCC personnel are responsible for verifying information for each shipment (e.g., indicate if dry ice is included.

Preparing Shipments Online

From "My FedEx Home", hover your mouse over "Ship" and a menu of choices will be displayed. Click on "Prepare Shipment Online". This link will take you to the "Ship" page, which contains a blank airbill. You will see the following tabs at the top of the page:

- ◊ **Ship** − Brings up a blank airbill. First, click on the arrow next to the "Company name" drop−down box and choose from "Add a new company name," "Use a Fast Ship profile," or "Ship to a group." Once you have made some entries in your address book, these will also appear as choices in the "Company name" drop−down box.
- ◊ **Track/History** − Displays a shipping history covering the past 45 days, and shipments currently in transit can be tracked from this page.
- ◊ **Address Book** − Provides access to stored addresses. New entries can be entered on the Address Book page, and existing entries can be edited.
- ◊ **Preferences** − Click on this tab to select default settings for your airbills. You may choose to include the required HALT PKD information, described above, as default settings for your airbills.
- ◊ **Fast Ship** − Provides access to stored Fast Ship profiles. New entries can be created on this page, and existing entries can be edited. Select an entry and then click on "Review Shipment" to pull up a shipping profile. If the shipping information is correct, click on "Ship" at bottom right to generate a FedEx airbill for printing. If the shipping information needs to be updated, go back to your Fast Ship profiles and edit the appropriate entry.
- ◊ **Reports** − Reports for any shipment that has been processed using FedEx Ship Manager within 45 days may be created and printed from this page.
- ◊ **My Profile** − Personal account information can be updated on this page.

FedEx Supplies:

- ◊ FedEx airbills do not need to be ordered, as they will be created online and then printed. However, it will be necessary for the study coordinator to order the FedEx plastic pouches in which a printed airbill is inserted and then affixed to the box being shipped. Alternatively, the study coordinator may wish to order the FedEx adhesive labels. FedEx supplies are free and may be ordered on line.

11.1.7. Lab Results Reporting

The DCC will send spreadsheets to all central labs and repositories that list all sample accession codes to be accounted for. The central lab, CCF will review these spreadsheets and report test results to the DCC. Study coordinators will receive e−mail notification from the DCC once test results are available. Of the test results reported by the central labs, only serum creatinine values are of clinical significance. At baseline, serum creatinine results must show a difference of 20% or less before the start of ACE +/− ARB therapy (if >20%, both samples must be repeated). Similarly, the two serum creatinine samples collected at the F5 visit must be within 20% of each other or be repeated within two weeks. Test results will not be reported by the NIDDK Repositories. Sites will not be informed of the urine aldosterone or urine chemistry results. These results will be used for research purposed only. QC sample results processed at CCF will be reviewed during the monthly Quality Control Committee conference calls.

For all PCC lab results reported on Required Lab Results Form 9 or Required Safety Lab Results Form 51, the PI and study coordinator will be alerted by e−mail whenever an abnormal PCC lab value has been entered into the database without the abnormal checkbox having been selected on the form. Safety alert values for serum creatinine and potassium (as defined per Table 10.3) will be flagged as clinically significant and/or concerning.

11.1.8. Informing Participants of Lab Results

Participants are to be informed of the following test results, as well as of any other clinical findings of particular concern. PCCs must communicate the following abnormalities to participants and encourage them to inform their PCP and/or nephrologist. If authorized by the participant, the PCC may also forward information on the following to the participant's PCP and/or nephrologist:

A. Acute, potentially life−threatening issues (to be managed by the PCC per Table 10.4 − Management of Adverse Effects of Medication).

a. Hyperkalemia (Serum Potassium is >5.6 mEq/l)

b. Hyperkalemia (Serum Potassium is >6.0 mEq/l).

Potassium values between 5.6−6.5 mEq/l are to be considered as concerning adverse events and must be data entered via Required Safety Lab Results Form 51 within two weeks of sample collection. Potassium values >6.5 mEq/l are reportable serious adverse events.

c. Rise in Serum Creatinine of.

a. >/=30% or 1 mg/dl within the first 12 weeks of ACE+/–ARB therapy.

b. >/=30% from most recent value (within 6 months) after the first 12 weeks of AC therapy.

Creatinine values increasing 30% over baseline, or doubling over baseline >12 weeks after the start of ACE +/− ARB therapy, are considered concerning adverse events and are to be data entered via Required Safety Lab Results Form 51 within two weeks of collection. Creatinine values doubling over baseline within 12 weeks collection. Creatinine values doubling over baseline within 12 weeks of the start of ACE +/− ARB therapy are reportable serious adverse events.

c. >/=100% of the baseline average any time after the start of ACE+/−ARB therapy.

B. Non−acute issues to be handled by the PCP and/or nephrologist:

a. Referral to nephrologist for patients with GFR <30 mls/min if they don't already have one; need creatinine and potassium every 3 months.

b. Phosphate is >5.5 mg/dl.

c. Total Calcium is <8.0, or Calcium is >10.5 mg/dl Hematocrit <33%.

d. Abnormal LFTs (screening only).

e. Elevated fasting glucose >126 mg/dl (screening only).

f. Any other lab result, physical exam finding or diagnostic imaging finding that requires further

Guidelines for informing participants of safety concerns or abnormalities may be found by clicking on the following link: Informing Participants of Safety Concerns.

11.1.9. Request Tracker (RT) – N/A–no longer in use

A Request Tracker Sample queue has been set up to handle suggestions, problems, and/or revisions in reference to samples, shipments and lab results in order to enable users to conveniently bring such suggestions, problems and/or revisions to the attention of the DCC. The RT Sample queue can be accessed online at http://rt.biostat.wustl.edu or by e−mail at rt−haltpkd−samples@rt.biostat.wustl.edu.

Complete instructions on using the RT system may be found in Section 3.14.4 − Request Tracker.

11.2. Participating Clinical Center (PCC) Laboratories

PCC laboratories are those located at the actual clinical center. All required lab assessments (See Section 8.5.9 − Laboratory Measures) must be run by the PCC lab at the Screening visit to determine eligibility for the study. For all subsequent clinic visits, the PCC lab is to run all tests except for those to be analyzed at a central lab (serum creatinine, 24−hour urine samples). PCC labs may be used for safety lab collections instead of a local lab.

11.2.1. Reference Ranges

Each PCC is responsible for reporting lab reference ranges to the DCC at least annually, as well as for reporting any updates as they occur.

11.2.2. Pregnancy Testing

A qualitative urine B−HCG test must be obtained at the Screening visit (S) to test for pregnancy in all women with childbearing potential. For all visits subsequent to the S visit, a qualitative urine B−HCG test is to be obtained for any woman who has missed a period or for whom pregnancy may be suspected. Pregnancy tests are to be sent to local PCC laboratories for analysis.

For more information on the protocol for pregnancy, please refer to Section 8.5.9.3.1.− Pregnancy Screening.

11.2.3. Instructions for Participants

Study participants should 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. Participants should take their antihypertensive medications, as they normally do, unless the visit is one during which MR imaging will be acquired (Study A participants at B1, F24, F48 and F60 visits). For a visit in which MR imaging will be done, the participant should be instructed to hold morning doses of all antihypertensive medications until the imaging exam has been completed. If the participant is on any second−line antihypertensive medications that require twice daily dosing, those medications should also be held the night prior to the MR visit. The purpose for holding the antihypertensive medications prior to the imaging exam is to reduce the hemodynamic effects of medications on renal blood flow measurement.

11.2.4. Data Entry

Study coordinators at each PCC are to enter HALT PKD Visit Schedule Form 40 for every day on which study visits occur at the PCC. For each date, list all participant ID codes and corresponding visit codes. The "date of the visit" is defined as the date of the first study procedure or participant contact. *HALT PKD Visit Schedule Form 40 must be completed prior to accessing visit forms for data entry.*

Required Lab Results Form 9 is to be entered within 3 business days of sample collection at the L1-L4 visits (safety labs), and within 2 weeks of sample collection at all subsequent visits. PCCs are to report their ranges of normal lab values to the DCC and update them as necessary. The ranges will be entered into the database and will automatically determine which value entered on the Required Lab Results Form 9 are considered abnormal at that institution. Whenever an abnormal value is entered, the "abnormal" box must be checked in order to avoid a query.

As of September 2012, the DCC will be completing internal reviews to evaluate the timely data entry of all forms generated during the participant's visit. Those forms not completed within the two week time frame will be considered a protocol violation.

Sample Collection Forms 16−19 are to be entered within two weeks of sample collection at all visits.

- Form16 − Urine Sample Collection Form
- Form17 − Genetic Sample Collection Form
- Form18 − Archived Blood Sample Collection Form
- Form19 − Central Serum Creatinine Collection Form

At any time during the study, Required Safety Lab Results Form 51 is to be entered within 2 weeks of additional safety labs (serum potassium, creatinine or digoxin) being collected. Safety lab results must be entered in

any of the following three situations:

- Additional safety labs are ordered per the PI's discretion (X visit).
- Additional safety labs are required at three−month intervals because the participant's GFR dropped below 30 (XF visit).
- The PCC becomes aware of creatinine or potassium lab results at any time during the study.
- Digoxin levels are required (e.g., if there is a dose modification of masked drug in a participant taking Digoxin).

11.2.5. Results Reporting

The PCC is to inform the participant of any alert values as they are received (see Section 11.1.8 − Informing Participants of Lab Results).

11.3. Local Laboratories: Quest Diagnostics and Hometown Labs

During the study drug titration period, participants who live at a distance from the PCC may obtain safety labs (L1−L4) at either Quest Diagnostics or a local, hometown laboratory. Safety Labs consist of the following four tests only: potassium, BUN, creatinine, and digoxin when necessary. Additional safety labs (potassium and creatinine, and digoxin when necessary) may be collected per investigator discretion, and are required when GFR drops below 30. There may also be cases in which serum samples need to be collected at a local non−Quest lab and shipped to the central lab at Cleveland Clinic for analysis of serum creatinine.

Though screening labs should always be obtained at the PCC lab, it may be necessary, in rare cases, to obtain a screening lab at a non−PCC lab. For example, a participant, who lives out of state, could forget to fast prior to the screening visit, the result being that a fasting glucose cannot be obtained during the visit. As the participant cannot be enrolled without a fasting glucose, it would be necessary to make alternate arrangements for obtaining that particular lab test. In a case such as this, it would be acceptable for the PCC to arrange for the participant to obtain the needed lab test from Quest or some other responsible, external lab close to his/her home.

The PCC would be responsible for working out payment arrangements for the lab test, as the DCC is responsible for payment of only routine safety labs obtained at Quest Diagnostics.

11.3.1. Quest Diagnostics Laboratories

A centrally−billed, commercial account has been set up with Quest Diagnostics Laboratories, a nationwide network, for HALT−PKD safety labs. If there is not a Quest lab available to the participant, safety labs may be obtained at a lab in the participant's hometown.

Participants may go to a Quest Patient Service Center in their community, where samples will be collected and forwarded to the laboratory for testing. Quest Diagnostics maintains several thousand collection offices around the country. Each of Quest's main laboratories (25 around the country) perform serum creatinine testing on the same instrumentation, with the same reagents and calibrator, which is traceable to IDMS.

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 to a rigorous quality control program, Quest Diagnostics utilizes a unique statistical program that monitors the distribution of patient results day−to−day, instrument−to−instrument, lab−to−lab.

11.3.1.1. Approved uses for Quest Labs

Quest Diagnostics Laboratories may be used when returning to the PCC between visits would be an undue burden on a participant. However, a Quest lab should not be used for local participants who are able to return to the PCC. Only approved tests, as listed below, may be ordered from Quest, or paid by the study if ordered from a hometown lab.

Quest Visit in Lieu of PCC Visit (if necessary)

The DCC re-negotiated the Quest Diagnostics contract in August, 2012. Now participants may utilize a Quest lab for the centrally processed serum creatinine labs required for the “Quest Visit/Remote Visit”.

The following rules apply to the Quest Visit (Telephone or Remote Visit”):

- The visit must take place within +/− 1 month of the target visit date and will be accepted in lieu of the PCC visit.
- Only one Quest Visit (in lieu of a PCC visit) is permissible a year.

- Quest Visits are calculated based on the occurrence within a *twelve month period* and not calculated based on the *calendar* year.
- All labs, such as, sodium, potassium and digoxin levels may be drawn and processed by Quest. The serum creatinine must be centrifuged within an hour of the draw and shipped within 24 hours to the Cleveland Clinic Laboratory for the purpose of central processing. Separate lab requisitions are provided by Quest—one for serum creatinine and a second requisition for all other labs.
- Once a Quest Visit is completed, it is imperative that the participant attend their next PCC visit.
- In order for study drug to be dispensed, participants need to complete Q six month follow up.
- Samples must be obtained for centrally processed serum creatinine (CSC) for all participants completing remote visits.
- Refer to:
    - 11.3.3 Hometown Labs
    - 11.3.3.4 Obtaining Serum Samples for Central Analysis of Creatinine.
- As of August 2012, Form 29-Protocol Violation Form is required for any participant completing a Quest visit without submitting a CSC sample.
- The Quest Visit should take place on during the 6-month visit (i.e.: F42, F54) to avoid missing the 24 hour urine collection and MRI procedure. For Study A participants, imaging scans should occur as near as possible to the months 24, 48, and 60 visits within +/− six months of the target visit date. Refer to section
  8.13.13 MRI/MRA/Cardiac MR (Study A)
- The Quest/remote visits are to be used in extreme circumstances, are an exception, are to be used only when attendance to a PCC appointment is unavoidable and reserved for those cases in which a routine clinic visit would be an undue burden for a participant.
- 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.

Safety Labs (L1−L4)

- Serum creatinine, BUN, Potassium, Digoxin (when necessary)

Additional Safety Labs (per Physician Discretion)

- Serum creatinine, Potassium, Digoxin (when necessary)

Repeat B1 or F5 serum creatinine samples if there is a difference of >20% between 2 samples

- Serum creatinine x 2

eGFR drops to <30 mL/min/1.73 m$_2$

- Serum Creatinine, Potassium, Digoxin (when necessary)

Confirm Endpoint of 50% Reduction in eGFR from Baseline

Participants that reach endpoint by 50% reduction in eGFR require a confirmatory serum creatinine to finalize the endpoint.

Confirmatory lab work may be obtained by:

- PCC draw with serum creatinine sample sent to CCF for central processing.
- Quest Diagnostics Lab draw with results being processed by Quest Labs because they use the IDMS traceable methods. (Note: The Quest lab confirmatory result must be entered into Form51 within 48 hours of PCC receipt of the results.
- Hometown lab draw utilizing the CSC kit—the lab sends the serum creatinine sample to CCF for central processing

Protocol Amendment: Confirmed endpoint of 50% reduction in eGFR from baseline, and Q12−month telephone visit confirms participant has not reached dialysis, nor been transplanted.

- Serum creatinine

Specifically, pregnancy tests are not part of the routine safety labs and may not be ordered from a Quest lab.

11.3.1.2. Quest Requisitions

Quest will print PCC−specific test requisition forms for the required tests, including the name and contact information of the PI. The appropriate number of requisition forms (at least two for Study A, or four for Study B) must be completed and sent home with the participant after the Baseline visit (B1). To complete the form, verify that the PI

contact information is correct and indicate the tests being requested. Complete the participant information (participant name, date of birth and sex), but do NOT write the HALT participant ID number on the form. Date and time collected, total volume and fasting/non−fasting will be completed by Quest lab personnel. All test requisition forms must be signed by the ordering physician, and the participant must bring the requisition forms to the Quest lab at the time of sample collection.

Quest requisition forms come in boxes of one−hundred. To order additional requisition forms, contact Nancy Setley at Quest Diagnostics. She is the HALT PKD contact at Quest and may be contacted by phone at (610) 454−4889 or fax at (610) 983−2206.

11.3.2. Quest Commercial Account for HALT PKD

To prevent Quest labs from treating HALT samples as though they belong to a research account, rather than to a regular, commercial account, it is suggested that study coordinators provide participants with a written reminder, using the model language below, that can be given to the phlebotomist at Quest along with the test requisition form. Providing the Quest phlebotomist with a reminder to process samples in−house should help avoid mix ups.

Model Language for Sample−Processing Reminder

✳ Halt PKD is a national clinical account and needs to be tested at the closest QLS laboratory. If your laboratory is on the standard platform, do not send out specimen, test at your facility. Account # is already set up in QLS.

If you have any questions, please contact the National Clinical Group at 610−454−6010.

11.3.2.1. Quest Commercial Account Contact Information

Whenever there is a change in account information (e.g., phone number) for a PCC, the study coordinator should contact Nancy Setley directly to request that the Quest system be updated. Her phone number is (610) 454−4889 and her fax is (610) 983−2206, Email: nancy.j.setley@questdiagnostics.com.

11.3.2.2. Ordering Physician and Additional Physicians

In most cases, the study investigator will be the ordering physician. Study investigators are to add a check mark by their name and sign at the bottom of the page. The study coordinator is to send the participant home from the PCC visit with the appropriate number of completed test requisition forms and must instruct the participant to bring the form to the appropriate Quest lab for sample collection.

Additional physicians may also order safety labs from Quest by completing the requisition form. Additional physicians are to write their names in the Additional Physician field and sign at the bottom of the page.

Additional physicians ordering tests from Quest for participants who live out of state must either a) be licensed in the state where the participants LIVES, or b) forward the following information to the DCC to be kept on file at Quest:

- Physician's name
- UPIN ID
- Medical license number
- State in which the physician licensed

11.3.2.2.1. Ordering Safety Tests in California

The state of California specifically requires that the physician ordering lab tests be licensed in that state. Dr. Theodore Steinman, the HALT PKD Study investigator at Beth Israel Deaconess Medical Center, is licensed in the state of California and has agreed to donate his time to assist participants needing samples collected at Quest labs in that state. Coordinators are to contact Dr. Steinman to request the necessary tests. Dr. Steinman will then complete the appropriate requisition forms and forward them to the participant. Quest will forward test results to Dr. Steinman and the participant's PI, as entered on the requisition form.

11.3.2.3. Participant Instructions for Quest Lab Draws

Once the physician orders the labs and signs the requisition, the participant is to be instructed to bring the signed test requisition form to the appropriate Quest laboratory at the time of sample collection. If sample shipment to the central lab at CCF is required, arrangements must be made with a non−Quest lab.

Site coordinators will provide the participant with:

- Requisition(s) for the Quest lab draw.
  - Centrally processed serum creatinine requisition for CCF processing
  - All other desired labs (sodium, potassium, Digoxin)—to be processed at the Quest facilities.
- Styrofoam CSC specimen kit for shipping samples to CCF.

- FedEx prepaid shipping label permitting Quest staff to ship to CCF.
- Instructions for management of the CSC specimen for:
  - the participant
  - Quest lab personnel
- Blood tube labels and CCF manifest for the samples

Styrofoam kit will contain:

- 4.25x3.75x5.75 white cardboard box (shipping container), “ThermoSafe Diagnostic Shipper” instructions, serum creatinine blood tube containing lithium heparin (supplied by PCC), 2.5x4.0 inch absorbent sheet, press seal plastic bag, the Styrofoam kit, 20” red waterproof tape, 2.5x3.0 inch “Un 3373 Biological Substance Category B” sticker.

The DCC is invoiced directly by Quest Diagnostics for the costs of the lab draws. Participants will not incur any costs associated with these labs.

Note: Pregnancy tests are not part of the routine safety labs and may not be ordered from a Quest lab.

For more information, please refer to Section 11.3.1.1 – Approved Uses for Quest Labs

11.3.2.4. Fax Authorization

Each PCC receiving test results from Quest Diagnostics Laboratories must forward a fax authorization letter to Quest to authorize Quest to send lab results to the fax number indicated. The authorization does not expire and there is no limit to the number of participants from whom a physician can order tests. Physicians having signed fax authorization forms are responsible for informing Quest of any changes in fax numbers.

- Quest Fax Authorization Letter

11.3.2.5. Results Reporting

Quest will fax test results to the secure fax number listed on the fax authorization letter. The PCC is to inform the participant of lab values per established guidelines (see Section 11.1.8 − Informing Participants of Lab Results). If authorized, PCCs may communicate test results directly to a participant's primary care physician (PCP) or nephrologist.

When labs are drawn at a Quest location, the samples are sent to regional centers for analysis, with the regional center the samples get sent to being determined by the states assigned to a particular HALT clinic site. For example, a participant from Nevada would normally be assigned to the Colorado site, so the labs would go to one of the Quest regional centers assigned to Colorado. A problem arises when a participant from a state assigned to one HALT site is actually being followed at another HALT site. If Quest is not notified that a participant is being followed in a different region, the samples will be sent to the wrong regional center for analysis, and lab results will be significantly delayed.

To help prevent delays in receiving lab results, the study coordinator should notify Quest whenever labs will be drawn for a participant outside her PCC's catchment area, so the participant can be correctly set up within the Quest system. The best way to notify Quest would be to send an email to es.contracts@questdiagnostics.com. Email sent to this address is monitored everyday by the Quest group. Alternatively, the study coordinator can notify Quest by calling the National Call Center at 866−226−8046.

If lab results are not received within one−or−two days of the samples being drawn, the study coordinator should contact Quest by email or by calling the National Call Center. If the representative from the National Call Center is unable to help, that individual will get in touch with Nancy Setley, the contact for HALT PKD at Quest, who will make every effort to track down the results that the coordinator is looking for. The study coordinator may also choose to contact the DCC for help in resolving any problems associated with Quest.

11.3.2.5.1. Care360 Online Results Reporting

Quest has created the Care 360 website, which allows HALT personnel to access laboratory results online, after setting up a username and password. To request a username and password, a User Request Setup Form must be completed and faxed to the number printed on the form (610−983−2206). Each PCC must use its own primary account number:

- 97505731 Halt PKD Study − Beth Israel Deaconess
- 97505732 Halt PKD Study − Cleveland Clinic
- 97505726 Halt PKD Study − Emory University
- 97505727 Halt PKD Study − Mayo Clinic
- 97505728 Halt PKD Study − Tufts Medical Center

- 97505729 Halt PKD Study − University of Colorado
- 97505733 Halt PKD Study − University of Kansas

11.3.3. Hometown Laboratories

If a Quest lab is not convenient to the participant, a lab in the participant's hometown may be used to obtain safety labs. During titration (L1−L4), safety labs consist of potassium, BUN, creatinine, and digoxin when necessary. Additional safety labs (potassium and creatinine, and digoxin when necessary) may be collected per investigator discretion and are required when GFR drops below 30. There may also be cases in which serum samples need to be collected at a local non−Quest lab and shipped to the central lab at Cleveland Clinic for analysis of serum creatinine. There is no central billing for such labs, and each PCC is responsible for reimbursing either the participant, the ordering physician, or the hometown lab for the costs of the tests. It is up to each PCC to establish its own methods for making such reimbursements.

When a Hometown lab is used for obtaining endpoint confirmatory samples or Quest/Remote Visit lab work, the site coordinators must contact the lab identified by the participant *prior* to sending the materials to the participant. Coordinators must confirm that the lab has the capability and equipment to draw, centrifuge and ship centrally processed lab work. Once confirmed, the site coordinator will provide the participant with the following:

- Lab requisition(s) for the Hometown lab draw.
  - Centrally processed serum creatinine requisition for CCF processing
  - All other desired labs (sodium, potassium, Digoxin)—to be processed at the Hometown facilities.
  - *Note:* Two separate requisitions are recommended for billing purposes.
- The DCC is responsible for the costs associated with the centrally processed serum creatinines. All invoices for the CSC samples should be forwarded on to the DCC Program Manager address: University of Pittsburgh DCC HALT PKD Project Manager Patty Smith 200 Meyran Avenue Suite 300 Pittsburgh PA 15213
- Costs for all “other” labs (i.e. sodium, potassium and digoxin) draws at the Hometown lab are covered by the PCCs.
- Participants will not incur any costs associated with these labs.
- Styrofoam CSC specimen kit for shipping serum samples to CCF.
- Fed Ex prepaid shipping label permitting Hometown lab staff to ship to CCF.
- Instructions for management of the CSC specimen for the participant and the Hometown lab personnel
- Blood tube labels and CCF manifest for the samples
- Styrofoam kit will contain: 4.25x3.75x5.75 white cardboard box (shipping container), “ThermoSafe Diagnostic Shipper” instructions, serum creatinine blood tube containing lithium heparin (supplied by PCC), 2.5x4.0 inch absorbent sheet, press seal plastic bag, the Styrofoam kit, 20” red waterproof tape, 2.5x3.0 inch “UN 3373 Biological Substance Category B” sticker.

11.3.3.1. Ordering Tests

Generally, PI will order the necessary tests. If PIs are unable to order tests, the study coordinator is to contact the PCP and ask him or her to order safety labs per protocol. If a PCP is unable or unwilling to order the tests, other arrangements must be made to obtain safety labs per protocol.

11.3.3.2. Participant Instructions

Participants should be instructed to have their safety labs drawn by the PCP or hometown lab if a Quest laboratory is not available to them. Coordinators need to arrange to have these tests ordered, have results reported, and instruct participants accordingly. If sample shipment is required, participants are to be given a FedEx airbill to complete and instructions on how to ship.

11.3.3.3. Results Reporting

Coordinators are responsible for obtaining test results from the PCP or hometown lab in order to monitor safety and adjust dosages of study medications if necessary. Arrangements for obtaining these test results should be made at the time of the initial contact with the PCP or hometown lab. Reference ranges for local labs must either be included in test results or reported to the PCC separately. The PCC will inform the participant of any concerning lab values as they are received.

11.3.3.4. Obtaining Serum Samples for Central Analysis of Creatinine

In some cases, serum samples may need to be collected at a Quest Diagnostics or local hometown lab or a PCP’s office and shipped to the CCF Reference Laboratory.

Scenarios include:

- repeat samples (at baseline or the F5 visit, if results of two serum creatinine samples are >20% different, initial creatinine doubling, confirming a 50% reduction in eGFR)
- follow up during modified participation (if participants are unable or unwilling to continue in the study but agree to having serum samples collected every 6−12 months).
- Quest Visit (Telephone or Remote Visits)
  - *Refer to 11.3.2.3, Participant Instructions for Quest lab draws*
  - Confirmatory Samples for endpoint (Hometown labs only)
    - *Refer to 11.3.3, Hometown Laboratories*

For hometown lab draw or a draw occurring at a PCP office, the coordinator is to contact the participant's PCP to confirm that samples can be processed per protocol (centrifuged within one hour of collection). If this is not possible, a local facility that is able to process the samples, per protocol, must be identified and the participant instructed to go to that facility for sample collection and processing. A sample collection kit, including shipping materials and prepaid airbill, is to be shipped to the participant to bring to the lab. The participant must be instructed to ship the sample to the CCF Reference Laboratory on the day of collection. The coordinator is to notify CCF that the sample is on its way.

11.3.4. Data Entry for Local Laboratories: Quest and Hometown Labs

Required Lab Results Form 9 is to be entered within 3 business days of sample collection at the L1−L4 visits (planned safety labs during titration). Whenever an abnormal value is entered, the "abnormal" box should be checked.

Additional safety labs (potassium, creatinine, and digoxin when necessary) may be collected, per PI discretion, at any time during the study and are required if the participant's GFR drops below 30. These additional safety labs, which are unforeseen at baseline, are to be entered on Required Safety Lab Results Form 51. All lab results must be data entered within two weeks after the receipt of the faxed results of sample collection. In addition, any potassium, creatinine and digoxin levels reported to the PCC (e.g., ordered by a participant's PCP or hospitalist) are also to be reported on this form, ideally within two weeks of collection. Whenever an abnormal value is entered, the "abnormal" box should be checked.

11.4. Cleveland Clinic Foundation (CCF) Laboratory – Serum Creatinine

The Reference Laboratory at the Cleveland Clinic Foundation in Cleveland, Ohio, will receive and analyze serum specimens for creatinine for the duration of the study, beginning with the baseline visit. While test results from the Screening visit (processed at the PCC lab) will be used to determine study eligibility, baseline values must be received from CCF prior to the start of randomized treatment. The CCF Reference Laboratory is to be notified when samples are shipped from the PCCs, and results should be available on−line within 24 hours of samples having been received by CCF.

11.4.1. Communications

HALT PKD personnel will communicate any issues with the CCF Reference Laboratory via email or telephone directly with the DCC Program Coordinator. *Contact information may be found below in Section 11.4.4.2.5.*

The CCF Reference Laboratory has a support team to field questions regarding the status of a sample. Site coordinators may contact the “CCF Client Services Group” by phone (800) 628-5755 or by email: clientservices@ccf.org.

11.4.2. Instructions for Participants

Study participants should 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. Participants should be instructed to hold morning doses of all medications prior to each study visit (*see Section 8 − Participant Visits).*

> *Please refer to Section 11.5.2.2 − Medication Restrictions for a complete list of medications with potential nephrotoxicity (NSAIDS, aspirin, antibiotics) or that alter serum creatinine independent of GFR (trimethoprim [Bactrim], cimetidine).*

11.4.2.1. Sample Collection at Local (Hometown) Labs

There will be cases in which serum samples are collected at a local lab and shipped to the CCF Reference Laboratory for analysis (See Section 11.3.2.4 − Obtaining Serum Samples for Central Analysis of Creatinine). However, the coordinator must:

- Confirm that samples drawn at the local lab can be centrifuged and sent by FedEx to CCF.
- Samples can be shipped at room temperature, as long as they are received at Cleveland Clinic within *one day*.
- Send the participant a kit that contains the supplies needed to obtain the sample locally.
- clinic sites are responsible for procuring the sample collection supplies, i.e., needles, tubes, to be included in each kit.
- Include a Federal Express airbill, on which the coordinator has filled in the address for Cleveland Clinic, the HALT FedEx account number, and the box for next−day delivery
- Include the CCF Shipping Manifests, one manifest for each sample.
- Complete any additional information that may be required for shipping serum samples.

The DCC provides the sites with a supply of small shipping containers, which accommodate 1−2 tubes, for inclusion in each kit. *Refer to 11.3.3. Hometown Laboratories for more information.*

It is imperative that remotely−obtained samples sent to Cleveland Clinic first be centrifuged. Samples may be shipped at room temperature, as long as they are received at Cleveland Clinic within one day

11.4.3. Laboratory Responsibilities

The CCF Reference Laboratory will provide shipping supplies to PCCs, and test results should be available online within 24 hours of samples having been received by CCF.

11.4.3.1. Test Methods

The method for creatinine determination is an enzymatic−based method performed on Roche−Hitachi Modular analyzers. This method can be standardized to the Beckman−Coulter Rate Jaffe method used for both the MDRD and AASK studies. This reference method is accessible in the NIH Core Biochemistry Laboratory, located in the Cleveland Clinic Foundation in Clinical Pathology.

Cleveland Clinic has been standardized to the IDMS−Traceable calibration standard since the start of the study, 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.

11.4.3.2. Reference Ranges

CCF Reference Laboratory will fax any changes in the serum creatinine range of normal to the DCC.

11.4.3.3. Test Price

Serum specimens will be analyzed for creatinine at a cost of $7 per tube received. The DCC will be billed centrally for analysis of all CCF and Quest Diagnostic specimens.

- The PCCs will absorb the cost of all standard hometown lab draw costs
- The DCC will absorb the costs associated with the centrally processed serum creatinine that are shipped to CCF.
- Separate requisitions for CSC and other labs should be provided to labs to facilitate the invoicing.
- *Refer to: 8.5.10.2 Screening labs obtained at non-PCC lab*

11.4.3.4. Supplies

The CCF Reference Laboratory will provide all necessary supplies to clinical centers for mailing serum creatinine samples. These include Styrofoam−insulated mailing containers with cardboard outer mailing boxes, cold packs, cryogenic serum mailing tubes, mailing tube labels, ziplock plastic bags, and packing tape.

Mailing supplies will be shipped to each PCC as needed. Styrofoam mailing containers are to be reused whenever possible and will be replaced by the CCF Reference Laboratory as needed. Plastic sample mailing tubes and ziplock bags are to be discarded and replaced by the CCF Reference Laboratory after each mailing. Supply order forms will be included with shipping boxes each time the boxes are re-mailed to PCCs.

The DCC will provide CSC kits to clinical centers for mailing serum creatinine samples. Site Coordinators should contact the DCC Program Manager to reorder a stock supply of CSC kits, allow two weeks for delivery.

These include:

- Styrofoam−insulated mailing containers, Cardboard outer mailing boxes, Mailing tube labels, Ziplock plastic bags, and packing tape.

The PCC will provide the lithium heparin blood tubes required for the centrally processed serum creatinine draws.

- A centrally processed serum creatinine (CSC)kit is to be utilized for the following:
  - Quest Visits (Remote Visit) Refer to 8.12.9. Quest Visits
  - Confirmatory samples drawn at a Hometown Lab. (*Note*: Quest Diagnostic Labs may draw endpoint confirmatory samples) Refer to 11.3.3 Hometown Lab and 14.2.4 Study B Endpoints.
  - Modified Participants that agree to follow-up at a PCP every 6-12 months.

Refer to: 11.3.3 Hometown Labs or 11.3.3.4 Obtaining Serum Samples for Central Analysis of Creatinine

11.4.3.4.1. Ordering Supplies from Cleveland Clinic Reference Laboratory

To order supplies from the CCF Reference Laboratory, the study coordinator should contact one or more of the following persons:

- Brian Kershaw: kershab@ccf.org, 214−444−1099 * Patty Blubaugh: blubaup@ccf.org, 214−445−5762 * Ingrid Raulinaitis: raulini@ccf.org, 216−444−8108.

11.4.3.5. Sample Receipt

It is the PCC's responsibility to confirm the receipt of sample results. Delayed or missing results are to be brought to the attention of the DCC Program Coordinator.

The CCF lab has a support team to field questions with regard to the status of a sample. Site coordinators may contact the "CCF Client Services Group" by phone: 800-628-6816 or 216-444-5755 or by email: clientservices@CCF.org.

11.4.3.6. Missing or Damaged Samples

CSC sample results processed at CCF trigger automated DCC emails to site coordinators. It is the responsibility of the PCC to monitor all submitted samples confirming receipt of sample results. Site coordinators will notify the DCC Program Coordinator if sample result is missing. The DCC will contact CCF and identify the rationale for the delay in processing and convey any feedback to the site. If back-up samples need to be sent, the DCC will generate a backup sample accession number and send it to the coordinator.

11.4.4. Participating Clinical Center (PCC) Responsibilities

Samples are to be processed, stored and shipped per protocol. All baseline and repeat samples (either at baseline or after initial doubling over the average at baseline) must be shipped the day of collection, unless to do so would result in samples arriving at CCF on a weekend or holiday (no Saturday delivery). All other samples are to be frozen and shipped within two weeks of collection.

11.4.4.1. Required Forms

1. Form 19 − Central Serum Creatinine Collection Form
2. Form 40 − HALT PKD Visit Schedule Form
3. Form 81 − Shipping Manifest − CCF

11.4.4.2. Sample Collection/Processing

Seven−to−ten (7−10) mls of blood are to be drawn in a single serum separator tube (SST), allowed to clot for 30 minutes, and centrifuged for at least 10 minutes in the usual manner. Following this, 1 ml of serum is to be transferred to a 2−ml tube and labeled with a unique accession number (#1−A).

If the sample is randomly identified for quality control, an additional 1 ml of serum must be aliquotted to a 2−ml tube and labeled with a unique accession number (#2−A). Quality control samples must be indistinguishable from original samples.

All excess fluid from the original sample is to be transferred to a storage tube and stored at −20 degrees Celcius as a back−up (labeled with accession #1−B) until serum creatinine results have been received by the PCC.

Two serum samples are to be collected at the Baseline (B1) visit, one drawn one hour apart from the other. If results for the two samples are different by greater than 20%, both samples must be redrawn and the results confirmed prior to the start of randomized study medication. The average of the baseline samples is used as the baseline serum creatinine value. Similarly, the two serum creatinine samples collected at the F5 visit must be within 20% of each other or must be repeated. If, at any subsequent clinic visit, the central serum creatinine value is twice the average of baseline, the PCC will be notified that the sample must be repeated within two weeks to confirm or deny doubling.

11.4.4.2.1. Supplies

PCCs are to provide sample collection supplies (e.g., tubes, needles). The CCF Reference Laboratory will provide all necessary mailing supplies as described above in Section 11.4.3.4 − Supplies. The Reference Laboratory will enclose a mailing supply order form each time mailing boxes are returned to PCCs. Any needed mailing supplies are to be noted on the mailing supply order form, with the form then being returned to the CCF Reference Laboratory with the next sample shipment.

Any necessary FedEx supplies should be ordered by the study coordinator. However, plastic pouches and airbills will need to be ordered through FedEx, as airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

For more information on supplies that PCCs are responsible for procuring, please refer to the Study Supplies Checklist.

11.4.4.2.2. Labeling

Each sample must be labeled with a unique accession number (see 11.1.4 − Labeling). Original samples should bear the suffix −A, and back−up samples should have the same accession number with the suffix −B. Quality Control samples will be given a unique accession number plus the suffix −A and will, thus, be indistinguishable from the original samples.

Labels are to be affixed near the top of the sample vial, so the barcode may be read along the length of the tube. The label should not be placed so near the top of the tube as to interfere with the seal. The effective date is to be selected to print on all labels for a given visit. PCCs are responsible for ensuring that labels remain securely affixed to sample tubes, especially for central lab samples stored below −53 Celsius. If problems arise with label adhesion, PCCs will need to apply additional clear labels on top of white labels. It is suggested that the edges of labels be taped to the tubes.

11.4.4.2.3. Storage

At the time of collection, the appropriate shipping manifest is to be completed to function as a storage log until the time of shipment. The form completer is to enter the effective date and the number of tubes per sample. Samples are to be refrigerated at 4−8 degrees Celsius if they will be shipped within 3 days of collection. Alternatively, multiple samples may be frozen at −20 Celsius and batch−shipped within 2 weeks of collection (being allowed to thaw en route). All excess fluid from the original sample is to be transferred to a storage tube and stored at −20 degrees Celsius as a back−up (labeled with accession #1−B) until serum creatinine results have been received by the PCC.

11.4.4.2.4. Packaging/Shipping

PCCs are to use FedEx to ship samples and alert the lab and the DCC that a shipment is on its way. PCCs must freeze cold packs prior to use in shipping. Samples should either be refrigerated at 4−8 degrees Celsius and shipped on cold packs within 4 days of collection or frozen at −20 degrees Celsius and shipped within 2 weeks of collection (being allowed to thaw en route). All samples collected at the baseline and F5 visits, repeat−collected at the baseline visit, and after initial serum creatinine doubling, must be shipped on cold packs to CCF the day of collection, unless to do so would result in samples arriving at CCF on a weekend or holiday. Baseline, F5 and repeat samples must be shipped as soon after collection as possible, except repeat F5 samples, which may be frozen and shipped within two weeks. If refrigerated, all samples must be shipped within four days of collection. When samples are shipped from a PCC, email notification must be sent to the lab via FedEx. For shipping, serum samples must be placed in a ziplock bag. Place two paper towels in the bags to absorb any leakage that might occur. The bags should be flattened by hand to remove excess air and then sealed and placed with a frozen coolant pack into the Styrofoam mailing container. Shipping manifests may be placed in the Styrofoam box, in which case they should be inserted into an individual ziplock bag to protect them from sample leakage and/or condensation. A better approach is to include the paperwork in the mailer by laying the form (unfolded) on the top of the Styrofoam box. No ziplock bag is needed in this case. The inner lid is put on, and the Styrofoam box is slipped into the cardboard outer mailing box. This box is sealed with packing tape. All samples should be sent by a next−day express service to the address listed below in Section 11.4.4.2.5.

Samples must not be shipped to arrive on a weekend. Also, samples must not be shipped on a Friday or on a day prior to a holiday.

Prior to shipping, complete the necessary CCF Shipping Manifests. There should be one manifest for each sample, including quality control samples. Verify the collection date and number of tubes per sample. Indicate on the form that samples are being shipped (or if lost or destroyed, enter the reason). Shipping information needs be completed on only the first page of the manifests that accompany each shipment. Retain a copy of the completed manifests at the PCC and include the original manifests with each shipment.

*For more information on FedEx shipping, please refer to Section 11.1.6.1 − FedEx Ship Manager. − **N/A−no longer in use***

11.4.4.2.5. CCF Shipping Address

The following address is to be used as of January 2013 for all samples being shipped to CCF which includes both serum and urine samples.

- Dr. Sihe Wang HALT PKD Study, Cleveland Clinic Laboratories, 2119 E. 93rd Street, Cleveland, OH 44106. Contact: Chris Sakenes, office; (216) 448-8416, cell; (216) 789-3955. Fax: (216) 444-8130. Email: sakenec@ccf.org

11.4.4.2.6. Back−Up Samples

All excess serum from a collection must be retained (frozen) at the PCC as a back−up to the original sample until serum creatinine results have been received by the PCC. These back−up samples must be stored in an area separate from the original samples and labeled with the same accession number as the original samples but with the suffix −B. Once results have been received at the PCC, back−up samples should be discarded in the appropriate manner.

11.4.4.3. Quality Control

Six percent of all samples for the CCF Reference Laboratory will be randomly identified as requiring quality control samples. QC samples are to be taken from the same collection tube as the original sample and must not be distinguishable from them. QC samples will be assigned a unique accession number (with the suffix −A) and may be shipped at the same time the original samples are shipped. Quality control samples should never be identified as such, either on the tubes or shipping manifests.

11.4.4.3.1. Laboratory Calibration

PCC laboratories will not be calibrated to the CCF Reference Laboratory or to each other, which, pertaining to serum creatinine samples, introduces a systematic bias in study assignment for individuals with a GFR close to the cutoff (GFR 60 ml/min/1.73 m_2) between Study A vs. B. However, given that the cutoff for study assignment is arbitrary and a center−specific difference in study assignment for the few individuals with a GFR close to 60 mlmin/1.73 m_2 will not affect the internal validity of the study, the added expense and time required for central measurements or calibration of PCC laboratories is not felt to be justified. All laboratory measurements to be used in assessment of the primary outcome of doubling of serum creatinine will be measured through the CCF Reference Laboratory, which will be calibrated to the MDRD study lab, to enable use of the MDRD prediction equation for conversion of serum creatinine values to GFR.

11.4.5. Data Entry

PCCs are to enter HALT PKD Visit Schedule Form 40 on the day of sample collection. For each date, list all participant ID codes and corresponding visit codes. The "date of the visit" is defined as the date of the first study procedure or participant contact. HALT PKD Visit Schedule Form 40 must be completed prior to accessing visit forms for data entry. Central Creatinine Collection Form19 must be entered within two weeks of sample collection.

11.4.6. Sample Storage and Shipment Logs (Shipping Manifests)

Confirm all samples to be shipped to the CCF Reference Laboratory and complete the necessary shipping manifests. The shipping manifests function as a sample storage log until shipment, then as packing slips when samples are shipped. A copy of the shipping manifests must be sent along with the samples, as it functions as an inventory of samples. Instructions for shipping are found in *Section 11.4.4.2.4 − Packaging/Shipping.*

11.4.7. Results Reporting

The DCC will send nightly spreadsheets to the CCF Reference Laboratory, listing sample accession numbers. Serum creatinine results will be entered on the spreadsheet as they become available and transferred to the DCC via e−mail. The DCC will communicate the results to the PCC by email within 24 hours of having received them.

Paper copies of every CCF serum creatinine result on each participant should be printed out and filed in the research chart.

As a reminder, the visit has to have been entered via HALT PKD Visit Schedule Form 40 (must be completed prior to accessing visit forms for data entry) in order for central serum creatinine results to be automatically sent to the PCC. If the study coordinator does not receive a serum creatinine result, an RT ticket should be created in the Samples Queue that includes the following:

1. Participant ID
2. Visit Code
3. Date of Visit
4. Accession Numbers
5. FedEx Tracking Number

6. Date of Delivery

Though this is a lot of information, it will help speed up the process of getting results to the study coordinator, as it will provide the necessary details to allow the DCC to troubleshoot effectively.

The DCC will notify PCCs immediately, via e−mail, of central serum creatinine results from the Baseline and F5 visits, as well as notify them of central serum creatinine values that have doubled over the average of the values obtained at Baseline. After the first doubling of serum creatinine, the site is responsible for repeating the central serum creatinine within two weeks in order to confirm or deny that creatinine has doubled.

11.5. Central Processing Laboratory for 24 Hour Urine Measurements

CCF is serving as a central laboratory for all HALT PKD urine samples. CCF will receive aliquots of 24−hour urine specimens and analyze samples for urine aldosterone and chemistries, which will include: sodium, potassium, creatinine and microalbumin. 24−hour urine specimens are to be collected at the Baseline visit (B1), 16 weeks (F5), 12 months (F12), and then annually until the end of the study.

Samples are to be stored frozen and then batch−shipped to the CCF monthly or within four months of collection. Payments for sample analysis and shipping will be handled centrally by the DCC.

11.5.1. Communications

PCC questions or concerns with regard to HALT PKD urine samples shipped to the CCF lab can be directed to the University of Pittsburgh DCC Program Manager. Instructions for Participants

A standardized procedure for collecting 24−hour urine samples has been established. Samples should be collected in a GCRC whenever possible and practical. Alternatively, subjects may be given a collection jug at a preceding study visit (e.g. S for the B visit), to allow them to start their collections at home. If collecting at home, coordinators are to instruct participants to begin sample collection the morning before the clinic visit. The first morning void must be discarded and then all urine over a 24−hour period, including the first morning void on the second day of collection (the day of the clinic visit), is to be collected. If necessary, sample collection may begin in the afternoon before a clinic visit.

Participants collecting their urine at home must be instructed to keep the urine refrigerated during collection (4−8 degrees C). Keeping the sample refrigerated, the participant is to bring the urine collection jug to the PCC, where the total collection volume will be recorded and the urine processed. Instructions for 24−hour urine collection have been included below, but sites are responsible for developing instructions for their own participants.

Supplies:

- Gallon jugs (no preservative) and label (patient name/ID#, start/stop date/time)
- Large ziplock bags for gallon jug storage
- Collection "hat" or urinal
- Funnel
- Cooler with handle for transporting sample
- Ice packs for transporting sample
- Written instructions

Preparation/Day One:

1. One−gallon sample collection containers (containing no preservative) are to be used.
2. Patients are to be given necessary supplies, written instructions and verbal instructions.
3. The importance of complete collections should be emphasized.
4. The participant should drink the usual amount of liquid.
5. Sample collection should start in the morning
6. First morning void: discard first void, but record the time and date on the container.

Sample Collection:

- Collect every bit of urine for the next 24 hours.
- Collect urine in the "hat" or urinal provided, and then carefully transfer all contents into the larger collection container.
- If the participant is going to have a bowel movement; all urine should be collected first so none is lost. (Do not collect stool.)
- After carefully transferring urine into the larger collection container close the container securely and store upright.
- Wash the "hat" or urinal and allow it to dry completely before next use.
- Participants may wish to use various reminder techniques so they do not forget to collect their urine (note on the toilet seat, string around a finger, safety pin on clothing).

Sample Storage:

1. Keep the collection container in a zip lock bag marked "biohazard."
2. Store the sample in a refrigerator during the entire collection period and after.
3. If refrigeration is not available, store the sample in a cooler with ice packs.
4. If no cooler/ice packs are available, store sample in a cool dark place.
5. Do not expose sample to extreme temperatures. Avoid freezing.
6. Always store the sample upright to avoid leakage.
7. Keep the sample refrigerated at all times during collection and after.

Completion/Day Two:

1. On day two, collect all urine up to the same time you started the day before.
2. Include the first morning void on day two and try to void at the end of collection.
3. Record the time and date of the last void on the container.
4. Do not stop collecting before this time. Do not collect urine after this time.
5. Bring the sample to the PCC (in a cooler with ice packs if possible).

. At the PCC a study coordinator will complete a 24−hour urine checklist to confirm satisfactory collection.

11.5.2.1. Dietary Restrictions

For information on dietary restrictions associated with 24−hour urine collection, please see Section 8.1.2.2. − Dietary and Medication Restrictions.

11.5.2.2. Medication Restrictions

Below is a list of common medications that must **not** be taken during sample collection or within 1 week prior to all PCC visits.

Table 11−1. Pain Medications:

Trade (Brand Name)	Generic Name
Arthropan	salicylate salts
Celebrex	celecoxib
Clinoril	sulindac
Dolobid	diflunisal
Feldene	piroxicam
Indocin	indomethacin
Medipren	ibuprofen
Motrin	ibuprofen
Naprosyn	naproxen
Various manufacturers	oxyphenbutazone
Rufen	ibuprofen
Disalcid	salsalate
Advil	ibuprofen
Anaprox	naproxen sodium
Excedrin	aspirin
Nalfon	fenoprofen calcium
Meclomen	meclofenamate sodium
Nuprin	ibuprofen
Butazolidin	phenylbutazone
Ponstel	mefenamic acid
Soma Compound	carisoprodol
Tolectin	tolmetin socium
Voltaren	diclofenac sodium

Table 11−2. Antibiotics:

Trade (Brand Name)	Generic Name
Anspor	cephradine
Ceclor	cefaclor
Keflex	cefalexin
Velosef	cephradine
Duricef	cefadroxil
Ultracef	cefadroxil
Cefadyl	cephapirin
Keflin	cephalothin
Ancef	cefazolin
Kefzol	cefazolin
Mandol	cefamandole
Mefoxin	cefoxitin
Zinacef	cefuroxime
Monocid	cefonicid
Precef	ceforanide
Cefotan	cefotetan
Claforan	cefotaxime
Cefizox	ceftizoxime
Cefobid	cefoperazone
Moxam	moxalactam
Rocephin	ceftriaxone
Fortaz	ceftazidime
Tazidime	ceftazidime
Tazicef	ceftazidime
Suprax	cefixime

Table 11−3. Anti−Ulcer Agents:

Trade (Brand Name)	Generic Name
Alka−Seltzer	antacid
Tagamet	cimetidine
Axid	nizatidine
Pepcid	famotidine
Zantac	ranitidine

Table 11−4. Urinary Tract Anti−Infectives:

Trade (Brand Name)	Generic Name
Bactrim	trimethoprim/sulfamethoxazole
Septra	trimethoprim/sulfamethoxazole
Co−Trimoxazole	trimethoprim/sulfamethoxazole
Cotrim	trimethoprim/sulfamethoxazole
Trimpex	trimethoprim

Proloprim	trimethoprim

11.5.3. Laboratory Responsibilities

11.5.3.1. Sample Acceptability

The 24−Hour Urine Checklist, Form 37, is to be completed by the study coordinator at or after the completion of sample collection to ensure that the correct collection procedures have been maintained. Form 37 does not require data−entry, but must be kept in the participant's research chart to document that the process was completed. Using the data collected on Form 37, the PI is to determine if the sample is acceptable in terms of the mechanics of collection (per #2 below).

1. If the PI determines the sample is *acceptable* based on the mechanics of collection, urine is to be aliquotted and sent to CCF and biosample repository per protocol.
2. If the PI determines that the sample is *unacceptable*, based on the mechanics of collection, the sample should be discarded and not repeated at that visit, although samples will be collected at all required subsequent visits.

Possible reasons why a sample could be deemed unacceptable in terms of the mechanics of collection are listed below:

- Sample is not refrigerated.
- Sample is exposed to extreme temperatures.
- Sample collection time is <20 hours or >28 hours.
- Sample start/stop time cannot be determined.
- One−half (1/2) cup or more of specimen is lost.
- Sample is spilled or leaks from container.
- Anything unusual that renders a sample unacceptable in the PI's opinion.

Samples are to be collected at all required intervals, even if the baseline collection is unacceptable.

24−hour urine collection is to be aliqotted on the day the collection is completed. However, if this is not possible, samples may be stored refrigerated for up to 24 hours after the collection is complete.

11.5.3.2. Aldosterone Excretion Rate (AER) Samples

CCF expects to receive approximately 100 samples of frozen urine for testing each month. Each 5 mL tube is expected to contain 4 mLs of frozen urine collected over 24 hours (boric acid added per instructions below) and is to be labeled with a unique accession number. A spreadsheet listing accession numbers and total collection volumes will be automatically forwarded to the CCF laboratory. CCF will fax changes in its reference ranges to the DCC whenever they occur.

11.5.3.2.1. Test Method

AER is measured by a radioimmunometric assay (RIA) as follows: The Coat−A−Count procedure is a solid phase radioimmunoassay, based on aldosterone specific antibody immobilized to the wall of the polypropylene tube. 125I−labeled aldosterone competes for a fixed time with aldosterone in the participant sample for antibody sites. The tube is then decanted, to separate bound from free, and counted in a gamma counter. The amount of aldosterone present in the participant sample is determined from a calibration curve. The sensitivity of this method is 16 pg/mL and the precision is 4−10%.

11.5.3.2.2. Reference Ranges

CCF will fax changes in its reference ranges to the DCC whenever they occur.

11.5.3.2.3. Test Price

AER will be analyzed at a cost of $15 per sample.

11.5.3.3. Urine Chemistry Samples

CCF expects to receive approximately 100 samples of frozen urine per month for chemistry testing (sodium, potassium, creatinine and microalbumin). Each 13−mL tube (preferred, or 15−mL tube if necessary) is to contain 10 mLs of frozen urine (without boric acid) from the participant's 24−hour urine collection and is to be labeled with a unique accession number. The PCC must send CCF the Shipping Manifest with each shipment. A spreadsheet listing accession numbers and total collection volumes will be sent to the CCF laboratory by email. Suggested Vendor and Order Numbers: 13mL (16.8x95) polypropylene tube Sarstedt 55.518 13mL tube caps Sarstedt 65.793 13mL tube box w/ cover (divider grid included) Sarstedt 95.064.949.

11.5.3.3.1. Test Method

Urine creatinine is measured by Jaffe reaction using an Alfa Wasserman ACE analyzer (Fairfield, NJ). Sodium and potassium are determined by ion selective electrode (ISE) method using the NOVA 13 plus (Nova Biomedical Corporation, MA). Microalbumin is determined by using a turbidimetric microalbumin assay (ALPCO, NH).

Assay for microalbumin is likely to change, which will likely increase the price (see below).

11.5.3.3.2. Reference Ranges

The CCF labs will fax changes in reference ranges to the DCC whenever they occur.

11.5.3.3.3. Test Prices – N/A no longer in use

Costs for testing each urine chemistry sample are Sodium $2, Potassium $2, Creatinine $4, and Microalbumin $15.

11.5.3.4. Sample Receipt

The CCF labs expect to receive approximately 100 samples per month of each type of sample (aldosterone and urine chemistries). PCCs should ship frozen samples (ideally on the last Monday of the month) when a sufficient quantity has accumulated (enough to fill a single mailer) but no later than four months after collection. A shipping manifest must be included with each shipment to serve as an inventory of samples in a particular shipment. Upon arrival of the shipment, CCF will confirm, via e−mail to the DCC that all samples listed on the packing slip have been received and, further, will report on the condition in which the samples were received. If there are any problems encountered with a shipment, CCF will notify the DCC.

11.5.3.5. Missing or Damaged Samples

If samples have been damaged during shipment or if any samples are missing from a shipment, CCF will communicate this information to the DCC via email, and the DCC will notify the coordinator. Sites will ship back−up (replacement) samples to the lab as necessary.

11.5.4. Participating Clinical Center (PCC) Responsibilities

11.5.4.1. Required Forms

- Form 16 − Urine Sample Collection Form
- Form 82 − Shipping Manifest – CCF

11.5.4.2. Urine Chemistry Sample (No Acid)

After gently mixing the collection sample, aliquot 10 mLs of urine into a 13−mL p.p. tube (preferred, or 15−mL tube if necessary) and label with a unique accession number (#1−A). One duplicate back−up sample (accession #1−B) must be retained at the site until test results are available. If randomly designated for blinded quality control, a single QC sample must be prepared from the same collection tube (accession #2−A). Samples are to be frozen and stored in a freezer at a minimum of −20 degrees Celsius. Original and QC samples must be batch−shipped monthly, or within four months of collection. When results are available, back−up samples should be discarded.

11.5.4.3. Urine Aldosterone Samples (Boric Acid)

Record the total collection volume, and gently mix the entire collection sample. Aliquot exactly 40 ml of urine into a pre−made 50−ml p.p. (polypropylene) tube containing 0.4 gm of boric acid (dry powder), shake and transfer 4 ml of urine/boric acid mixture into a 5−ml p.p. tube and label with a unique accession number (#3−A). One duplicate back−up sample (accession #3−B) will be retained at the site until results are made available. If randomly designated for blinded quality control, a single QC sample will be prepared from the same collection tube (accession #4−A). Samples will be stored in a freezer at least −20 degrees C. Original and QC samples must be batch−shipped within four months of collection. When results are made available, back−up samples may be discarded. (maximum volume 12 ml for all three samples − original, back−up and QC).

For more information on procuring and preparing the boric acid to be added to urine samples, please refer to Sections 11.5.4.3/11.6.3.2.2 − Boric Acid Information.

11.5.4.4. Back−Up Samples

One duplicate back−up of the original sample for aldosterone and one duplicate back−up of the original sample for urine chemistries must be retained at the PCC (frozen at −20 degrees Celsius or colder) until results of the original samples have been received by the PCC. Back−up samples must be stored in an area separate from the original samples, and are to be labeled with the same accession number as the original samples, but will include the suffix −B. Once results have been received at the PCC, back−up samples should be discarded in the appropriate manner.

11.5.4.5. Quality Control Samples

Ten percent of all samples to be sent to the CCF laboratory will be randomly identified as requiring quality control samples. Urine samples were originally processed at Diagnostic Laboratory Facility at Brignam and Women's Hospital. This was suspended as of June 1, 2010 due to prohibitive costs. The DCC developed an agreement with a lab at the University of Pittsburgh Cancer Institute (UPCI) to process urine samples starting June 1, 2010 through January 2013. Initially there were higher than expected proportions of quality control samples that were out of range. In August 2011, the DCC increased the QC sampling to 10% to improve precision, but the QC issues persisted. In October 2011, UPCI began sending all urine chemistries and urine albumin to UPMC Shadyside Hospital Laboratory for processing. The QC for the SAE measures has improved. Urine aldosterone samples are processed by UPCI Biobehavorial Laboratory. On October 10, 2012, the DCC suspended sample shipments to UPCI due to ongoing issues with aldosterone processing. In January 2013, the Cleveland Clinic Foundation Laboratories assumed the processing of all HALT PKD urine samples. QC samples will be assigned unique accession numbers (with suffix −A) and must be indistinguishable from the original samples. QC samples may be shipped at the same time the original samples are shipped.

Quality control samples should never be identified as such, either on the tubes or shipping manifests.

11.5.4.6. Labeling

Each sample type must be labeled with a unique accession number (see 11.1.4 − Labeling). Original samples will bear the suffix −A, and back−up samples will have the same accession number with the suffix −B. QC samples will be given unique accession numbers plus the suffix −A and will, thus, be indistinguishable from the original samples. Total collection volumes associated with the accession number are to be listed on the spreadsheet that is emailed to the CCF laboratory.

Labels are to be affixed near the top of the sample vial, but not over it, so the barcode may be read along the length of the tube. The effective date entered will appear on each label. PCCs are responsible for ensuring that labels remain securely affixed to sample tubes, especially for central lab samples stored below −53 Celsius. If problems arise with label adhesion, PCCs will need to apply additional clear labels on top of white labels. It is suggested that the edges of labels be taped to the tubes.

11.5.4.7. Supplies

Sites will provide all materials required for urine sample collection, storage and shipment to CCF Any necessary FedEx supplies should be ordered online by the study coordinator. However, plastic pouches and airbills will need to be ordered through FedEx as printed airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

For more information on supplies that PCCs are responsible for procuring, please refer to the Study Supplies Checklist.

11.5.4.8. Storage

At the time of collection, the appropriate shipping manifest is to be completed to function as a storage log until the time of shipment. The form completer is to enter the effective date, the total collection volume for 24−hour urine, and the number of tubes per sample. Samples are to be stored at each site in a freezer at −20 degrees Celsius. The maximum stability for aldosterone samples at −20 degrees Celsius is six months. Therefore, samples must be shipped within four months of collection, ideally on the last Monday of the month. Chemistry samples are stable for upwards of two years; however, these should also be shipped within four months of collection to avoid a backlog.

24−hour urine collection is to be aliqotted on the day the collection is completed. However, if this is not possible, samples may be stored refrigerated for up to 24 hours after the collection is complete.

11.5.4.9. Packaging/Shipping

PCCs are to use FedEx Ship to ship samples and alert the central lab and the DCC that a shipment is being sent. The CCF laboratory prefers to receive approximately 100 samples of each type (chemistry and aldosterone) on a monthly basis. PCCs should pack and ship samples when a quantity sufficient to fill a single mailer has accumulated (but within four months of sample collection). Shipments should be sent on the last Monday of the month. A spreadsheet, listing accession numbers and total collection volumes, will be attached to the e−mail on which CCF reports results.

The CCF laboratory will not provide any shipping supplies. Participating Clinical Centers (PCCs) are to provide all required tubes, labels, and shipping materials. Care must be taken to ensure that samples are maintained at −20 degrees Celsius while in storage and that they remain frozen during shipment. Thus, samples must be shipped on a minimum of 5 pounds of dry ice. Monthly shipments are to be sent via next−day service on the last Monday of the month, unless that Monday is a holiday, in which case the shipment is to be sent on a Tuesday. Shipments must not be sent on Wednesdays, Thursdays, or Fridays. No shipments will be received on Saturdays at the CCF laboratory.

Shipping charges will be paid centrally through the DCC, and the DCC will provide each PCC with the appropriate account number to reference on shipping airbills.

Prior to shipping, complete the necessary CCF Shipping Manifest. There should be one manifest for each sample, including quality control samples. Verify the collection date and number of tubes per sample. Indicate on the form that samples are being shipped (or if lost or destroyed, enter the reason). Complete the shipping information on the first page of the manifest to accompany the shipment. Retain a copy of all completed manifests at the PCC and include the original manifest with each shipment. The study coordinator must make sure that the FedEx number is completed on the manifest.

The CCF shipment tool allows timely and accurate accounting of CCF samples. It requires PCCs to provide information about specific samples in shipments in order to generate accurate spreadsheets including all accession numbers in each shipment to CCF. A pick−list format allows PCCs to create lists in any order (by participant, collection date, accession number). The order of the list must coincide with the order in which samples are placed in the box (from left to right, starting with the cell in the upper left corner). Once all accession numbers have been selected and samples arranged in matching order, an electronic spreadsheet will be generated and sent to the lab and the DCC.

*For more information on FedEx shipping, please refer to Section 11.1.6.1 − FedEx Ship Manager. − **N/A−no longer in use***

11.5.4.9.1. Central Processing Laboratory at CCF

Ship samples to: Dr. Sihe Wang HALT PKD Study, Cleveland Clinic Laboratories, 2119 E. 93rd Street, Cleveland, OH 44106.

- Contact: Chris Sakenes, office; (216) 448-8416, cell; (216) 789-3955. Fax: (216) 444-8130. Email: sakenec@ccf.org

11.5.4.10. Adequacy of 24 Hour Urine Collections

Provided proper collection procedures are maintained (see Section 11.5.3.1 − Sample Acceptability), 24−hour urine samples are to be considered valid (complete) if creatinine excretion is within 75−125% of that predicted using Walser formulas, based on actual body weight *(Walser−1987)*. Only valid samples will be used for determination of aldosterone excretion rate. If a sample falls within the 50−150% range of predicted, based on Walser formulas, it will be considered adequate to be used for determination of aldosterone to creatinine ratios.

If a sample is determined to be unacceptable or incomplete, even at baseline, participants are to continue to collect 24−hour urine samples for all subsequent visits at which they are required.

11.5.5. Data Entry

PCCs are to enter HALT PKD Visit Schedule Form 40 on the day of sample collection. For each date, list all participant ID codes and corresponding visit codes. The "date of the visit" is defined as the date of the first study procedure or participant contact. *HALT PKD Visit Schedule Form 40 must be completed prior to accessing visit forms for data entry* to allow the DCC to update spreadsheets sent to central labs for timely results reporting. Urine Sample Collection Form16 must be entered within two weeks of sample collection.

11.5.6. Sample Storage and Shipment Logs (Shipping Manifest)

Confirm all samples to be shipped to the CCF Laboratory and complete the necessary shipping manifests. The shipping manifests function as a sample storage log until shipment, then as packing slips when samples are shipped. A copy of the shipping manifests must be sent with the samples to serve as an inventory. Ship samples per instructions in 11.5.4.9 − Packaging/Shipping.

11.5.7. Results Reporting

The DCC will send spreadsheets to the CCF Laboratory, listing sample accession numbers. Test results will be entered on the spreadsheet as they become available and transferred to the DCC via email.

11.6. Archived Specimens

Blood and urine samples are to be collected from all HALT PKD participants from whom a sample is not already stored in the NIDDK Repository (i.e., CRISP participants) and stored for use in future studies. Archived specimens (blood, plasma, and urine) are to be collected at the Baseline visit (B1), after 16 weeks (F5), and at annual visits. Genetic samples are optional and cannot be collected until written consent is obtained from the participant. Once written consent is obtained, genetic samples are to be collected, on only one occasion, at the F5 visit or after.

A separate, written, informed consent must be obtained from any participant from whom a genetic sample is to be drawn.

Labeling of archived specimens is to be done according to the instructions outlined above in Section 11.1.4.

11.6.1. NIDDK Genetic Repository

At the F5 visit, all participants enrolled in HALT PKD, from whom a sample is not already in storage at the NIDDK Repository (i.e., CRISP participants), are to be asked if they are willing to provide blood specimens for EBV transformation. Participants must be informed that the specimens will be sent to the NIDDK Genetic Repository at Rutgers University (RUCDR) to be saved for use in future studies related to kidney disease. A separate, written, informed consent must be obtained from each participant who agrees to provide blood specimens for genetic analysis. Participants do have the option to refuse to provide genetic samples. Specimens are not to be obtained from participants who consent to provide genetic samples but refuse cell immortalization.

The DCC provides PCCs with a summary list of participants that:

- do *not* have genetic samples stored in the NIDDK repository
- are documented as "*will re-approach later" (never declined* genetic consent).

For those participants who were never approached for genetic consent at the F5 visit or those requesting additional time to consider the option of signing genetic consent, coordinators will:

- review the genetic consent summary lists and identify eligible participants
- approach eligible participants for genetic consent at a PCC visit prior to the end of the study.

Three 8.5 mL Vacutainer tubes (2 ACD yellow−top and 1 EDTA purple−top) are to be obtained from each participant at the F5 visit. (If necessary, the genetic sample can be obtained from the participant at a visit subsequent to the F5 visit.) The specimens will be coded and only the clinical center has access to names of participants. Whole blood samples must be sent to the Genetic Repository on the day of collection, where, upon receipt, they will be stripped of existing 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 as requested by the HALT PKD Steering Committee. When the HALT PKD study concludes, NIDDK will ultimately be responsible for how these genetic samples can be used.

11.6.1.1. Required Forms

- Form 17 − Genetic Sample Collection
- Form 83 − Shipping Manifest − Genetic Repository
- NIDDK Phlebotomy Collection Form

Terms proper form completion Accession Number: Random 8−digit code used to identify sample (barcoded) NIDDK Site Code = Three−digit code assigned by RTI (301−307) HALT−PKD Participant ID code = A site−specific letter followed by 7 digits NIDDK Subject ID = HALT−PKD Participant ID code (as above) NIDDK Sample ID Code = Site Code plus NIDDK Subject ID NIDDK Alternate ID = Sample Accession Number (as above).

11.6.1.2. Sample Collection; Processing/Packaging

PCCs are to use FedEx to prepare samples for shipping. RUCDR has provided the instructions below for collecting, processing, packing and shipping genetic samples. A copy of these instructions may also be found by referring to the NIDDK Genetics Initiative − Flow Sheet for Blood Sample Collection.

1. Attach I.D. labels to the tubes. **Do not cover expiration date or clear glass necessary to see the fluid along the length of the tube. Do not write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**

   The blood level must be seen throughout the length of the tube. Labels must not wrap entirely around the circumference of the tube making it impossible to see the full length.
2. Collect blood specimen in the 2 yellow top tubes with ACD and 1 purple−top tube with EDTA. *Be sure to invert each tube gently 8−10 times to mix blood with additives and keep them at room temperature.*
3. Double check NIDDK ID #, verify that ID information on tube matches that on the enclosed NIDDK Phlebotomy Collection Form.
4. Date and sign the NIDDK Phlebotomy Collection Form in the "to be completed by the Phlebotomist" area.
5. Place tubes with labels facing down in Stryofoam container. Package the blood tubes in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red water resistant tape.

6. Place the collection form (NIDDK Phlebotomy Collection Form) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.
7. Use FedEx Online to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.
8. For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in compliance with IATA Packing Instruction 650." Samples are shipped at room temperature.
9. Call **Federal Express, (1−800−463−3339)**, and a courier will be dispatched to pick up the samples. *Be sure to give FedEx the Zip Code of the pickup address, not that of the destination. Do not under any circumstance, put mailer into a FedEx drop box!*
10. Notify Dana Witt and Elva Peralta at the Rutgers University Cell and DNA Repository that blood is being shipped and provide the FedEx tracking number(s)_____and NIDDK ID #(s)_____. This can be done by email witt@biology.rutgers.edu; peralta@biology.rutgers.edu, fax (1−732−445−1149), or phone (1−732−445−1498).

In addition to the above instructions from RUCDR, Genetic Sample Collection Form17 must be filled out and data−entered for each participant contributing genetic samples. The Genetic Sample Collection Form does **not** get sent to RUCDR.

Also, the Genetic Repository Shipping Manifest must be completed at the time of collection. The Form completer is to enter the date of collection and number of tubes per sample and then indicate the samples have been shipped. Completed shipping manifests are to be retained at the PCC but do not need to be included with sample shipments.

11.6.1.3. RUCDR Web Portal

PCCs are to notify Rutgers University of all shipments (including FedEx tracking number) by using the RUCDR Web Portal (http://rucdr.rutgers.edu). Please refer to the RUCDR Portal Instructions for instructions on accessing and using the RUCDR Web Portal. The Web Portal may also be used to ask questions or to find information.

Please click on the link below to establish a username and password for the RUCDR Web Portal
http://rucdr.rutgers.edu.

11.6.1.4. Supplies

Rutgers will supply all materials for sample collection and shipment. Supplies are to be ordered using the RUCDR Web Portal (http://rucdr.rutgers.edu). Allow three weeks for delivery. Any necessary FedEx supplies should be ordered online by the study coordinator. However, plastic pouches and airbills will need to be ordered through FedEx, as printed airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

11.6.1.5. Storage

Ideally genetic samples should be shipped the day of collection, but must be shipped within 4 days of collection and must be received no later than the morning of the fifth day after collection. Samples must remain at room temperature until processed and must not be refrigerated or frozen at any time. The Genetic Repository Shipping Manifest is to be completed at the time of collection per the instructions listed above in Section 11.6.1.1.

11.6.1.6. Shipping

PCCs are to use the online FedEx Ship Manager to ship samples, as well as to alert the Repository and the DCC that a shipment is on its way.

For more information on FedEx shipping, please refer to Section 11.1.6.1 − FedEx Ship Manager.

11.6.1.6.1. Genetic Repository Shipping Address

Ship Samples to:

- Dr. Douglas Fugman/Genetics Rutgers University/Cell Repository Division of Life Sciences − Nelson Labs 604 Allison Road (Rm. C120A) Piscataway, NJ 08854-8082. Phone: (732) 445-1498.

11.6.2. NIDDK Biosample Repository – Blood

On the morning of the B1 visit and at each annual visit thereafter, a maximum of 36 mL of whole blood should be collected, processed and sent to the NIDDK Biosample Repository at Fisher BioServices (formerly McKesson). 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 are to be centrifuged and shipped refrigerated (on frozen cold packs) to the NIDDK Biosample Repository at Fisher BioServices on the day of collection, where they will be aliquotted into 1 mL tubes and archived. Samples will be coded and only the clinical center will have access to the names of participants.

If serum/plasma samples are hemolyzed, or otherwise lost or destroyed, they should be redrawn if the participant lives locally to the PCC and sent to Fisher BioServices via FedEx. The decision to redraw blood is left up to the site. If a sample is to be redrawn, the site must notify the DCC in advance so a new set of accession numbers can be generated.

For further information on collecting, processing and sending blood serum and plasma samples to Fisher BioServices, please refer to Handling Samples for Fisher BioServices Required Forms

Form 18 − Archived Blood Sample Collection

Form 84 − Fisher BioServices Shipping Manifest−Serum/Plasma

11.6.2.1. Required Forms

- Form 18 – Archived Blood Sample Collection
- Form 84 – Fisher BioServices Shipping Manifest-Serum Plasma

11.6.2.2. Sample Collection/Processing

Serum samples: Draw 2 SST tubes (tiger−top, 10 mL draw volume serum separator tubes), containing gel separation layer and appropriate for shipping centrifuged samples (no decanting). Item number: 367985 (Becton Dickenson).

Plasma samples: Draw 2 PST tubes (green/grey−cap, 8 mL draw volume plasma preparation tubes containing heparin appropriate for shipping centrifuged samples (no decanting). Item number: 367964 (Becton Dickenson).

1. Gently invert tubes (but do not shake). Invert SST tubes 5 times and PST tubes 8−10 times.
2. Let SST tubes clot in a vertical position for a minimum of 30 minutes. Note: PSTs contain an anticoagulant (heparin), so there is no need for clotting time.
3. Centrifuge all tubes, ideally within one hour of collection, but certainly within two hours.* Spin SST tubes at 1300 RCF (g) for 15 minutes. Spin PST tubes at 1300 RCF (g) for at least 10 minutes. No decanting is necessary.
    - ✳ If centrifugation is not possible within 1−2 hours of collection, refrigerate samples until centrifugation is possible. Allow tubes to acclimate to room temperature prior to centrifugation (approximately 10 minutes), as cool temperatures may prevent proper separation.

A separate Archived Blood Sample Collection Form18 must be filled out and data−entered for *each participant*.

11.6.2.3. Supplies

PCCs are to supply all materials required for venipuncture. Fisher BioServices will supply all tubes and materials for sample shipment. Any necessary FedEx supplies should be ordered online by the study coordinator. However, plastic pouches and airbills will need to be ordered through FedEx, as printed airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

To order supplies from Fisher BioServices, contact Clifford Snell - Phone: (240) 686−4706 Fax: (301) 515−4049 E−mail: Clifford.Snell@thermofisher.com.

For more information on supplies that PCCs are responsible for procuring, please refer to the Study Supplies Checklist.

11.6.2.4. Storage

If it is not possible for the repository to receive samples within one day of collection, centrifuge tubes and store in a refrigerator (4 degrees Celsius) until they can be shipped (to be received by the lab within 1 day of shipping). At the time of collection, Fisher BioServices Shipping Manifest−Serum/Plasma is to be completed to function as a storage log until the time of shipment. The form completer is to enter the date of collection and the number of tubes per sample.

If samples are shipped on Thursday and are delayed en route, they will not arrive at the lab until the following Monday. Although refrigeration lasts only about 24 hours, these samples may still be viable at room temperature. However, if samples are stored too long in a shipping warehouse with extreme temperatures, they may spoil.

11.6.2.5. Packaging/Shipping

For information on assembling the refrigerated laboratory shippers to be used for shipping blood samples to Fisher BioServices, please refer to the document HALT−PKD Refrigerated Laboratory Shipper.

11.6.2.6. Serum/Plasma Shipping Manifests

Prior to shipping, complete the necessary shipping manifests (Fisher BioServices Shipping Manifest−Serum/Plasma). Verify the collection date and number of tubes per sample. Indicate on the form that samples are being shipped (or if lost or destroyed, enter the reason). Complete the shipping information on the first page per shipment. Retain a copy of completed manifests at the PCC and include originals with each shipment.

The 3−digit NIDDK site code must be filled in at the top of the page on each shipping manifest. This information needs to be included on every manifest because it is a part of how the samples are coded by the Repository, and it is the manifest that is used to check samples in. The site code for each PCC has been noted below:

Beth Israel – 305
Emory – 301
Kansas – 302
Mayo Clinic – 303
Tufts – 304

Shipping manifests include the visit date (same as the date of collection) and, when generated through forms generation, also include the "forms date of action" (meaning "date this form was generated"). Go into forms generation and enter the participant ID, visit code and "effective labels date" at the top of the page. The date entered for "effective labels date" will print on the sample labels and will need to be written on the shipping manifest as the "visit date." The "form date of action" will be plugged in automatically so the coordinator can tell when the forms/labels were printed. The Repository will use "visit date" as the official date of collection and will disregard "forms date of action." The study coordinator may wish to draw a line through the "form date of action" to avoid confusion. Study coordinators will need to verify that the correct date of collection is listed on the sample labels and that the date on the labels matches the "visit date" on the shipping manifest. If forms/labels are printed with one "effective labels date" and the visit is subsequently rescheduled, the labels will show the wrong date of collection. Should this happen, there are two choices: 1) reprint the labels with the correct date (a waste of expensive labels); or 2) line through the auto−printed date and handwrite the correct date of collection (always a good idea to initial changes, though not required for labels). It may be helpful to refer to the "forms date of action" because this is the date that will appear on all labels if the forms packet included labels when it was generated.

11.6.2.7. FedEx Ship Manager – N/A–no longer in use

PCCs are to use the FedEx Ship Manager to ship samples and alert the repository and the DCC that a shipment is being sent. The email address that should always be entered to alert the repository of the FedEx shipment is BIO−NIDDKRepository@thermofisher.com. Cold packs (frozen) should keep the blood samples cool for at least 24 hours, but not frozen. Samples should be received by the repository within 1 day after collection.

Individual FedEx accounts were set up to be charged to when we ship the various samples obtained at study visits. The account numbers are:

- UPitt DCC account #165309723
- NIDDK Biosample Repository account #282009021
- NIDDK Genetics Repository account #276870645

The following steps are used when shipping samples and/or forms:

1. Log onto the FedEx account.
2. Set up a shipment profile that includes the following information:
   - □ The name of the recipient; detailed address;
   - □ Package and shipping details including service type (priority overnight)
   - □ Billing details including “bill transportation to Third party” , account # and reference “HALT PKD”
   - □ Email notifications to the recipient, the DCC and the coordinator name that a shipment has been sent and when it is delivered.
3. When needing to ship, click on the appropriate profile, confirm the information or modify if necessary. When completed, click on the button that reads ”ship”.
4. The next screen shows the details of the shipment. Click ”ship” again and the shipping label is displayed. The shipping label includes the sender, addressee and the tracking number. Then print the label, which is placed on the package.
5. The package can then be left at a FedEx drop box for pick up.

The coordinators should expect to receive email notification the following day that the package has been delivered. The tracking number can be used to check the delivery status if the email has not been received.

Samples collected Monday−Thursday: Ship the day of collection.

Samples collected on Saturday, Sunday, or holiday: Invert, allow to clot (SSTs), centrifuge, refrigerate, and ship on Monday or next business day.

**If it is not possible for the repository to receive samples within one day of collection, centrifuge tubes and store in a refrigerator (4 Celsius) until they can be shipped (to be received by the lab within 1 day of shipping).

For more information on FedEx shipping, please refer to Section 3.11.5.; 11.1.6.1; 11.6.2.7 and 11.6.3.7

11.6.2.7.1. Biosample Repository Shipping Address

Ship samples to: Sandra Ke NIDDK Repository Fisher BioServices, 20301 Century Boulevard Building 6, Suite 400 Germantown, MD 20874. Phone: (240) 686-4702. Email: BIO-NIDDKRepository@thermofisher.com or Sandra.Ke@thermofisher.com.

11.6.3. NIDDK Biosample Repository – Urine

Freshly voided urine and 24−hour urine samples are to be collected from all HALT PKD participants and subsequently forwarded to Fisher BioServices for use in future studies.

11.6.3.1. Required Forms

- Form 16 − Urine Sample Collection
- Form 85 − Fisher BioServices Shipping Manifest−Urine

11.6.3.2. Sample Collection/Processing

Collect and aliquot urine per instructions below, and store samples in a freezer (−20 degrees Celsius or colder). For all frozen samples to be sent to the NIDDK Biosample Repository at Fisher BioServices, an additional clear label is to be placed over the white label and part of the tube itself prior to freezing. Samples are to be stored (in specimen boxes containing cell locations) in such a way as to reflect the order in which they appear on shipping manifests. Verify that all samples listed are accounted for and ship to Fisher BioServices monthly, or within four months, including a copy of the required shipping manifests. All frozen samples must be shipped with enough dry ice to keep samples frozen for at least 24 hours.

⚠ A separate Urine Sample Collection Form 16 must be filled out and data−entered for *each participant.*

11.6.3.2.1. Freshly−Voided Urine Sample

On the morning of the B1, F5, F12, and subsequent annual visits, participants are to be instructed to collect their second morning void (the first morning void having been collected as part of the 24−hour urine collection sample). Twenty (20) mL of urine is to be collected (over a 2−3 hour period if necessary) and poured off into 4, 5mL tubes. These samples are to be frozen and subsequently 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.

11.6.3.2.2. 24 Hour Urine Samples

Collect samples per Section 11.5.2 − Instructions for Participants. In addition to the two aliquots from each participant's 24−hour urine collection that will be analyzed at CCF, urine samples are to be collected and archived at the NIDDK Biosample Repository at Fisher BioServices for future analysis. Twenty (20) mL of urine containing boric acid, and 20 mL of urine without boric acid will be aliquotted (into 4, 5mL tubes each), coded and subsequently batch−shipped to the repository. Only the clinical center will have access to the names of participants.

i. *Sample Containing No Acid:* After gently mixing the collection sample, aliquot 20 mL of urine into four 5−mL cryovials and label with a unique accession number (suffix −24N).

ii. *Sample Containing Boric Acid:* Record the total collection volume, and gently mix the entire collection sample. Aliquot exactly 40 ml of urine into a pre−made 50−ml p.p. (polypropylene) tube containing 0.4 gm of boric acid (dry powder), shake and transfer 5 ml of urine/boric acid mixture into each of four 5−ml cryovials, label and ship appropriately. No back−up or QC samples are required (maximum volume 16 ml).

For more information on procuring and preparing the boric acid to be added to urine samples, refer to Sections 11.5.4.3/11.6.3.2.2 − Boric Acid Information.

11.6.3.3. Supplies

PCCs are to supply all materials required for sample collection. Fisher BioServices will supply all materials for sample storage (specimen boxes) and shipment. Any necessary FedEx supplies should be ordered online by the study coordinator. However, plastic pouches and airbills will need to be ordered through FedEx, as printed airbills need to be placed inside the plastic pouch and then affixed to the box. Alternatively, FedEx adhesive labels may be ordered. FedEx supplies are free and can be ordered online.

To order supplies from Fisher BioServices, contact Clifford Snell, Phone: (240) 686−4706, Fax: (301) 515−4049 E−mail: Clifford.Snell@thermofisher.com.

> *For more information on supplies that PCCs are responsible for procuring, please refer to the Study Supplies Checklist.*

11.6.3.4. Storage

Samples are to be stored in the specimen boxes provided (numbered sequentially) in such a way as to reflect the order in which they appear on the Fisher BioServices Shipping Manifest−Urine. A cell−location grid is to be placed in the bottom of the specimen box before vials are placed in the box. At the time of collection, the shipping manifest is to be completed in order to function as a storage log until the time of shipment. The form completer is to enter the date of collection, the total collection volume for 24−hour urine, and the number of tubes per sample. Samples are to be stored in a freezer maintained at 20 degrees Celsius or colder and shipped to Fisher BioServices monthly, or within four months.

11.6.3.5. Packaging/Shipping

Samples are to be stored (for up to four months) in the specimen boxes provided sequentially) in such a way as to reflect the order in which they appear on the Fisher BioServices Shipping Manifest – Urine Forms.

Although a cell−location grid is to be inserted in the bottom of each specimen box before vials are placed in the box, recording cell locations on the shipping manifest is optional. However, recording cell locations would be helpful for Fisher BioServices, as samples will be stored in these specimen boxes until they are requested for future studies, at which time they will be thawed and aliquotted into smaller vials. For instructions on assembling the shippers to be used for shipping urine samples to Fisher BioServices, refer to the documents below.

- HALT PKD Medium Diagnostic Shipper (STP 320)
- HALT PKD Large Diagnostic Shipper (E−65)

11.6.3.6. Urine Shipping Manifests

Prior to shipping, complete the necessary shipping manifests (Fisher BioServices Shipping Manifest−Urine). Verify the collection date, number of tubes per sample, and total collection volume for 24−hour urine samples. Indicate on the form that samples are being shipped (or if lost or destroyed, enter the reason). Complete the shipping information on the first page of the manifest for the shipment. Retain a copy of the completed manifests at the PCC and include the original manifests with each shipment. Always include enough dry ice to keep samples frozen for at least 24 hours.

The 3−digit NIDDK site code must be filled in at the top of the page on each shipping manifest. This information needs to be included on every manifest because it is a part of how the samples are coded by the Repository, and it is the manifest that is used to check samples in. The site code for each PCC has been noted below:

Beth Israel – 305
Cleveland Clinic – 306
Colorado – 307
Emory – 301
Kansas – 302
Mayo Clinic – 303
Tufts – 304

Shipping manifests include the visit date (same as the date of collection) and, when generated through forms generation, also include the "forms date of action" (meaning "date this form was generated"). Go into forms generation and enter the participant ID, visit code and "effective labels date" at the top of the page. The date entered for "effective labels date" will print on the sample labels and will need to be written on the shipping manifest as the "visit date." The "form date of action" will be plugged in automatically so the coordinator can tell when the forms/labels were printed. The Repository will use "visit date" as the official date of collection and will disregard

"forms date of action." The study coordinator may wish to draw a line through the "form date of action" to avoid confusion. Study coordinators will need to verify that the correct date of collection is listed on the sample labels and that the date on the labels matches the "visit date" on the shipping manifest. If forms/labels are printed with one "effective labels date" and the visit is subsequently rescheduled, the labels will show the wrong date of collection. Should this happen, there are two choices: 1) reprint the labels with the correct date (a waste of expensive labels); or 2) line through the auto−printed date and handwrite the correct date of collection (always a good idea to initial changes, though not required for labels). It may be helpful to refer to the "forms date of action" because this is the date that will appear on all labels if the forms packet included labels when it was generated.

11.6.3.7. FedEx Ship Manager

PCCs are to use FedEx to ship samples and alert the Repository and the DCC that a shipment is on its way. The email address that should always be entered to alert the Repository of the FedEx shipment is BIO−NIDDKRepository@thermofisher.com.

For more information on FedEx shipping, please refer to Section 11.1.6.1 − FedEx Ship Manager **−N/A−no longer in use**

11.6.3.7.1. Shipping Address

Ship samples to: Heather Higgins NIDDK Repository Fisher BioServices 20301 Century Boulevard Building 6, Suite 400 Germantown, MD 20874. Phone: (204) 686-4702. Email: Bio-NIDDKRepository@thermofisher.com.

11.6.4. PCC Repositories

Any request to create and maintain an archival repository at a PCC must be forwarded to the Publications/Ancillary Studies Subcommittee as an application for an ancillary study. The Steering Committee has final approval on all ancillary studies applications.

11.7. Reporting Lab Results to Participant PCP/Nephrologist

11.7.1. PCC and Local Laboratory Results (Quest/Hometown)

Normal laboratory results will not be routinely communicated by the PCC to participants and/or their PCP/nephrologist if authorized. However, the study coordinator is to communicate any abnormal lab results to the participant, who is responsible for informing his/her own PCP/nephrologist.

11.7.2. Central Reference Laboratory Results (CCF)

Central laboratory results are for research purposes only and will not be used for patient care. In the event of confirmed serum creatinine doubling, the study coordinator is to inform the participant of the dates and values of the following: average at baseline, initial doubling, and confirmed doubling. If a participant's required authorizations are on file, lab results can be faxed automatically to the PCP/nephrologist, if desired.

11.7.3. Archived Sample Results

Laboratory tests performed on archived samples are for research purposes only. Results will not be shared with participants, primary care physicians or nephrologists or investigators.

Chapter 12. Magnetic Resonance Imaging (Study A)

12.1. Participants

12.1.1. Frequency of Imaging Exams

Imaging studies will be obtained at Baseline (B1), 2 years (F24) and 4 years (F48) and 6 years (F60) for all participants enrolled to Study A.

MRI scans may be obtained +/- six months of target date (i.e. F 48 MRI: In the event the participant cannot attend his/her F48 visit, the F48 MRI scan may be obtained at the F42 or F54 visit. The F60= may obtain at F54 or F66).

12.1.2. Dietary Restrictions

NPO or light diet several hours prior to the scan to minimize intestinal motility.

12.1.3. Holding Medications

For visits during which imaging exams are scheduled, Study A participants are not to take their antihypertensive medications either the evening prior to or the morning of the visit.

12.1.4. Contraindications

Exclusions specific to MR imaging acquisition and measurement:

1. Cardiac Pacemaker.
2. Presence of MR incompatible metallic materials (e.g. clipped cerebral aneurysm, metal rods and artificial joints)

This exclusion may be center−specific as some institutions permit MR compatible metallic clips.

3. Body weight >159 kg (350 lbs)
4. Untreatable claustrophobia
5. Pregnancy

12.1.5. Incidental Findings or New Findings of Concern

MR scans are to be read and interpreted at the PCC. However, the PCC is not responsible for work−up/diagnosis, follow−up, or treatment of any abnormalities revealed by these imaging studies. Rather, if an abnormality is found on a scan (e.g., an unusual mass) the radiologist must notify the principal investigator, who, in turn, must immediately notify the participant. If the participant grants written authorization, the participant's PCP and/or nephrologist may also be notified by the PCC. It is recommended that the final MRI report is reviewed by site coordinators prior to filing in document in the research chart. Any incidental findings or new findings of concern should be reviewed. Coordinators should confirm the investigator is aware of the result and that appropriate follow-up has been arranged.

12.2. HALT PKD Imaging Protocol

12.2.1. Summary

- Kidney Imaging
  - Kidney volume (T2, T1)
- Liver Imaging
  - Liver cyst volume (T2)
- Cardiac Imaging
  - Left ventricle size and wall mass and optional ejection fraction (Cine 2D FISP)
- Renal artery blood flow (may not be available at some sites)

12.2.2. MR for Kidney Volume and Liver Cyst Measurement

The change in total kidney volume, as assessed by abdominal MR, is the primary outcome for participants enrolled to Study A. In addition, MR images for the liver cyst volume measurement will be acquired. The MR techniques for imaging and interpretation of volumetric measurements established in the CRISP Study will be employed. MR images will be obtained at each PCC using a protocol developed by the HALT PKD Imaging Subcommittee. Following acquisition, MR images will be reviewed locally at each PCC and then transferred securely, via the World Wide Web, to the Image Analysis Center (IAC).

12.2.3. Phase−Contrast MRA for Renal Blood Flow Measurement

The rate of change in renal blood flow over time, as assessed by phase−contrast MRA, is a secondary outcome for participants enrolled to Study A. Methods established in the CRISP Study, specifically, rapid image acquisition during a single breath−hold, will be employed. MRA for measuring renal blood flow will be obtained at the same sitting in which MR imaging of the kidney, liver, and left ventricle, is performed.

12.2.4. MR for Left Ventricular Size and Wall Mass Measurement

Left ventricular size and wall mass, as assessed by cardiac MR, is a secondary outcome for participants enrolled to Study A. MR for imaging the left ventricle will be performed during the same sitting of the MR for imaging the kidney and liver and the MRA for renal blood flow.

12.2.5. Imaging Forms

12.2.5.1. MRI Session (Renal) Form

MRI Session (Renal) Form 21 is to be completed by the radiology technologist and reviewed by the radiologist at the time of the scan. This form must be entered promptly, with images transferred to the Imaging Analysis Center (IAC) right after the scan. Imaging accession numbers will be automatically printed on imaging forms when the forms are generated.

12.2.5.2. MRA (Renal) Information Form

Renal Blood Flow (MRA) Form 22 is to be completed by either the study coordinator or radiology technologist and reviewed by the radiologist at the time the MRA is obtained. This form must be entered promptly, with the data transferred to the Imaging Analysis Center (IAC) right after the scan. Imaging accession numbers will be automatically printed on imaging forms when the forms are generated.

12.2.6. Scanning Procedure

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. (Optional) 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. (Optional) 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. (Optional) 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.
10. **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 â¤15o. 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.
11. 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.
12. 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.
13. (Optional) **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.

14. **(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: 192x256matrix, 75o 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). - Drafted December 29, 2003; Revised September 25, 2005; Revised February 2, 2007.

Figure 12−1. 2D Fat−Saturated FIESTA Renal Artery Localization

The image plane was selected from the sagittal scout image.

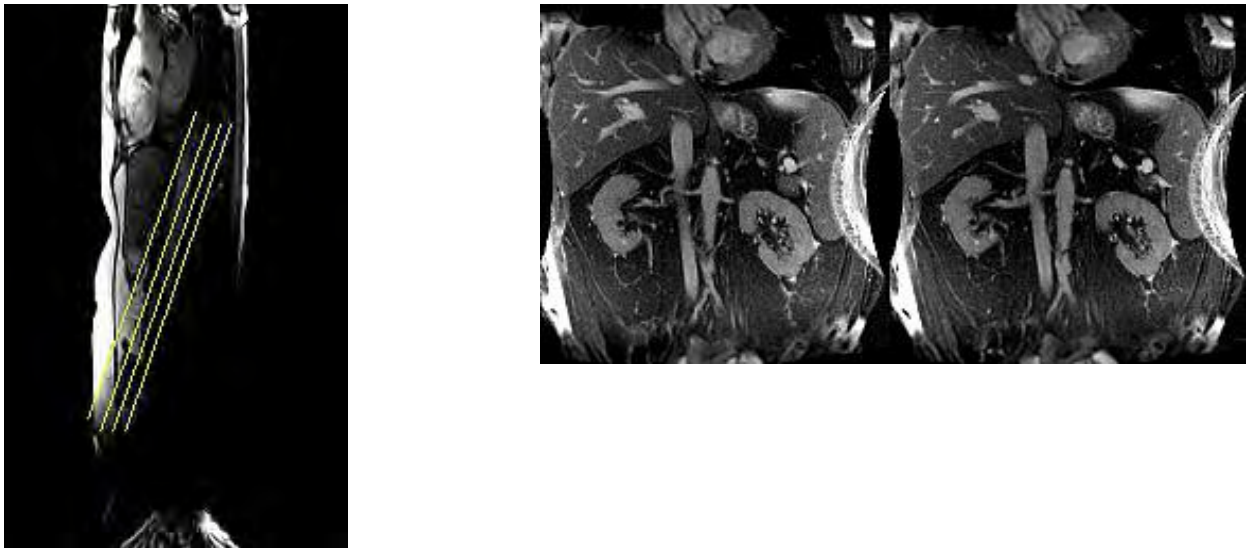
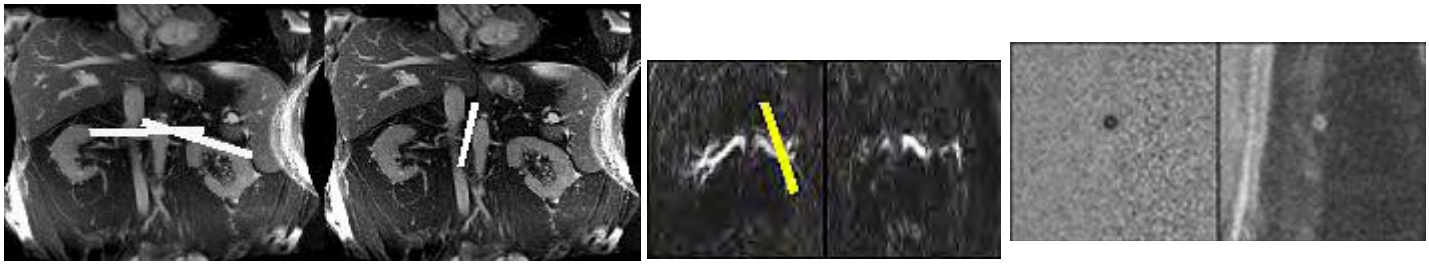


Figure 12−2. Cine PC scout image for renal artery localization and the phase and magnitude images



12.3. Image Quality Control

The HALT study radiologist at each PCC will monitor the quality of images immediately after the acquisition of each sequence while the participant is on the scanner. The adequacy of images will be determined by evaluating the scan coverage and recognizing the presence of artifacts and respiratory motion. Radiologists and technologists will be thoroughly trained and certified and will have access to examples of image quality (CD and hard copies). If the quality of images is in question while the participant is still on the scanner, a repeat scan should be conducted and sent to the IAC along with proper documentation. If the repeat renal blood flow (a secondary outcome) is unacceptable, the participant will be dropped from further blood flow measures.

12.3.1. Rescanning after the Participant has left the PCC

Once images have been transferred, the IAC will contact the PCC to request a rescan if the quality of images received is unacceptable. In such cases, participants should be rescanned as soon as possible and within the following timeframe: At baseline, local participants should be rescanned within four weeks and participants travelling greater distances to the PCC should be rescanned within four months (at or before the F5 visit). Because kidney size should not be affected by study drugs within this relatively short amount of time, participants will not repeat drug washout before re−imaging. Although renal blood flow will be affected by study drugs, it is a secondary outcome and so will be repeated (at baseline only) while the participant is on study medication. If the repeat MRA is unacceptable, the participant will be dropped from further blood flow measures. If images of kidney volume obtained after baseline (at visits F24 or F48) are unacceptable, scans should be repeated at the subsequent six−month visit.

Although PCCs are free to rescan, per the clinical judgment of the PI and in accordance with budgetary constraints, the study analysis must include only authorized images (i.e., rescans requested by the IAC).

12.4. Image Transfer Methods

After the initial PCC visit has been scheduled, the participant will be registered to the study (entered into the database) and randomly assigned a HALT participant ID code. Prior to imaging, an image study identifier (accession number) will be assigned for each imaging study. These image study identifiers are printed on the imaging forms when the forms are generated at the local PCC. Images are sent from the imaging modality (MR scanner) to the PCC Workstation, and software on the workstation allows study personnel to de−identify or "scrub" images by removing the participant's confidential information from image headers and replacing it with the HALT participant ID code and image study identifier. The de−identified image study is then queued and ready for transmission to the IAC. Initiation of the Jupiter (network connect) client software enables the establishment of a secure virtual private network (VPN) channel over the Internet. The digitally−encrypted transfer is initiated by study personnel at the PCC.

Complete details for de−identification and image transfer are outlined in the subsections below.

Process Summary: Quick Guide to Image Transfer

1. DICOM files are sent from the scanner to the PCC Workstation.
2. Establish the VPN connection via Jupiter client in order to transfer.
3. Open CSW program in order to de−identify and send images.
4. *Scrub Headers*: Select imaging study, replace name and local patient ID with HALT ID and imaging accession number.
5. *Queue De−identified Images*: Click Export, Destination IAC, and Export again.
6. *Transfer*: Images will be transferred via VPN, check status of transmission.
7. *Archive*: Burn a backup CD of the imaging study if necessary. Exit VPN and CSW after all images have been transmitted.

12.4.1. PCC Workstation

A standardized computer has been purchased and configured by the IAC for each PCC. This system is to be used for printing forms and labels, data entry and transferring images to the IAC. Each system is equipped with Clinical Studies Workstation (CSW) and Jupiter client software. CSW is a software product developed by Washington University to facilitate research studies involving image data from clinical or research instruments. The software allows the user to store images and modify header attributes, such as patient name and local patient ID, before the data is sent to a research system. This allows the user to protect study participant confidentiality and substitute appropriate research identifiers which cannot be entered at the clinical device. The Jupiter client software allows for the secure transmission of de−identified images to the IAC.

12.4.2. Image Acquisition

Image studies are sent from the imaging modality (MR scanner) to the PCC Workstation. Individual images are uniquely identified by DICOM attributes which are embedded in the image header. When the PCC Workstation is started, a process is activated which provides the ability to receive and store DICOM images. This feature of CSW software allows images to be stored on the PCC Workstation for de−identification prior to transfer.

12.4.3. Header Scrubbing and Image Transmission

12.4.3.1. Establish VPN Connection

After the entire imaging study has been sent from the imaging modality (MR scanner) to the PCC Workstation, start the Jupiter client and enter the assigned password. This step connects your computer to the virtual private network (VPN) used by the IAC and allows you to send de−identified data to the IAC storage system.

☞ Establishing the VPN connection removes your computer from your campus network until the VPN software is disconnected. Therefore, it is important that this step take place after the MR scanner has completed its transmission to the PCC Workstation.

12.4.3.2. De−identify Headers and Transmit Images via CSW Software

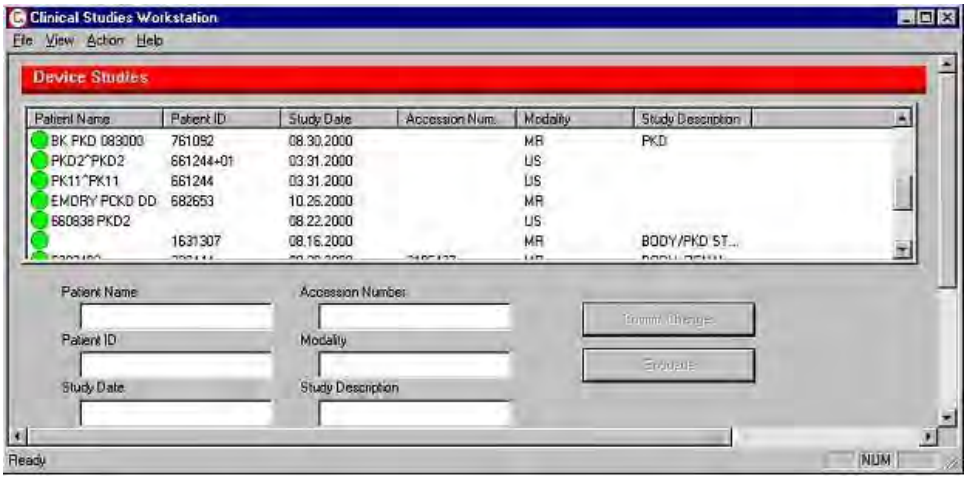
The Clinical Studies Workstation (CSW) program is launched from the shortcut icon on the PCC Workstation.

The program allows the user to modify certain header attributes and queue images for transmission to the IAC. The goal of scrubbing headers is to replace personal identifying information (participant's name and local patient ID) with HALT participant ID and imaging accession number in order to protect the privacy of study participants.

☞ Changes made for de−identification are not retained by the CSW application. When the application is exited and started again later, the system will show the original patient name and local patient ID which came from the scanner.

The CWS application provides several different views of the data received from the MR scanners and stored by the DICOM Storage Service on the PCC Workstation. Figure 1 is an example of the Study View from the CSW application. The red Device Studies banner denotes that these are imaging studies which have been received from a scanner. Although a Series View is also available you will usually send an entire study to the IAC.

Figure 12−3. Screenshot − Study View from CSW Application



To de−identify and send an imaging study to the IAC, follow these steps in Study View:

1. Select the study to be transmitted (single click).
2. De−identify images: Remove the Patient Name. Replace the local Patient ID with the HALT participant ID. Add the imaging study identifier (accession number).
3. Select the ***Commit Changes*** button. The circle icon next to the study will change color from *green* to *yellow* to indicate the study has changed. As noted above, this stores the changes in local memory (desktop) and does not change files on disk.
4. Select the study to be transmitted again (single click). You should see your new values for Patient Name, Patient ID, and Accession Number appear in the text boxes. Make sure the participant's name and local patient number do not appear.
5. Select the ***Export*** button.
6. Queue images: Select the destination "IAC" and click the ***Export*** button.
7. Repeat the steps above for each study or series in the study protocol.

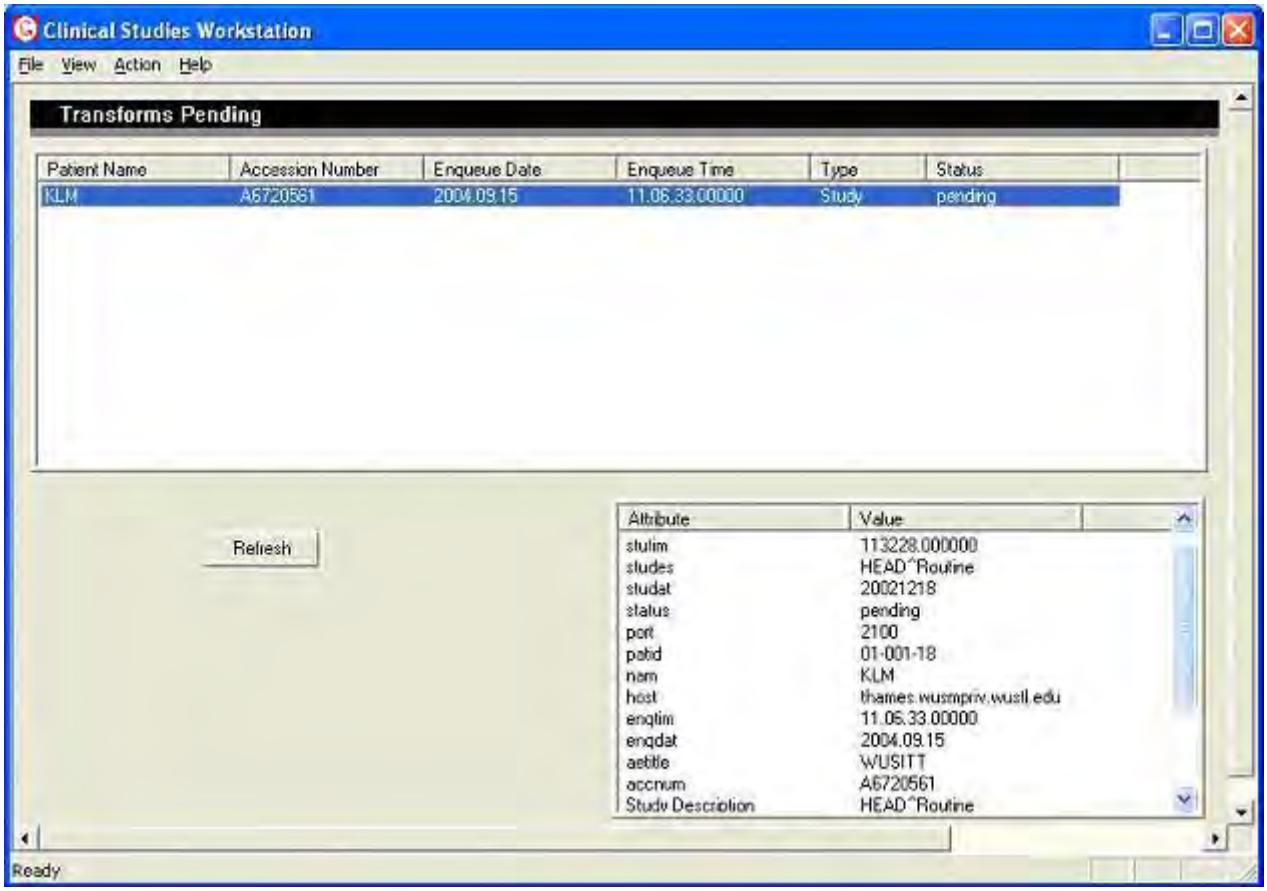
12.4.3.3. Transmissions Pending

Selecting the Export button the second time (step 6 above) writes a text file in the queue area and instructs the DICOM Export Service to send images to the IAC. Transmission will begin after about one minute and may take upward of 15 minutes to complete. The CSW application can be used to view the queue entries for images to be transferred to the IAC.

You can monitor the progress of the transmission by following these steps:

1) On the menu bar of the CSW application, select View and Queue Pending. A screen similar to Figure 2 below will appear and provide the current status of the studies being transmitted.
2. Click the Refresh button to update the status. A "failed" status usually indicates the VPN connection is not active.
3. When the queue is empty, the Jupiter client software can be disconnected to allow the PCC Workstation to return to its normal network connection.
4. To confirm that images have been sent, refer to Figure 3 in the next section.

Figure 12−4. Screenshot − Current Status of Studies being Transmitted



12.4.4. Transfer

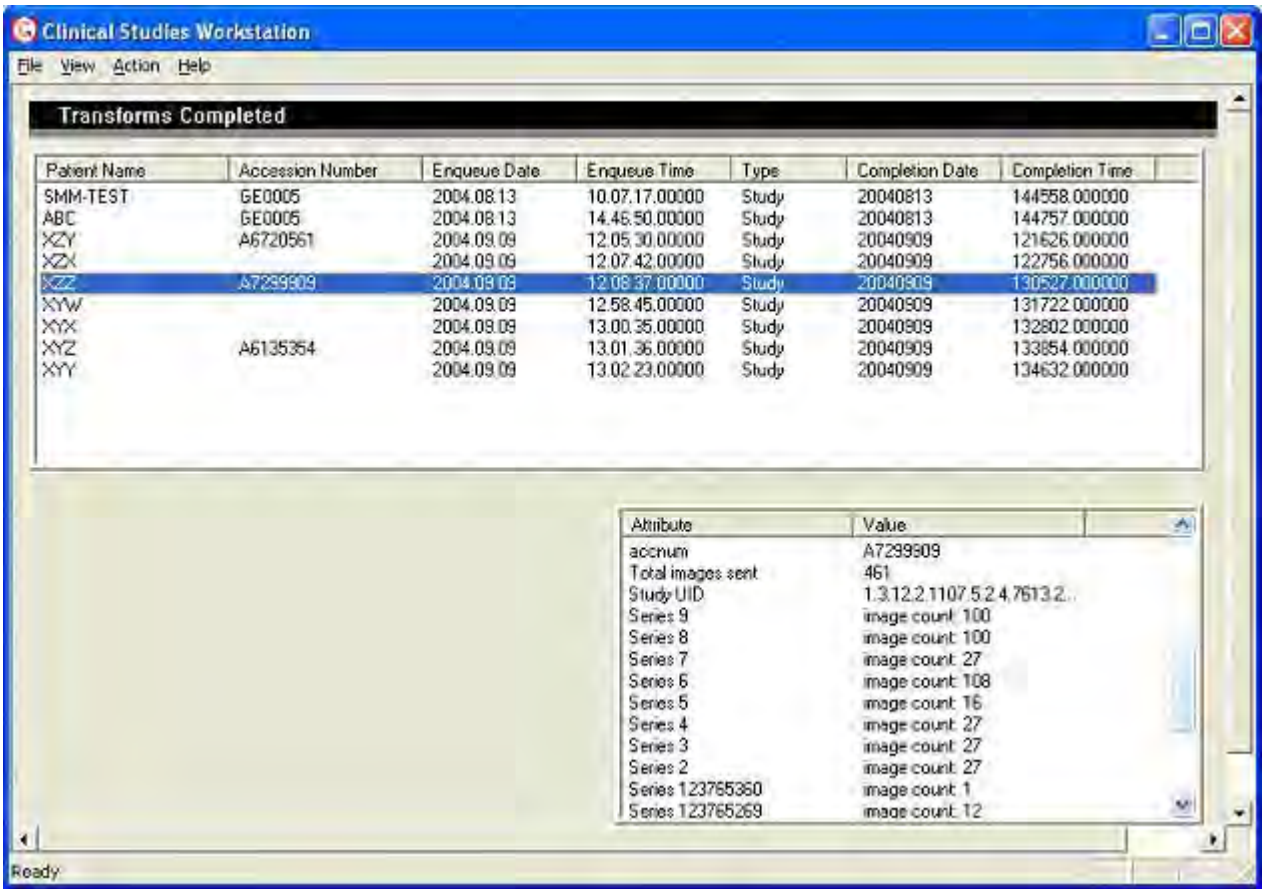
The DICOM protocol is used to transfer images from the acquiring modality to the PCC Workstation via the local area network. This provides a facility for removing participant demographics ("header scrubbing") from the DICOM image study sets and substituting HALT participant ID codes and imaging accession numbers assigned by the IAC. This operation allows participants' confidential information to remain at the PCC site.

Following header scrubbing, study personnel enable a software client which creates a virtual private network (VPN) connection between the PCC Workstation and the firewall device at the IAC. Point−to−point Tunneling Protocol (PPTP), Layer 2 Tunneling Protocol (L2TP), and IPSec are used to establish a secure channel over the Internet. Encryption (Data Encryption Standard − 128 bits) is then applied to the image data sent via VPN.

Images are decrypted by the firewall device at the IAC and forwarded over a private local area network to a DICOM storage application on the LINUX computer system dedicated to HALT PKD.

To see if a study has been transmitted, select View and Queue Complete. A screen similar to Figure 3 will appear providing a list of all studies transmitted. Clicking on individual studies provides details on the study in the lower right hand corner of the window. Scroll down to the "total images sent" attribute to confirm the number of images that were transmitted.

Figure 12−5. Screenshot − List of all Transmitted Studies



12.4.5. Archive

PCCs are to archive all HALT PKD imaging studies received from the MR scanner. Some PCCs may wish to create backup copies on CD−ROM at the time of transfer, and a CD−ROM drive is provided with the PCC Workstation for this purpose. To create an archive copy of a study, repeat the steps in section 12.4.3.2 but change the destination in Step #6 to "Local Disk for Backup/Media Export". The studies are saved in the C:/CSW/Export/Images folder on the PCC Workstation. Use the available CD burning software to copy the study to a CD−ROM (multiple images will fit on a single CD).

Studies that have been successfully transmitted to the IAC, once archived, may be deleted from the PCC Workstation. To delete a study from the PCC Workstation, simply highlight the study in the Device Studies View, click Action in the menu bar, and click Delete from the drop down list. Click **Y**es to delete the study. Be careful that you don't accidentally delete studies that have not yet been archived or transmitted to the IAC.

12.5. Central Processing and Analysis

HALT PKD will include acquisition, storage and analysis of data from a variety of different sources. First, the PCCs will enter a variety of types of data directly into the web−based data−entry system. This data−entry system includes all features of a data−management system, including data−editing, data−entry and data−deletion. Second, the image data will be transmitted to the imaging section at the IAC. After data analysis has been performed by the imaging group, relevant data will be transferred to the data−management system. Third, a variety of data will be analyzed at each PCC and will also be entered into the web−based data−entry system.

12.6. Scanner

12.6.1. Breakdown

It is likely that at some point during the HALT PKD study, an MR scanner will undergo technical failure such that the imaging protocol cannot be performed or completed as scheduled. At those sites with more than one scanner, a backup scanner should be designated. If an identical scanner is available, it should be validated as the backup scanner. If a scanner is available but not identical, as long as it can perform the study sequences, it may be validated as a backup. The validation may be done using a kidney phantom or human subject. The study protocol then needs to be saved in the memory of the designated backup scanner. At sites where there is no available backup scanner, the participant will need to be rescheduled for the earliest available date for rescanning, preferably within 2 weeks. If only MR imaging must be performed, the participant may be rescheduled as an outpatient.

12.6.2. Replacement

At present it is expected that the MR sequences, developed and finalized for the HALT PKD protocol, will be in use for the duration of the study. There may be some modification in MR sequences and scanning techniques, but no dramatic change requiring new hardware. Over the course of the study, however, upgrade or replacement of the designated MR scanner(s) may occur. This change must be communicated to the IAC, and it is the responsibility of the PCC radiologist to validate a new scanner. If only a software upgrade is performed, as long as the study protocol can be followed, there is no concern. If a new device is installed, it must be validated for equivalent magnetic field strength and homogeneity, as well as for its ability to perform the study sequences (or equivalents), preferably by use of a kidney phantom. Alternatively, comparison of a scan on a study subject that has had a previous MR may be used. If new technologists are added to a site, they must be trained in the objectives and procedures for HALT PKD imaging at the direction of the PCC radiologist, with the assistance of the study technologist(s).

12.6.3. Quality Control

It is the responsibility of the PCC radiologist to assure continued image quality. It is expected that a regular Quality Control Program of the MR facility (as is routine for clinical purposes) has been established at each site. The radiologist is to monitor study procedures as they are performed and document proper performance. The radiologist is also to document any and all reasons for variations from standard protocol or variations in quality. Overall quality should be reviewed weekly or monthly, depending on volume, over the course of the study. Periodic review with the technologist to address any decline in quality should be done as needed.

12.7. Certification

It is required that HALT PKD study/imaging personnel undergo training and be certified prior to performing imaging procedures for HALT PKD. Imaging equipment must also be certified prior to performing any imaging procedures for HALT PKD.

12.7.1. Personnel

Inter−rater reliability will be assessed across radiologists in a quality control exercise to be conducted prior to the start of HALT PKD. Once each site has been certified, imaging examinations can be performed.

For best image quality, MR examinations should be performed by experienced MR technologists who are ARRT−registered radiologic technologists, preferably with MR Registry. At the discretion of the PCC radiologist, a specific technologist may be designated as HALT PKD study technologist. A backup study technologist should also be designated. Depending on local operations, the radiologist may choose to designate a pool of technologists to perform MR scans on HALT PKD participants. It is the responsibility of the PCC radiologist to thoroughly train all participating technologists in proper study procedures, as well as to make certain they understand the objectives and proper imaging protocol.

12.7.2. Equipment

It is the responsibility of each PCC, under direct supervision from the study radiologist, to identify the MR scanner to be used for MR data collection in HALT PKD. This should, hopefully, be the most up−to−date scanner, 1.5 or higher Tesla. The scanner will be identified and validated by means of scanning a series of normal or PKD subjects, such that the capability of the scanner to perform the imaging sequences required by the study protocol will be documented. The validated study scanner is then to be used for collection of MR imaging data on HALT PKD participants.

An institution with multiple, similar scanners may elect to validate more than one scanner for study use. The preferred approach would be to have a single, designated scanner that has been validated with phantoms. Imaging sequences should be saved as a clearly−identified HALT PKD protocol so that each participant is scanned with the proper set of sequences.

Chapter 13. Safety

13.1. Safety Monitoring

The HALT PKD study will undertake a number of activities to minimize risks to participants and ensure their safety. Potential participants undergo complete screening evaluations to determine whether it is safe for them to take part in the study. Safety is to be monitored during examinations, and selected results from study assessments are to be provided to participants when there are health and safety implications. At the Screening visit each participant is required to identify a physician (PCP and/or nephrologist) who may be called on by HALT PKD in any cases in which treatment and/or follow−up of an event or abnormality is needed.

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 10−4. Standard measures will be used to control potassium, including dietary modifications and/or use of furosemide and/or use of exchange resins (sodium polystyrene sulfonate). If necessary, the participant may be sent to 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 Study B participants must be sent home from the baseline visit with 3, 15g doses of sodium polystyrene sulfonate liquid suspension to be saved for later use, if needed. This may be deemed unnecessary at the discretion of the PI in such cases as participants are known to be hypokalemic and/or require KCL. Study A participants with high normal potassium or frank hyperkalemia must also be given 3, 15g doses of sodium polystyrene sulfonate at the baseline visit to be saved for later use, if needed.

From the drug washout period through the first six weeks of the study, changes in medications and/or doses are expected to be frequent. Participants are to be advised to monitor blood pressure every four days and contact the study coordinator immediately if BP readings are out of the accepted range given the phase of the study (as summarized in Table 9.6). Participants are also to be instructed to contact the study coordinator if they develop symptoms of hypotension (lightheadedness, postural lightheadedness). The frequency of home blood pressure monitoring and 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 are to be measured at the PCC, or at the nearest local laboratory, one week after the study drug has been initiated, as well as after each increment of the study drug. Serum potassium may be monitored more frequently in individuals with borderline hyperkalemia, at the discretion of the principal investigator (PI).

Co-administration of Telmisartan and Digoxin, both metabolized by the liver, can lead to an increase in the peak concentration of Digoxin by up to 50%. Thus, digoxin levels are to be checked at baseline and along with potassium, BUN and creatinine, as described above, between dose increments of ACE−I and telmisartan/placebo in the first 8 weeks of the study, or until stable. Dose adjustments for digoxin are to be made, as necessary, by the PI. Digoxin levels are to be checked every six months and one week after any change in the dose of study medication.

At each PCC visit blood pressure is to be measured using a standardized, automated blood pressure monitoring device. At each PCC visit, a systematic review of anticipated side effects is to be conducted. A panel of laboratory measurements is to 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 PCC visit, a systematic review of anticipated side effects is to be conducted. Individuals currently on a BP drug for a non−hypertensive indication will be allowed to enroll in the study.

Participants taking a "relatively small dose" of a beta or calcium channel blocker may be enrolled to the study, with the approval of the principal investigator, as this is not expected to significantly impact BP or put participants at greater risk. Individuals on a large dose of beta or calcium channel blocker for a non−hypertensive indication will not be enrolled to 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. When a participant on a "relatively small dose" of a beta or calcium channel blocker is enrolled, this information will be collected on Enrollment Form 10 (by checking "yes" for the exclusion and then checking a box to indicate "approved by PI"). The Quality Control Committee will follow cases of BP drugs being taken for non−BP indications, and a computer routine will be set up to flag

whether these medications were preexisting or began after the start of washout. This information will be communicated to the QC Committee in its monthly report.

Once eGFR 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 3−month telephone visits or 6−month PCC visits.

13.2. Data Safety and Monitoring Board (DSMB)

The NIH has appointed an independent DSMB, made up of nephrologists, who have expertise in the areas of renal progression and clinical trials, experts in the treatment of hypertension, and expert statisticians. 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. The DSMB will meet annually to review the progress of HALT PKD, at which time a summary of adverse events and other interim results will be reviewed. All substantive changes to the protocol require approval from the DSMB.

The HALT PKD trial received DSMB approval to extend the Study A and Study B Though June 30, 2014. Participants will be followed up to their last visit prior to the June 30, 2014 time point.

13.3. Abnormal Lab Values

PCCs are to inform participants of any concerning lab values received from local laboratories (PCC, Quest or hometown lab) and may, if authorized, communicate the values directly to the participant's primary care physician. The DCC will query sites in regard to any abnormal PCC lab values that have not been flagged as such. However, the DCC will not have a routine method of checking for abnormal values received from local labs. PCCs will not be informed of any abnormal lab values resulting from specimen analyses performed by CCF testing the 24 hour urine aliquots, or by the Cleveland Clinic Reference Laboratory (serum creatinine), except in the event of serum creatinine doubling. However, PCCs will have access to routine central serum creatinine results.

Guidelines for informing participants of safety concerns or abnormalities may be found referring to Sections 8.1.4/11.1.8/13.4 − Informing Participants of Safety Concerns.

13.4. Protocol Deviations/Major Violations

Please refer to Table 13.1 below for a listing of major protocol violations and the appropriate actions to take in addressing them.

Table 13−1. Major Protocol Violations

Protocol Violation	Continue in Study	Unmask	Impact on PCC	Comment
Failure to acquire valid, signed, informed consent prior to screening, randomization, or genetic sample collection	Yes − *If participant willing to consent*	No	Review processes, consent ASAP, report to IRB	
Participant included in another study that is not an approved HALT PKD ancillary study	Yes − *If no safety concern*	No	Review processes, consent ASAP	
Breach of confidentiality	Yes	No	Review processes	If the breach leads to unmasking of therapy, the participant may still be continued on study with regular follow−up visits and tests.
Missed endpoints, such as MR/MRA/Cardiac MR, failure to check creatinine doubling within 2 weeks, failure to collect central creatinine or aldosterone samples (24 hour urine collection), lost to follow up, delays in data entry of any participant visit form greater than 2 weeks.	Yes	No	Review follow−up procedures and subject compliance	Missing measurements are detected ASAP and obtained with minimal delay. Acceptable visit ranges are found in Table 8.1 − Acceptable Ranges and Missed Visits.

Open−label drugs given out of order. (Refer to stepped protocol for either Study A or Study B.)	Yes	No	Review procedures and protocols, report to IRB	Note on appropriate forms, IRB issue
Safety issues, such as enrolling/randomizing non-eligible participants, required tests not completed by participants, enrollment form not entered within 3 days of beginning drug washout	No	Yes	Review screening/ informed consent procedures, report to IRB	IRB issue. PI and medical monitor will determine safety of participant's continuation on−study. All randomized participants are followed under intent−to−treat policy.
Failure to report SAE in a timely fashion	Yes	No	Review procedures and protocols, report to IRB	IRB issue
Participant is misdosed (over or under per protocol section) or inappropriate drug cards are dispensed	Yes	No	Review procedures and protocols, report to IRB	Dose of study drug adjusted, in steps if necessary, to appropriate level. Dose adjustment guided by blood pressure and participant symptoms, if any. Reporting based on nature/severity/duration of clinical response
Non−participant use of medication − any dose taken by non−participant is a violation, not just an overdose (i.e, participant's spouse takes study drug or child of participant takes OD) − this is not, in definition, an SAE	Yes	No	Report to IRB, review medication safety issues with participant	Notify IRB of misuse of study drug. Study drug must be accounted for, especially if drug dispensed or cost covered by HALT PKD. It does NOT have to be reported as SAE
Missed safety labs or missed visits during titration period up to and including F5	Yes	No	Review procedures and protocols, review participant compliance	
Other significant protocol deviations	Yes	No	Review procedures	

13.5. 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. 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 the Symptoms Checklist (Form 5) has taken a targeted approach in regard to the more common or concerning side−effects of medications. Because the relatedness of an event to study medication cannot be determined with certainty after the start of medication, all adverse events will be reported from the screening visit until up to thirty days after the last dose of study medication (whether masked or open−label drug). AEs are to be recorded every three months on the Symptoms Checklist (Form 5). For AEs not listed on the Symptoms Checklist (Form 5), the study coordinator should enter a free−text description.

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

13.6. Adverse Effects of Study Medications

Adverse symptoms of drug effects are to be recorded throughout the study. Please refer to Table 10.4 − Management of Adverse Effects of Medications for information on how participants who develop anticipated adverse effects of study drugs are to be managed.

Per Table 10.4, all concerning lab values are to be reported within two weeks of sample collection, and all lab values defined as serious, if verified, are to be reported within 24 hours, per SAE Reporting Guidelines.

13.7. Serious Adverse Events (SAE)

In addition to the information below, complete information on the definition of an SAE, as well as reporting guidelines for SAEs, can be found by viewing Section 13.8 − SAE Definition/Reporting Guidelines.

13.7.1. Definition of an SAE

An SAE is defined as any undesirable experience meeting one or more of the following criteria, regardless of relatedness to study participation,[7] occurring from the time a participant signs the informed consent (before the screening visit) until the end of the study.[8][9][10].

- *Resulting in Death* − All deaths must be reported as SAEs.
- *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.
- *Life−threatening* − If the patient is at substantial risk of dying at the time of the event, or if continued use of a study medication [11] or study procedure [12] would result in the patient'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.
- *Resulting in significant, persistent or permanent harm or disability.*
- *Exceeding the nature, severity or frequency of risk described in the protocol.*
- *Congenital anomaly − If there is suspicion that exposure to a study medication or procedure prior to conception or during pregnancy resulted in an adverse outcome in the child.*
- 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.

13.7.2. SAE 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 Form13. Information not available at the time of the initial report should be submitted to the DCC as a follow−up report in a timely fashion. All SAEs will be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. Some study SAEs may also reach the threshold of requiring reporting to your local IRB. Sites will follow local IRB policy and procedures for reporting serious adverse events within their institution.

Reporting requirements for the FDA differ depending on relatedness to study interventions as follows:

SAEs that are reasonably related to study participation*:*

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.

Unexpected/Unanticipated: An event is defined as being unexpected/unanticipated if the event exceeds the nature, severity, or frequency described in the protocol. Only events that are considered reasonably related to study drug can be considered unexpected.

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.

Adverse events that are "expected" appear as risks in the informed consent. Adverse events that are 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. Principal investigators 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.

There are six terms, as noted in the table below, used in determining if an event is related or unrelated to the study.

Table 13−2. Determining SAE Relatedness

Is the event related to study participation?	Related	Unrelated
Definitely	X	
Probably	X	
Possibly	X	
Unlikely		X
Not related		X
Unknown (*to be used sparingly, if at all*)	X*	
*An event classified as unknown would likely be considered related to error on the side of safety. The PI should use his/her judgment to determine the relatedness of an event, according to the first five terms above and should choose "unknown" on only very rare occasions, if at all.		

- Whether an event is expected/anticipated needs to be addressed only if the event is considered related to study participation (definitely, probably, possibly).
- If an event is unrelated to study participation, it is not necessary to determine whether or not it was expected/anticipated.

Table 13−3. Reporting of SAEs from PCC to DCC

An event is serious or results in:	Study-Related ?	Report to PI + DCC (Form 13)	Report to Local IRB (may vary by site)
Death or Hospitalization	Yes	24 Hours	5 Business Days
	No	24 Hours	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 Hours	5 Business Days
	No	24 Hours	Annually

Table 13−4. Reporting of SAEs by DCC

Reporting by DCC to:	NIDDK	#	QCC	DSMB	FDA
Study Related SAEs	1 Busine	5 Busines	Monthly − except 1 business day *	5 Busines	%*
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.

> *PCCs are responsible for providing SAE reports to the DCC within the required timeframe, regardless of technical difficulty. The study coordinator should call and/or fax an SAE report to the DCC.*

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 drug related and unanticipated, the DCC sends electronic notification to all PCCs (including the reporting PCC) within five days of the original report, accompanied by 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 per the table above (Table 10, Section 12 of the study protocol).
6. DCC reports events to the FDA per the table below (Table 11, Section 12 of the study protocol).

Table 13−5. Reporting of SAEs from DCC to FDA

Event	Anticipanted/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

Per FDA Guidelines: ***Unexpected adverse drug experience***: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the labeling of the medication) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

13.7.3. 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, but unmasking is not anticipated for most SAEs.

13.7.4. Cardiovascular Events

All SAEs are to be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. This allows tracking of cardiovascular events throughout the duration of the study.

13.7.5. Death

Upon receipt of information regarding the death of a participant, the Study Coordinator must request supporting materials, such as death certificates, autopsy reports, and/or other medical records, to confirm the cause of death. For each death the study coordinator is to fill out and data−enter Death Notification Form 31, as

well as an ESRD Death Notification Form (HCFA Form 2746), if appropriate. The latter form is required by the U.S. Department of Health & Human Services. A consent for release of information from the deceased participant's next−of−kin must be obtained by study coordinators to allow her/him to request the records.

13.7.6. Hospitalization

At each 3−month study visit (over the telephone or at the PCC), participants must be asked if they have been hospitalized since the last study visit. If a participant has been hospitalized, the study coordinator must ask the participant to sign a release−of−information form that authorizes the institution in which he/she was hospitalized to release pertinent medical records to the PCC via fax or mail. Once the release form is signed by the participant, the study coordinator should request the discharge summary from the institution named in the release form and review it upon receipt. For each hospitalization, the study coordinator must complete Hospitalization Form 30, listing the dates and the primary reason(s) for the admission. The PI must review and approve the completed Hospitalization Form 30, after which the study coordinator must data−enter it. Hospital Discharge summaries should be faxed to the DCC.

Amendment I *- The DCC will distribute them to the Endpoints Committee for adjudication.*

13.7.6.1. Hospitalization for 23 Hour Observation or Pregnancy

The following admissions qualify as study serious adverse events requiring submission of a study serious adverse event Form13 and hospitalization Form30:

- ☐ Participant admissions for an overnight "23 hour observation"
  - o Obtain HIPPA release and obtain discharge summary for adjudication
- ☐ Pregnant participants admitted for labor and delivery
  - o Obtain HIPPA release and obtain discharge summary for adjudication
  - o Form 13 study SAE comments should include documentation of the infant's health status that may be found in the maternal medical record or obtained from the participant's verbal report. Any congenital malformations or complications of the labor and delivery should be documented

Emergency room admissions per se, without subsequent admission to the hospital, do not require the submission of a serious adverse event report unless these otherwise meet the criterion for a severe adverse event. *Refer to section: 5.9.1.1.1*

13.7.7. Unexpected Events During Participation

Throughout the course of the study, participants face unusual or extraordinary circumstances that were not anticipated during the study design.

Examples include:

- o military deployment
- o relocation to foreign countries due to changes in employment,
- o International travel where study drug is confiscated by international customs.

The DCC implemented a document for internal use called "Unexpected Events Report"(UER) to document minor deviations or unexpected events in a systematic manner. The UER is available in hard copy only.

At the time the coordinator is informed of the event, he/she will: notify the site investigator of the event

- o complete the study Unexpected Event Report (UER)
- o place a copy in the UER in the participant's research record
- o notify the DCC Program Coordinator within 24 hours of UER completion
- o scan or fax a copy of the report to the DCC for review.

Some unexpected events may reach the threshold requiring the investigator to report the event to the local IRB. Sites will follow local IRB policy and procedures for reporting unexpected events within their institution.

Refer to Chapter 18.4 Data Collection Forms.

13.8. Stopping Points

Per the intent−to−treat principle, every effort must be made to follow each randomized participant until the end of the study or death. Table 14.1 − Follow−Up after Primary Endpoints, Early Withdrawal or Modified Participation outlines procedures to be followed for participants who meet primary endpoints or withdraw prematurely from the study, as well as other circumstances for which modified follow−up is anticipated.

For more information on modified participation in HALT PKD, please refer to Section 8.18 − Modified Participation.

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

Smokers will be identified at the screening visit by means of a self−reported questionnaire. Any participants identified as smokers are to be referred to their primary care physician for smoking cessation counseling and therapy. At every visit study personnel are to provide encouragement and support in working to motivate participants to stop smoking. HALT PKD personnel will not manage lipids but, rather, will leave such care to primary care physicians and/or nephrologists. Management per the National Kidney Foundation's K−DOQI Guidelines to, specifically, target an LDL cholesterol of less than 100 mg/dl using HMG−CoA reductase inhibitors after dietary interventions should be recommended.

Chapter 14. Discontinuation of Participants

14.1. Study Completion and Post Closeout Forms

A participant's full involvement in the study will end when all required study tests and procedures have been completed. Study A and Study B participants will be asked to continue to sign study extension consents and remain in the study until June 30, 2014. At the conclusion of study participation, the study medications and blood pressure goals will be discontinued. Participants must be asked to return all study medications, but they may keep their home blood pressure monitor. Participants will have study medications stopped/tapered by the PI. The PI will send a letter to the participant's primary physician informing him/her of the participants study completion. Study Coordinators will complete Form 35 at this time point and yearly thereafter. PCCs are to follow up with a final phone call to the participant 30 days after study completion in order to report all medications and adverse events during that period.

14.1.1. Post Closeout Participation

For those participants that complete their original study commitment (F48) and *decline* the HALT PKD study extension, the coordinator is required to complete:

- Form 35 Post Closeout Follow-up (Study B participants).
- Form 52 Post Closeout Follow-up (Study A participants).
- Annual follow-up for those participants that agree to post closeout follow-up.
  - Form 35 (Study B)
  - Form 52 (Study A)
  - Forms will be completed annually from the initial date of post closeout until the end of the study (June 30, 2014) or death has occurred.

For those Study B participants that meet endpoint, complete:

- Form 32—if ESRD (dialysis or transplant have occurred)
- Form 33 – if 50% reduction in eGFR has occurred
- Form 35 Post closeout follow up (Study B participants)
- Endpoint consent
- Form 31 – (if death has occurred), refer to 7.4.2. Endpoints, Study B

Participants that stop study involvement (modification or study closeout)

- If on study drug, the proper study drug taper procedures are followed. Refer to 10.3.6.2, Discontinuation of Study Drugs.
- all study drug cards and unused study medications must be returned to the site coordinator
- Home blood pressure monitors may be kept by the participants
- Investigators will generate a letter to the participant's primary physician informing him/her of the participants study completion
- PCCs will follow up with a final phone call to the participant 30 days after study completion in order to report all medications and adverse events during that period

Refer to: Chapter 17.1 Participant Closeout for additional information

14.1.2. Participants that Consent to Study A and B Extension

In August 2010, the Study A study arm was extended through June 30, 2014. In May 2012, Study B was also extended to June 30, 2014. Participants in both study arms agreeable to extending their participation will be asked to sign an addendum consent prior to or on the date of their F48 visit.

Study extenders that withdraw after consent to extend:

In the event a participant consents t study extension and later decides they no longer wish to continue in the study, the site coordinators will:

- Offer the participant the option to modify study involvement to a lesser degree of participation
  - Complete Form 28 and identify level of participant follow-up desired

The post closeout forms (forms 35 and 52) are not to be completed on these participants.

14.2. Early Termination of Study Drugs or Follow−Up

Early withdrawal takes place whenever a randomized participant discontinues study medication and/or does not complete study requirements. Reasons for participants to withdraw from HALT PKD include voluntary withdrawal, pregnancy, inter-current illness precluding continuing enrollment, and reaching an endpoint(s). Participants will not be withdrawn from the study for non−compliance. Per the intent−to−treat principle, every effort must be made to follow each randomized participant until the end of the study or death. Table 14.1 − Follow−Up after Primary Endpoints, Early Withdrawal or Modified Participation outlines procedures to be followed for participants who meet primary endpoints or withdraw prematurely from the study, as well as other circumstances for which modified follow−up is anticipated.

Table 14−1. Follow−Up After Primary Endpoints, Early Withdrawal or Modified Participation

Event	Continue Masked	Follow−Up Visits
50% reduction of baseline eGFR (Study B)	No	Confirm 50% reduction by obtaining repeat eGFR within two weeks of obtaining the original sample. If not confirmed, continue full protocol until participant again reaches 50% reduction in eGFR from baseline.[ab] If 50% reduction in eGFR from baseline is confirmed, discontinue study drugs, BP goal, and PCC visits **AND** Q12−month telephone visits to determine current status. If participant has not reached dialysis, nor been transplanted, obtain serum creatinine From a PCC or Quest lab, if possible
		Discontinue Q12−month telephone visits once informed of first event of dialysis, transplant or death.
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 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 and other protocol continue.
Cyst reduction/nephrectomy (Study B)a	Yes	Full protocol.
Pregnancy (>12 weeks duration)	Resume 3 months postpartum and post−lactation	Stop all study meds, transfer care to PCP, continue to follow Q3 months (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 duration)	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 Q6 months[a]	Yes	All investigations scheduled for 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 HALT regiona	Yes	Transfer care to nearest HALT PKD PCC. However, participant does have the option to continue follow−up with the original PCC.
Participant lost to follow−up without study knowledge	If participant reappears	1. Exhaustive efforts to contact 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 eGFR 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 3−month telephone visits or 6−month PCC visits. The HALT PKD study will continue to provide study medications until participants reach a 50% reduction in eGFR from baseline, ESRD (start of dialysis or transplant), death or another reason for terminating study medication ensues. [b] Section 14.2.1 defines instruction for collection/reporting of confirmation sample.		
[b] Vital status ascertained through 12−month telephone follow−up.		

14.2.1. Reaching >50% Reduction in eGFR Endpoint

In order for a lab value to meet criteria for endpoints declaration, it must be:

a) obtained during a PCC visit and processed at CCF.
   - A Quest Visit (Remote Visit) with a centrally processed serum creatinine (CSC kit to CCF) is the *only* exception and

b) be confirmed with the "endpoint confirmatory lab" drawn within two weeks of the PCC "endpoint notice" value.
   - Confirmatory labs cannot be drawn on the same day of the PCC lab. The confirmatory is used to establish the mean eGFR %.

You will be notified by the DCC via a *purple* e−mail if the eGFR from a regularly scheduled study visit (E.g. F24, F30 etc) is more than 50% below baseline. The e−mail will also include a label for the confirmation sample and a copy of Form 81 with the accession number. Also, at this time a Form 33 will be generated by the DCC. The baseline eGFR data (Initial Sample Collection) will be input by the DCC.

This includes:

- Date of baseline visit
- Serum creatinine value
- Age
- eGFR

Data associated with the 50% reduction in eGFR (50% reduction collection) will be input by the DCC. This includes:

- Date
- Serum creatinine value
- Age
- eGFR
- % Reduction
- Visit

Collecting the Confirmation Sample

Once the purple notification e−mail is received, the site has two weeks to draw a confirmatory sample. This can be done in three ways.

1. The site draws the blood and sends it to CCF
2. The participant goes to a quest lab for blood draw
3. The participant goes to a local lab for the blood draw which is then sent to CCF

Our first preference is choice 1 above. In this case you would:

- Draw the blood
- Place the accession number label that was generated as part of the purple e−mail, onto the tube and put the date of the blood draw on the label.
- Complete Form 81 Shipping Manifest Central Lab−CCF
- Send sample to CCF

Our second preference is choice 2 above. In this case you would:

- Complete a Quest requisition from (this contains the information for Quest to charge the processing to the HALT−PKD study)
- Send the label and order to the participant
- The participant goes to the Quest lab for blood draw
- The serum creatinine results are sent to the site. You may want to make note of the accession number associated with this confirmatory blood draw and verify that it matches the number on Form 33
- The site completes Form 51 indicating the sample was processed at Quest. The Date of the Visit should be the date that the sample was drawn at the Quest lab. We have added a check box on Form51 for you to check that this was a Confirmatory Sample. *The important thing to remember is that you need to generate and enter this form for the same visit associated with the 50% reduction in eGFR and NOT as a BV visit.*

Our third preference is choice 3 above. In this case you would:

- Complete Form 81 Shipping Manifest Central Lab−CCF
- Complete an order for the blood draw
- Complete the FedEx shipping label
- Send the completed Form 81, the order for the blood draw, the label, and any other packaging materials you use to the participant
- The participant then needs to go to their local lab
- The local lab draws the blood and sends the results to CCF. Please have the local lab record the date of the blood draw on the tube label. It is critical that Form 81 accompany the shipment so we can track it as a HALT−PKD sample.

Procedures to be Followed in the event of a Confirmed Endpoint

Once the DCC has received the CCF results for the confirmatory sample, or you have completed Form 51 indicating a Quest result **the DCC** will:

Send you an **orange** e−mail confirming that the DCC has received the results of the confirmatory sample along with the mean reduction and endpoint confirmation (Question 4)

- Complete the Confirmatory Sample section of Form 33, this includes:
  - Date (Collection Date from CCF spreadsheet or Form 51 Date of Visit for Quest visit)
  - Serum creatinine value
  - Age
  - % Reduction
  - Lab Used
  - Accession #

The site will then need to complete Question 5−7 on Form 33. These questions allow the site PI to dispute that the endpoint has been reached and to indicate his/her reasoning.

The DCC will review all Form 33's completed since the last Endpoint Committee meeting and present those results to the committee at their next meeting. If the average of the 2 eGFR values (study visit and confirmatory sample) is more than 50% below baseline, an endpoint has potentially been reached and will be confirmed by the Endpoints Committee. **If the average of the eGFR is less than 50% below baseline, an endpoint has not been met and the patient will continue to be followed per the regular protocol.**

If the decision is that "endpoint has been reached", the site needs to complete Form 35 Post−Closeout follow−up (Study B) and have the participant sign and End of Study Consent. The participant concludes study participation except for the annual information requested on Form 35.

If the decision is that "endpoint has not been reached", the participant continues to be followed by the protocol. When a Study B participant reaches endpoint, the PI will stop/taper study medications and send a letter to the participant's primary physician notifying him/her of participant's completion in the study. A copy of the letter will be sent to the participant. Study B participants will be asked to sign an addendum to the consent (waver of consent) agreeing to allow the study team to collect yearly lab samples and medical status. Form 35 will be completed at this time and yearly thereafter.

14.2.2. Modified Participation

Per the intent−to−treat principle, every effort must be made to follow each randomized participant until the end of the study or death. For each participant enrolled in Study A and Study B, the "end of the study" is defined as the participant's last visit prior to the June 30, 2014 time point.

Table 14.1 − Follow−Up after Primary Endpoints, Early Withdrawal or Modified Participation outlines procedures to be followed for participants who meet primary endpoints or withdraw prematurely from the study, as well as other circumstances for which modified follow−up is anticipated.

Coordinators will complete Form 28, Modified Participation for all participants changing their level of study participation. Participants must continue to be followed at the PCC every six months in order to continue on study medications. If the participants do not agree to six month follow up visits at the PCC, study medications are to be discontinued (refer to 10.3.6.2, Discontinuation of Study Drugs). Each participant is asked to indicate the intensity and frequency of follow up to which they are agreeable.

Follow up on Modified Participants:

- Study B participants will be followed for endpoint determination if they have indicated 5a (follow up at the PCC every 6 or 12 months) or 5b (follow up at the local PCP/nephrologist every 6 or 12 months) on the modification form. Those followed locally (5b) will require a CSC kit to be sent
- Form 28 question 5b: *every six months*—on the question "follow-up every six or twelve months with the PCP and/or Nephrologist". Form 120 will be completed every six months from the date of modification.
- Form 28 question 5b: *every twelve months*—on the question "follow-up every six or twelve months with the PCP and/or Nephrologist". Form 120 will be completed annually from the date of modification.
- Form 28 question 5c: *records only.* Form 120 will be completed annually from the date of modification.

In cases for which follow−up must be modified, it may be necessary to obtain the participant's consent (per local IRB guidelines) for modified follow−up. It is also *strongly* recommended that the study coordinator obtain documentation from the participant as to the specific option for modified participation he/she consents to. The Modified Participation Checklist was developed for this purpose. If a participant's modified status is changed, a new modification form is to be completed.

14.2.2.1. No Contact Policy

Occasionally sites have participants who, for whatever reason, do not contact the PCC for extended periods, despite coordinators' best efforts to reach them. For these situations, the study has adopted the policy that once a single visit has been missed, participants are given a period of 6 months of non−contact before considering them to have withdrawn their consent.

Coordinators will make regular attempts to contact participants, at least biweekly during the first month, either by phone, email, or U. S. Postal Service, and at least monthly during subsequent months. Toward the end of the six month period of no contact, the coordinator will send a certified letter to the participant in a final attempt to contact and schedule a visit.

If no response from the subject is received within 6 months of repeated efforts to contact them, the participant will be considered “lost to follow up” and to have withdrawn consent to participate in the study.

Modified Participation Form 28 should then be completed, selecting the option 3a “Participant has withdrawn consent, not otherwise specified” and 5d. “refuses all follow up”. The terms “lost to follow up” should be documented in Form 28 comments detailing the site’s attempt to contact the participant.

The Form 28 question 3M “other” is not used to document a “lost to follow up” participant. Once the participant has been modified as withdrawn, the coordinator should make no further attempts to contact the participant.

When filling out Form 28, Q4, drug stop dates on the lost to follow up, participants drug use information is commonly unknown.

To document the drug stop date on withdrawn participants, use the most conservative date and calculate the last know date which the participant was known to be using study drugs based on the amount of drug supplied at the last PCC visit.

14.2.2.2. Reappearance of Lost to Follow Up Participants

Occasionally, participants that have been modified due to “lost to follow-up” contact the site coordinator or re-appear showing a renewed interest to continue in the study. In May 2012, the HALT PKD Steering Committee approved the following management:

- any “lost to follow up” participant that contacts the PCC or reappears requesting resumption of study involvement may re-modify back into study.
- re-modification can only occur if the participant reappears *within one year from the date of initial “lost-to-follow-up” modification.*
- If re-modified, the PCC may reintroduce study medication as outlined on Table 13.

14.2.2.3. Study A and B Extenders that Withdraw

In the event a participant consents to study extension and later decides they no longer wish to continue in the study, the site coordinator will:

- Offer the participant the option to modify study involvement to a lesser degree of participation
  - Complete Form 28 and identify level of participant follow-up desired

If no additional participation is desired, the participant is considered to have withdrawn from study participation.

  - Complete Form 28 and indicate 3a. “Withdrawn”.

Note: A post closeout Form is not applicable for those participants agreeing to the extension and then withdrawing prior to June 30, 2014.

14.2.3. Pregnancy

Because ACE−Inhibitors and ARBs are harmful to a fetus in the second and third trimesters, pregnancy is an exclusion criterion. Thus, prior to randomization, every effort must be made to exclude participants who intend to become pregnant over the course of the study, and all women of childbearing potential are to be screened for pregnancy by a qualitative urine B−HCG test.

If a 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 medication must be discontinued immediately and Screen Failure Form14 (Reason #6) completed and data−entered as soon as possible. Any pregnant participant is to be referred to her primary care physician (PCP) for management of the pregnancy and will not be followed by HALT PKD 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.

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), but study participation is to be modified in accordance with the HALT PKD Pregnancy Policy.

For an overview of follow−up requirements in cases of pregnancy, please refer to Table 14−1 − Follow−Up After Primary Endpoints, Early Withdrawal or Modified Participation.

14.2.4. Study B Endpoints

For an overview of follow−up requirements in cases of an endpoint being reached, please refer to Table 14−1 − Follow−Up After Primary Endpoints, Early Withdrawal or Modified Participation.

14.2.4.1. Reduction of eGFR by 50% from Baseline (Study B)

Whenever there is a drop of >50 in eGFR from the baseline value, the following forms are to be completed:

- Form 33 - eGFR Reduction for Kidney Function Endpoint
- Form 35 – Post Closeout Follow up (Study B)
- Study B Endpoint Consent

Participants that meet endpoint and agree to annual follow up will be contacted annually from the date they reach endpoint and complete Form 35. Those participants declining any additional study involvement conclude study participation at this time.

14.2.4.1.1. Confirming 50% Reduction in eGFR from Baseline

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.

Refer to 11.3.3. Hometown Laboratories.

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 is to 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 between study visits, shows a 50% reduction in eGFR, it is not considered an endpoint, and a confirming sample should not be drawn.

Refer to Section 11.4.2.1 − Sample Collection at Local (Hometown) Labs for information on obtaining serum creatinine samples remotely.

14.2.4.1.2. Confirmed Endpoint of 50% Reduction in eGFR from Baseline

Once the reduction of 50% in eGFR from baseline has been confirmed, study medications, BP goal, and PCC study visits are to be discontinued. If the participant agrees to annual post closeout follow up, the participant will complete a telephone visit with the site coordinators annually from the date they reach endpoint. If a participant has neither died, nor reached dialysis, nor been transplanted, the coordinator should ask the participant to obtain a serum creatinine sample from a PCC or Quest lab, if possible. Refer to 14.2.2 - Modified Participation, Follow up on Modified Participants

The serum creatinine sample is to be obtained annually until the participant starts dialysis or receives a transplant or dies, whichever comes first. Once a participant starts dialysis or receives a transplant, he /she will be contacted annually to ascertain vital status only.

The PI and/or study coordinator must obtain the participant's approval to be contacted annually. The participant has the option to sign the addendum to the consent form or wavier of consent. Once a participant meets an endpoint, the PCC is to send the study completion letter to the participants PCP or nephrologist and a copy of the letter is to be sent to the participant.

14.2.4.1.3. Disputing an Endpoint

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.

Reasons why an endpoint might be disputed include the following:

- Cyst infection/pyelonephritis
- Other type of infection
- Kidney stone obstruction Dehydration
- Other acute illness that might lead to AKI Recent IV contrast
- Dietary non−compliance
- Medication error
- AKI related to drug
- AKI for other reason

The reason and explanation for a disputed endpoint must be noted on the eGFR Reduction Form for Kidney Function Endpoint (Form 33).

For disputed endpoints:

An additional lab value may be drawn at the discretion of the investigator to re-evaluate the renal function prior to sending a confirmatory sample. The additional lab result is for the investigator's information only and will not be utilized by the Endpoint committee decision to accept or decline the endpoint. The extra lab value will not be maintained in the database.

The rationale for the endpoint dispute must be documented in the comments section of the eGFR Reduction Form33. The PI *must* attend the Endpoint Committee conference call to provide his/her rationale for disputing the result. If unable to attend the call, the PI must submit a detailed email to the Endpoints Committee haltendpoints@list.pitt.edu citing the rationale for the dispute prior to the conference call.

The coordinator responsible for the participant is asked to attend the teleconference in the event the committee has additional questions.
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 should continue to follow the full protocol. If the participant's labs obtained during the next 6 month PCC visit continues to reveal a >50% decline in eGFR, the Endpoints committee will declare the date of the original endpoint as the true endpoint designation.

14.2.4.1.4. Management of Study Drug After Endpoint is Reached

Refer to 10.3.6.2., Discontinuation of Study Drug

14.2.4.2. Death

Upon receiving information regarding the death of a participant, the study coordinator is to request supporting materials that document adverse events and cause of death, including the hospital death summary, death certificate, and/or ESRD Death Notification Form (HCFA Form 2746), if appropriate. A consent for release of information from the deceased participant's next−of−kin must be obtained by the study coordinator in order to request records.

In the event of sudden death or cardiac arrest, coordinators are to obtain the participant's medical records and a copy of the most recent EKG obtained prior to the event.

The study coordinator must also complete and data−enter a Death Notification Form 31 and Post−Closeout Follow−up (Study B) Form 35. These forms must be reviewed and signed by the principal investigator.

All deaths must be reported as serious adverse events

14.2.4.3. End−Stage Renal Disease (ESRD)

When a participant reaches ESRD (dialysis/transplant), study medications and blood pressure goals are to be discontinued. Participants enrolled in Study A are to be asked to continue three−month telephone visits and six−month PCC visits, including MR scans per protocol. Participants enrolled in Study B are to be followed clinically by their PCP and/or nephrologist, with the study following vital status only.

The study coordinator must complete and enter End Stage Renal Disease Form 32 and Post−Closeout Follow−up (Study B) Form 35 when ESRD is reached. Both forms must be reviewed and signed by the principal investigator.

The ESRD Medical Evidence Report (CMS 2728) which is required by the Department of Health & Human Services, will be completed by the admitting hospital dialysis/transplant staff and submitted to the DHHS. A copy of the appropriate HCFA Form, either ESRD Medical Evidence Report (2728) or ESRD Death Notification (2746) will be retained at the PCC.

14.3. Non−Compliance

Participants cannot be discontinued from the study for reasons relating to non−compliance. Rather, at the time of screening and potential enrollment, the importance of the longitudinal aspect of the study should be emphasized to the participant by the study coordinator; and those participants who feel they may not be able to comply with the protocol for the length of the study need to be discouraged from enrolling in it.

Chapter 15. Protocols for Primary and Secondary Outcomes

15.1. Study A − Primary Outcome

15.1.1. Total Kidney Volume by MR

The change in total kidney volume, as assessed by abdominal MR at baseline, 2 years, 4 years and 5 years follow−up, is the primary outcome for participants enrolled to Study A. The MR techniques for imaging and interpretation of volumetric measurements established in the CRISP Study will be employed. MR images will be obtained at each PCC using a protocol developed by the HALT PKD Imaging Subcommittee. Following acquisition, MR images will be reviewed locally at each PCC and then transferred securely, via the World Wide Web, to the Image Analysis Center (IAC) at Washington University in St. Louis.

For more information on acquisition of abdominal MR images, please refer to Section 12.22 – MR for Kidney Volume and Liver Cyst Measurement

15.2. Study A − Secondary Outcomes

15.2.1. Rate of Change in Renal Blood Flow over Time by MRA

The rate of change in renal blood flow over time, as assessed by phase−contrast MRA obtained at baseline, 2 years, 4 years and 5 years follow−up, is a secondary outcome for participants enrolled to Study A. Methods established in the CRISP Study, specifically, rapid image acquisition during a single breath−hold, will be employed. Inter−rater reliability will be assessed across radiologists in a quality control exercise to be conducted prior to the start of the HALT−PKD Study. Once each site has been certified, study participants will be assessed.

For more information on acquisition of phase−contrast MRA, please refer to Section 12.22 – Phase-Contrast MRA for Renal Blood Flow Measurement

15.2.2. Left Ventricular Mass by MR

Left ventricular size and wall mass, as assessed by cardiac MR at baseline, 2 years, 4 years, and 5 years follow−up, is a secondary outcome for participants enrolled to Study A.

For more information on acquisition of cardiac MR images, please refer to Section 12.2.2 – MR for Left Ventricular Size and Wall Mass Measurement

15.3. Study B – Primary

15.3.1. Composite Endpoint of Time to Event

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. The outcome of time to the 50% reduction of baseline eGFR is based on measurements analyzed at Cleveland Clinic Foundation Reference Laboratory every 6 months.

In cases of death, study coordinators should request a release of information from the next−of−kin. The study coordinator at each PCC is to request supporting materials, such as death certificates, autopsy reports, and/or other medical records, to confirm the cause of death. For each death the study coordinator is to fill out and data−enter Death Notification Form 31.

To document ESRD, copies of ESRD Medical Evidence Report (#2728) or ESRD Death Notification (#2746) are to be retained at PCCs. Run sheets of first dialysis treatments should be obtained, if possible. Participants are to be contacted directly if a kidney transplant was received. For each case of ESRD, the study coordinator is to fill out and data−enter End−Stage Renal Disease Form 32.

15.4. Studies A and B − Secondary Outcomes

15.4.1. Rate of Change of GFR over Time

The secondary endpoint of primary importance for the HALT PKD Study A is eGFR. This will be calculated using the IDMS traceable methods. The former calculation of eGFR is more accurate, namely at higher levels of GFR (>60ml/min). Serum creatinine samples will be obtained at the baseline, F5, and F12 visits and at all 6−month visits thereafter. Samples will be forwarded to the Cleveland Clinic Foundation Reference Laboratory for analysis.

15.4.2. Rate of Change in Albuminuria

The rate of change in albuminuria is a secondary outcome for participants enrolled to both Studies A and B. Twenty−four−hour urine specimens will be analyzed for albumin and creatinine at baseline, 4 months, 12 months, and annually thereafter. The change in albumin to creatinine ratio over time will be compared among intervention arms.

15.4.3. Rate of Change in 24−Hour Aldosterone Excretion Rate (AER)

The rate of change in 24−hour AER is a secondary outcome for participants enrolled to both Studies A and B. Twenty−four−hour urine specimens will be analyzed for AER at baseline, 4 months, 12 months and annually thereafter. The rate of change in 24−hour AER over time will be compared between intervention arms.

15.4.4. Hospitalizations (All−Cause and Cardiovascular Cause)

At each 3−month study visit (over the telephone or at the PCC), participants are to be asked if they have been hospitalized since the last study visit. If yes, the participant should be asked to sign a consent form to authorize the release and forwarding of pertinent medical records to the PCC. The study coordinator is to enter the date(s) and the primary reason(s) for admission on Hospitalization 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. The PI is required to review the hospital encounter information entered on Form 30 prior to submission to the DCC.

15.4.5. Adverse Event Reporting

15.4.5.1. PKD−Related Symptoms or Medical Conditions

Differences in the frequency of PKD−related symptoms or medical conditions (e.g. ruptured renal cyst), as collected on the Symptoms Checklist (Form 5), will be compared across study arms. Detailed information on reporting PKD−related symptoms or medical conditions may be found in Section 13.6 − Adverse Events.

15.4.5.2. Adverse Effects of Medications

Adverse effects of medications will be compared across study arms and may be collected as adverse events or serious adverse events (SAEs). Detailed information on reporting PKD−related symptoms or medical conditions may be found in Section 13.6 − Adverse Events. Detailed information on reporting SAEs may be found in Section 13.8 − Serious Adverse Events.

15.4.6. Quality of Life and Pain

Quality of life and pain are important secondary outcomes of the HALT PKD study. 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 Quality of Life Questionnaire (SF−36v2 Health Survey) (Form 38) 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 (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 patient's physical, mental, and social well−being.

The Quality of Life Questionnaire (SF−36v2 Health Survey) (Form 38) assesses how the disease, as a whole, affects one's health status, while the HALT PKD Pain Questionnaire (Form 39) specifically addresses how pain/symptoms from enlarged organs affect’s one's health status.

The Quality of Life Questionnaire (SF−36v2 Health Survey) (Form 38) and the HALT PKD Pain Questionnaire (Form 39) are to be administered to participants after blood pressure has been measured, but before all other study procedures, to avoid affecting participants' responses to the questionnaires. The Quality of Life Questionnaire (SF−36v2 Health Survey) (Form 38) must be administered **before** the HALT PKD 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.

Chapter 16. Data Management – Quality Control - Quality Assurance

16.1. Study Forms

Approximately 40 required data collection forms and a number of optional forms (tools) have been developed for use in HALT PKD. Paper copies of the required forms for each visit are to be printed prior to a visit for completion during the visit; and in fact, these paper copies serve as source documentation in some cases. After each visit, data is to be reported to the DCC via the Web Data−Entry System (WDES). Only authorized personnel have access to the forms.

The University of Pittsburgh has instituted double data entry. It is the policy of the University of Pittsburgh, when paper data collection forms are used, all forms are entered twice. A validation and adjudication process identifies errors and makes appropriate changes to the master database. Sites are provided a report detailing the changes made to the database for their records. Sites do not edit their paper forms to reflect changes made to the master database. Sites are required to send forms 5, 6, 9, 12, 15, 62 and 63 for *each* visit. Forms should be sent to the DCC using Federal Express #165309723, and addressed to the attention of: HALT PKD - Fern Schwartz − 200 Meyran Avenue, Suite 200, Pittsburgh, PA 15213.

16.1.1. Forms Development

Data collection forms for HALT PKD have been carefully developed for quick, thorough and consistent data collection over the course of the study. Once approved, "locked," posted and tested, forms should NOT be modified, except in extreme cases. [The Forms Subcommittee is responsible for form issues, and must approve all original forms and major modifications. PAT 11/13/2007].

16.1.2. Forms Revisions

Forms are to be revised only in extreme cases, with revisions expected to occur rarely. The Forms Subcommittee must approve all significant form revisions, with subsequent approval by the Steering Committee also required for the final revised version. Once the revised form gains Steering Committee approval, it is "locked" and changes are added to the printable and web−based versions. The DCC is responsible for notifying sites whenever a form has been revised and posted.

16.1.3. HALT PKD Website

Website access is given to site personnel affiliated with the study. A registration form must be completed and sent to the DCC. When information has been received, login information will be provided. All new study personnel are required to perform training before access is given.

In addition to the web form portal for data entry, the website provides minutes of all committee meetings, with additional resources such as the MOP and Protocol, printable forms and tracking reports.

16.1.4. Data Collection

All required data collection forms must be completed and subsequently entered into the WDES per guidelines defined in Data Entry Time Frames. Most forms should be completed by hand during the visit. However, this is not required for certain forms (i.e., a lab sheet listing all required values and normal ranges may replace the paper copy of Required Lab Results Form 9 stored in the research chart). Some sites may allow data collection forms to serve as source documentation (i.e., Clinical History Form 4 in lieu of a progress note). In all cases, the official case report Form (CRF) is the data entered into WDES. When data is entered into WDES, the data entry person is to write his/her name and the date and check the appropriate box at the foot of the paper copy.

When data is unavailable, enter the appropriate missing data code where indicated at the top of each applicable paper form:

1) Participant Refused
2) Reading not Possible
3) Institutional Error

16.1.4.1. Investigator Sign−off on Data Collection Forms

There are six data−collection forms that require the signature of the investigator *prior* to data entry. The six forms are listed below:

1) Enrollment Form 10
2) Serious Adverse Events Form 13
3) Randomization Form 20
4) Unmasking Drug Form 26
5) Major Protocol Violation Form 29
6) End Stage Renal Disease Form 32

All other forms may be entered into the database before they are signed off on by the investigator, who will have up to 30 days after the visit to review all forms and sign off on a visit checklist. By signing the visit checklist, the investigator confirms that all forms from a visit have been reviewed and that all data are complete and accurate. This procedure streamlines the forms verification process by allowing investigators to review multiple visits at a given time.

The study coordinator needs to assure the visit checklist was generated with the data collection forms for each study visit. The visit checklist will serve as source documentation that the investigator has reviewed all forms for the current visit, as well as all forms completed during the interval between the previous visit and the current visit. Once the visit checklist has been signed the investigator, the date on which the signature of the investigator was obtained must be data−entered within 2 weeks, using a modified version of HALT PKD Visit Schedule Form 40.

All study visits must be entered on HALT PKD Visit Schedule Form 40 prior to entering data from the visit. The investigator signature must be entered on Form 40 within six weeks of the visit.

Minor edits to data collection forms do not require the signature of the PI. The study coordinator may make the appropriate edits on the applicable paper forms, date and initial all changes and then data−enter them.

16.1.4.1.1. Radiologist Sign−off on Imaging Forms

The MRI Session (Renal) Information Form (21) and Renal Blood Flow (MRA) Form (22) must be signed by a radiologist. However, to facilitate the timely transfer of images, Forms 21 and 22 may be data entered before being signed by the radiologist.

Forms 21 and 22 must be data−entered and signed by the radiologist, either before or after data−entry, within 2 weeks of the date on which images were obtained.

16.1.5. Request Tracker (RT) − N/A−no longer in use

A data queue has been set up to handle suggestions, problems, and/or revisions in reference to either the printable or WDES versions of data forms and is to be used to bring such suggestions, problems and/or revisions to the attention of the DCC. The RT data queue can be accessed online at http://rt.biostat.wustl.edu or by e−mail at rt−haltpkd−data@rt.biostat.wustl.edu.

Complete instructions on using Request Tracker may be found in Section 3.14.4.

16.1.6. Effective Troubleshooting and Problem Solving

If a problem occurs while entering data, sites can contact haltweb@pitt.edu and the problem will be resolved. Sites will be contacted once the issue has been resolved.

The DCC recommends that coordinators select the review button and check the data that they have entered to assure accuracy.

16.2. Web−Based Data Entry System − N/A−no longer in use

The DCC has developed a Web Data Entry System (WDES) for entering, editing and evaluating data associated with HALT PKD. Below is a description of the methods for registering and randomizing study participants using WDES.

16.2.1. Definition of Terms

WDES

Web Data Entry System, the program used to work with all study data. Entry requires a login name and password.

Forms Portal

A web page that offers links or entry to other web pages. HALT PKD uses a secure portal.

Firewall

A program or hardware device that filters information transmitted over an internet connection into a private network or computer system. If an incoming packet of information is flagged by a filter, the firewall will not allow it to go through.

Browsers

Basic programs used to work on the World Wide Web (WWW). Netscape Navigator (Version 6 or higher), Microsoft Internet Explorer (Version 5 or higher), Mozilla Firefox (Version .8 or higher), Mozilla (Version 1.6 or higher), Opera, or other contemporary browsers may be used. All browsers are acceptable.

Radio Button

Selection device on an HTML form. Only one radio button on a given item may be selected (for example, either a or b, but not a and b).

Drop Down List

Selection device on an HTML form, like a pull−down menu. When the selection list is clicked on, it opens to reveal a series of choices. Often, only one of these may be selected, but in some cases multiple items may be chosen.

Checkbox

Selection device on an HTML form. It may be checked or left blank. If left blank, it is assumed a selection was not made.

Text Box

Selection device on an HTML form. Free text is entered, although there are usually some guidelines as to the type of information. Note that text is additional information and does not replace accurate data entry. Text should be kept to a minimum as it cannot be easily tracked or queried.

HTML

Hyper−Text Markup Language, the language in which data forms in WDES are written.

Forms Generation Function

Allows for printing of all required forms and labels for a participant/visit.

Focus

Clicking on or near an item is called "focusing on an item." In WDES the item that has focus will have a little blue arrow pointing at it. Text box items will have a little cursor symbol showing in the focus item. When you focus on a select list, the list opens. When a checkbox or radio button item is focused on, a little shadow will appear on the item itself. When an item is focused on, all keyboard commands happen with respect to that item. So, if the focus is on a text box, and the "PAGE−DOWN" key is pressed, the system will try to go to the next page of the textbox item. Since many textbox items do not have several pages of information, it will seem like nothing has happened, but actually, the system has performed an action that has no effect.

Blur

After focusing on an item and performing some task, you will leave the item to go to another item. This is called "blurring the focus." It just means to leave an item, and place the focus somewhere else.

Navigation

Moving around within a form. The WDES includes two basic methods of navigation:

Using the Mouse to Navigate

- Text Box: Click on the text box, then type in the information.
- Radio Button: Click to select.
- Checkbox: Click to select
- Select List: Click on the select list to open it, then move the pointer to the item to be selected. Occasionally, this is difficult to do in IE. If a problem arises in IE, click on the select list, then move up and down using the arrow keys.

Using the <TAB> Key to Navigate

- Starting Out: Begin by using the mouse to click on the first item on the form. A small blue arrow will point to the item with focus.
- Next Item: Go to the next item by pressing the <TAB> key.
- Previous Item: Return to the previous item by pressing <SHIFT>−<TAB> (hold the <SHIFT> key and press <TAB>).
- Text Box: Use <TAB> to move to the desired text box, then type in the information.
- Radio Button: Use <TAB> to move to the desired radio button, then use the < â â > bar to select.
- Checkbox: Use <TAB> to move to the desired checkbox, then use the <SPACE> bar to select.
- Select List: Use <TAB> to move to the desired select list, then move up and down in the select list using the arrow keys.

16.2.2. Basic Functions of WDES

Using a browser to access WDES, data is entered into a database (physically located at the DCC − University of Pittsburgh). Data−collection forms (paper forms) must be completed (filled out) and signed by the PI before data entry.

It is very important to data−enter visits, in a timely manner.

1. **Enter − Review − Edit**

16.2.3. Data Entry Process

Select the desired form and then follow the steps below to add, edit or list.

Add or Enter Data

1. Navigate to web form portal, select #4 and data enter visit forms.
2. Select participant ID and visit.
3. Enter visit date on Form 40 and enter visit data.
4. Click the submit button.
5. Review information entered on form and edit if necessary.
6. Select as needed forms.

Edit or Modify Data

1. Navigate to web form portal, select #4 and data enter visit forms
2. Select participant ID and visit.
3. Select as needed forms.
4. Review information entered on form and edit if necessary.
5. Click the submit button.
6. *Note:* Only personnel with coordinator status can edit

List Data: Select "List" to view data already stored in the system in a table format. To view data for a particular participant, select the ID number first and then select "List."

Form Portal: Select "Form Portal" to return to the portal page to select additional forms.

16.2.4. Speed of Web Data Entry System

WDES employs a "client/server" model, meaning that some of the processing takes place on the server (DCC end), and some takes place on the user end (PCC computer). Functions operating on the client PC may take longer than usual, depending on the configuration at the PCC. The DCC can do nothing to speed the time of such operations. PCCs should contact their own IT staff if delays occur.

16.2.5. Registration and Randomization − N/A no longer in use

The following four forms must be entered in order to register, enroll and randomize participants.

1. **Registration:** Select Registration Form 3 and enter the following information:
   a) "Date of Registration" (MM/DD/YYYY): Date of data entry of the registration form. The default is the current date.
   b) "Date of Birth" (MM/DD/YYYY).
   c) "Gender"
   d) "Race" (Black/African American or Non−Black).
   e) "Date of Scheduled S or SB1 Visit" (MM/DD/YYYY): Must be after or same day as date of registration.
   f) "Registration Type": Select regular (actual participant) or test (pretend participant). Information about completion of the paper data−collection form (names and dates).

When "Add" is selected, the form is sent to the DCC and a participant ID is returned. The ID begins with a site−specific letter and has 7 digits. The ID is to be logged onto the ID log sheet (kept in a locked file). Remember, no personal identifying information is to be entered into the system (e.g., name, social security number, etc.). It is the responsibility of the Study Coordinator to ensure that the link between the ID number and the uniquely identifying information necessary to contact the participant is maintained at the PCC.

To avoid transcription errors, study coordinators are encouraged to print the registration page as documentation of the participant's ID code. It is important to make sure the correct ID and date of visit appear on data collection forms.

Once the Registration Form has been added to WDES, it will return a link that enables forms required for the initial visit, including Forms 9 and 10, to be printed immediately. This is done as a convenience for study coordinators, as these forms are required to complete the initial visit and enrollment process. If the initial visit is a combined SB1 visit (no washout required), Form 20 will be included in the packet in order

to complete the randomization process as well.

2. **Lab Results Form:** Select Lab Results Form 9.

   When the Lab Results Form presents, a participant ID and visit must first be selected. For enrollment and randomization, information for the Screening Visit must be entered. After selecting the participant ID and the visit "S" or "SB1," select "Add." The Lab Results Form with data entry blanks will present for completion.

   All necessary data must be entered on the Lab Results Form before Enrollment Form10 may be entered. However, Form 9 may be partially completed and edited later. If a lab value is out of range, select "abnormal."

   Enter all data, and click "Add" to store it in the database and to compute the estimated GFR and albumin/creatinine ratio. The estimated GFR is used to determine which of the two studies (A or B) a participant may enroll in.

3. **Enrollment Form:** Select Enrollment Form 10, also called the Inclusion/Exclusion Form.

   The Enrollment Form lists the many conditions that must be met to enroll in HALT PKD. The first section has inclusion criteria (10 items currently), which must be answered affirmatively in order for a participant to be added to HALT−PKD. The next section has exclusion criteria (16 items currently), which must be answered negatively in order for a participant to be added to HALT PKD. Items 17−21 are additional exclusion criteria for Study A, and items 22−23 are additional exclusion criteria for Study B. All applicable items, including final eligibility status, must be addressed in order to enroll the participant in appropriate study. The Enrollment Form must be signed by the investigator prior to data entry and cannot be partially entered. Certain data are pulled from Forms 3 and 9 and inserted into Form 10. Therefore, Form 9 must be entered before Form 10 and Form 10 entered before Form 20.

Each clinical center is responsible for determining each of its participants' eligibility for the HALT PKD Study. A participant is enrolled when a paper copy of Lab Results Form 9 (if applicable) and Enrollment Form 10 has been completed and signed by the PI, and in which the patient is eligible on the criteria specified on the paper form. These forms must be entered via WDES within three business days of the start of the drug washout and before randomization.

4. **Randomization Form:** Select Randomization Form 20.

   Participants are randomized by entering Randomization Form 20 at the Baseline visit (B1), after Forms 3, 9 and 10 have been entered. Study assignment is determined by data stored in the database, so the first 5 items on Form 20 will be automatically populated on the Randomization Form. Additional information about consent and washout are entered on the Randomization Form. Once the Randomization Form has been added to WDES, the system will return the participant's study treatment arm (A or B − blinded) and blood pressure goal assignment.

For any registered participant who does not go on to randomization for any reason, Screen Failure Form 14 must be completed and data−entered.

16.2.6. Forms Generation Function

The Forms Generation Function in WDES allows for printing of all required data−collection forms and/or labels for a participant/visit, including specific identifiers, in preparation for a study visit. With the exception of Drug Card Assignment Form 62, all forms and labels may be printed as many times as needed. To generate paper Form 62, select option #2, Study Medication Assignment.

1. At the top of the page, select the web form portal and select option #1; generate paper forms/labels.
2. Next, select HALT ID; visit and visit date
3. Review the required forms that are pre−populated. You will have the option to click on the ï¾ button and delete a form if it is needed.
4. Select form needed by clicking on the box
5. Select the generate forms packet.
6. Next, select print forms packet and/or print barcodes.

16.2.6.1. Generating Masked Drug Card Numbers

Drug card numbers for telmisartan/placebo are assigned by generating Drug Card Assignment Form 62, via Study Medication Assignments, in anticipation of a study visit or date of action (i.e. dose modification). Designated personnel are to calculate a best estimate of the strength and quantity of drug remaining in a participant's possession and, based on this information, the strength and quantity of drug needed for a new supply. When assigning new drug cards, enter the quantity of drug cards of each strength (40 mg and 80 mg

pills) needed for the next period.

Note that Drug Card Assignment Form 62 is fundamentally different from all other data collection forms. Form 62 has been set up to control both the ***issue and management*** of the masked drug cards. When Form 62 is generated for a visit or date of action, several very important things happen in real time: 1) the quantity of drug cards needed is confirmed, 2) pill strength needed is confirmed and 3) drug card numbers are automatically assigned to a specific participant for dispensing at a given visit or date of action. Each of these actions significantly alters the information in the database and must be done with accuracy. Study drug should not be pulled until coordinator has confirmed participant will keep scheduled appointment.

If the form is generated in error or the visit does not occur, contact the DCC immediately so that the status of the assigned drug cards can be reset. After the status of drug cards has been reset by the DCC, drug cards pulled in error must be returned to stock and erroneous copies of Form 62 are to be destroyed.

16.2.6.2. Image Lab Accession Numbers

When imaging forms are generated, accession numbers will be pre populated.

16.2.7. Multi−Edit Function (Form Suite Data Entry) N/A no longer in use

It is very important to data−enter visits, particularly B2, in a timely manner

While the Forms Portal in WDES allows for clicking on a specific form to enter data for a given participant, or for multiple participants in sequence, the Multi−Edit Function allows entry of multiple forms in sequence for a given participant. Multi−Edit, or Form Suite Data Entry, contains the most commonly−used forms and allows for selection of entire visits or just specific forms. Less commonly−used forms are not listed in the Multi−Edit Function and need to be accessed directly from the Forms Portal.

In Multi−Edit select the participant ID and visit code for the forms suite you wish to enter. The form completer, dates of form completion and PI signature will also need to be selected. Note that this information must match the information on all handwritten forms in the suite and that the system will automatically identify the name of the individual who is entering these forms, as well as the date of data entry.

Next, select the visit or forms to be entered. To select a contiguous group of forms, select the first form in the group, then hold down the shift key and select the last form in the group. A contiguous group of forms can also be selected by using the control key and dragging the mouse over the forms. To select a non−contiguous group of forms, hold down the control key and select each desired form.

The form completer and dates of form completion and PI signature must match the information on *all* hand-written forms within the suite of forms being entered.

16.2.8. Tracking Reports

The DCC has implementing Tracking Reports that are available on the Website. These reports allow study personnel to access their site's status in a number of areas and may be viewed by participant or by form. Reports by participant allow the status of specific participants to be checked, while reports by form allow the number of registrations, randomizations, etc., and timeliness, to be viewed. Types of reports are listed below:

Recruitment Status − N/A no longer in use
This report gives a breakdown of current status of enrollment by site and study.

Completeness Report
This report shows visit and form completeness by site and study.

Concomitant Medications − N/A no longer in use
This report shows concomitant medications by participant.

BP Medications for non−BP Indications − N/A no longer in use
This report lists all BP medications taken for non−BP indications by center.

16.2.9. Editing or Deleting Forms

The WDES is designed to be a data entry and data editing system. Often forms may need to be reviewed and edited. Once entered, a form cannot be deleted. Forms are to be edited in order to correct any incorrect items and/or add the correct data. Forms may sometimes be entered with the wrong date of visit. The date of the visit is to be entered on Form 40 before entering data. Review the date after entering to assure accuracy. Do not enter a date for a missed visit, but complete Form 25 (missed visit).

16.2.10. Subject Confidentiality

HIPAA guidelines require that patients' health information be treated with great care. In the HALT study, the personally identifying information (e.g., name, telephone number, home address, social security number, etc.) for participants is not entered in the WDES. However, certain HIPAA−protected information (e.g., birth date, appointment dates and times, etc.) is entered and stored in the WDES. Access to the system is

password−protected; each user is given a password which must be used in order to access the system.

This study requires that coordinators at PCCs provide a very good system for retaining the identity of the participants in the HALT study. Required subject contact information may be stored on a paper copy of Participant Contact Information Form 2. This form is to be completed at the PCC, and may be stored in the participant's chart. The data is not entered into the WDES because the information is not used in the HALT study.

16.2.11. Subject and Form Tracking

Data from participants are gathered during telephone and clinic visits. These data are recorded on paper forms which can be obtained on the website. The data are then entered in a timely manner from the forms in WDES. Forms are to be entered within either three days or two weeks of data collection to be considered on time. All study visits are to be entered via Daily Visit Tracking Form 40, on the day of the visit for timely and accurate tracking of information about the visits. Target dates for all subsequent visits are based on the date of the B2 visit.

On a periodic basis, a report on visit completeness and form completeness is generated. Visits are considered on time if they occur within the acceptable visit range or "window" for the visit (See Table 8.1). This window varies during titration, but after the F5 visit, the range is 1 month before and after the target visit date, as computed using the B2 visit date as the start of official study activities for each participant. Visit completeness is determined by checking on whether the official date of visit has been entered via Form 40. If a visit is not completed, the Missed Visit Form 25 is required to be filled out.

For all visits that occur, visit timeliness is determined by checking to see if the visit occurred within the visit window. If a visit occurs within the window, it is considered to be on time, regardless of when within the window the visit occurred.

PCCs are responsible for ensuring that all forms are completed for each visit as required per protocol.

1. Select Web Form Portal
2. Option #1, then generate paper forms/labels
3. Select required forms, as needed forms
4. Select non data entry forms, then generate forms button and the selected forms will be printed

Information about samples is also tracked. Urine aldosterone and urine chemistry samples are analyzed at the DLF laboratory. Blood and serum samples are archived. Urine samples (fresh−void, acid−stabilized, no−acid) are archived. Genetic samples are also obtained. Serum creatinine samples are obtained. These samples are tabulated by determining which samples are due at various locations, and determining if the sample has been received at the relevant repository or central laboratory.

16.2.12. Missing Data

Data gathered during clinic and telephone visits is to be entered into the study database using the WDES. There are several reasons why data might not be entered. These include, but are not limited to, the following:

1. Omitting a form item/data not collected –
   - This can usually be avoided by working directly from the forms to ensure that no item is overlooked.
2. Laboratory error in processing samples –
   - This may be avoided by providing clear instructions to and problem−solving with the laboratory.
3. Spoiled or damaged sample −
   - This is usually an inadvertent problem that occurs intermittently.
4. Data lost during data entry −
   - Such data is to be re−entered.

Missing forms and data are to be entered with the missing data codes, which are A: participant refused B: reading not possible and C: institutional error.

16.2.13. Security and Backup

Security for the data entry and data feedback processes have been discussed elsewhere in the MOP. Essentially, all access to the system is password−protected. Within the WDES system, the database is backed up on a daily basis.

16.3. Quality Control/Quality Assurance

The quality of data collection and data entry will be ensured by means of a number of proactive and retroactive measures. Study personnel are to be trained and certified prior to the start of enrollment and then retrained annually. Site visits will be conducted at each institution during the first year of the enrollment period and every two years thereafter. Site visit reports will be generated to point out any problems in study procedures, as well as to make recommendations for corrections and improvements for such problems to the PI and research team. Double

data entry has been instituted and will help to eliminate data entry errors.

16.3.1. Training

Coordinators at all participating clinical sites are required to complete training and certification in the areas of study procedures, data collection, and data entry. New research personnel must complete the tests provided by the DCC and the site is required to send the score card to the DCC. In addition, all new personnel are required to view the training video for data entry.

Trained HALT PKD study coordinators are responsible for ensuring that 1) other study personnel at their PCC are properly trained and have reviewed pertinent sections of the Manual of Procedures; and 2) study procedures are properly carried out at their institutions. Radiology technologists must review the scanning protocol and then register with the Imaging Analysis Center (IAC).

16.3.2. Certification

All study coordinators are required to demonstrate that they can perform study procedures satisfactorily. Prior to enrolling participants to the study, coordinators were required to take a written test for certification, covering blood pressure, sample collection/processing/shipping, study medications, imaging and data entry.

16.3.3. Retraining

All Coordinators are required to attend the annual coordinator meeting. At that time, study procedures will be reviewed with any changes in study procedures to be discussed. Training materials will be sent to each of the PCCs for training new staff and to allow study staff to review procedures as needed.

16.3.4. Training and Certification of New Study Coordinators – N/A no longer in use

Coordinators who begin working on HALT PKD study after the initial training session and before the annual meeting for retraining are to be trained by a certified coordinator at the PCC. Trainees are to review training materials, demonstrate study procedures, and pass the written tests for certification before they may perform any study procedures for HALT PKD. If, for some reason, a certified coordinator is not available at a PCC, the DCC staff can assist in training and certification of new personnel.

16.3.5. Standardized Recordkeeping

16.3.5.1. Source Documentation

Clinic charts are to serve as original source documentation. If a site does not maintain clinic charts, the research chart will serve as the source documentation. In most cases, source documents will consist of progress notes or other medical records. However, some sites may allow staff to use actual HALT PKD data collection forms to gather source documentation. Any documents provided or completed by the participant (e.g., home BP diaries) are considered source documentation and are to be stored according to Good Clinical Practices. Data entered on WDES forms are considered case report forms (CRF) for the HALT−PKD study. It is not necessary to print forms once data has been entered. During an audit data (CRFs) entered will be checked against hand−written forms, or other documentation, in the research chart. If there are any discrepancies, CRFs will then be checked against separate source documentation, as applicable.

The following table defines the terms Research Chart, Source Document, and Case Report Form, which are listed in bold italics.

Table 16−1. Standardized Recordkeeping in HALT PKD

	Data/Document	*Source Document*	*Case Report Form*
Clinic Chart	Site−specific documents	Yes, if the site uses clinic	No
Research Chart	Site−specific documents	Only if site does not use clinic charts or if HALT paper forms are not required*	No
	HALT forms completed by coordinator/P	Yes, if site does not use clinic charts**	No
	HALT forms completed by participant	Yes, in all cases	No

Data Entered		No	Yes

*Copies of site−specific documents may also be added to the research chart and may replace HALT paper forms if those forms are not required (e.g., a copy of a lab results sheet may replace a paper copy of Lab Results Form 9). In such cases, the HALT participant ID is to be written at the top of the site−specific documentation and the investigator is to sign and date it prior to data entry.

**Some sites may use clinic charts, but will allow HALT paper forms to serve as original documentation (in research chart or clinic chart). Most data collection forms will have to be completed by hand (as part of the research chart) prior to data entry (e.g., a hard copy of Clinical History Form 4 must be completed before the data is entered). This may serve as source documentation in lieu of site−specific documentation, if the site accepts it as such. If not, data will be gathered in the usual manner (using site−specific forms), transferred to the research chart (HALT forms completed), and then entered into the database (CRF).

16.3.5.2. Editing Study Data

When a paper form is completed, the form completer is to sign it and enter the date of completion. The PI then signs and dates forms and the data is subsequently entered into WDES. Once the data has been entered in WDES, the need for editing data is expected to be rare. However, in the event that editing is necessary, study personnel are to follow the policy outlined below. Changes are to be written on the completed paper form, and all changes are to be dated and initialed by the form completer editing the form. When the data is edited in WDES, there is no need to change the date of form completion. The WDES system will identify the form completer editing the form and the date of the edit. If a significant change is made to the data, the form completer should inform the PI. The PI may then wish to date and initial the edited paper form as well, but this is not required.

16.3.5.3. Quality Control Checks of Data Entered − N/A no longer in use

In−house quality control checks will be conducted for the first five participants enrolled at each site to confirm that data has been accurately entered into WDES. In these cases data is to be entered into WDES from hand−written copies of forms, with accuracy being checked by another person at the site, and later checked during a site visit. Coordinators will have editing capabilities in WDES, but investigators will be given only auditing capabilities that allow them only to view data and not edit it. Once the study is well underway, a random sampling of hand−written data forms will be requested by the DCC to check against the data entered. Research charts must be stored in accordance with Good Clinical Practices.

16.3.5.3.1. Goals for Quality Control of Data Entered

Listed below are the percentages that are required to achieve a "passing" grade in each area of Quality Control. Site visits and monthly reports will be used to assess quality of data collection and data entry at each site on both a quarterly and an annual basis.

- 100% of all serious adverse events must be reported within 24 hours of study personnel learning of the event.
- >95% of all other required forms must be data entered within the specified time frame.
- >95% of all images must be transferred to the IAC within the required time frame.
- >90% of all queries should have been resolved within 14 days of initial request.
- >90% of all required medical documentation (discharge summaries, death certificates, ESRD forms) should be forwarded to the DCC, or on file at the PCC, within the required timeframe (all personal identifiers removed).
- >90% of all drug accountability logs at each site are current and accurate.
- >80% of all forms should be received without the need to generate queries.

N/A − More information on standardized recordkeeping may be found by referring to Section 16.3.5.2.1 − Standardized Record Keeping in HALT PKD.

16.3.6. Site Visits

16.3.6.1. Purpose of Site Visits

The primary objective of conducting site visits is to improve communication between the DCC and PCCs, and among the different PCCs. The process will facilitate and enhance the sharing of information and will also help investigators and coordinators identify problems in procedures and the solutions to improve them. In addition, site visits will provide quality assurance of data entry and encourage adherence to the procedures outlined in the Manual of Procedures.

16.3.6.2. Frequency and Scheduling

Staff from NIDDK, the DCC and PCCs will conduct audits of all participating clinical sites over the course of the study. Each site will be audited within the first year of the study and again every two years thereafter. Auditors will tour the facility, review regulatory documents and drug accountability logs, compare data reported (CRF) to actual research charts, observe procedures, and meet with study personnel to discuss findings and make recommendations. Auditors will work with PIs and coordinators to schedule site visits when all study personnel will be available. PIs and coordinators will be notified in writing at least one month prior to the scheduled site visit. Notification will provide details of what is to be done at the site visit, including an agenda and requests for specific data, charts, and any other items needed before or during the site visit.

Example 16−1. Sample Site Visit Agenda

- ***Introduction and Purpose of Site Visit***
- ***Site Overview by Principal Investigator and Coordinator***
- ***Research Chart Review***

During the site visit, ten percent of the PCC participant research charts are randomly selected for review by the site audit team. Randomly selected participant visit dates and the associated visit forms are audited. The content of the visit forms and source documents will be compared to the data contained in the DCC web database. The primary audit of participant consents will be completed by the DCC on all charts selected for audit.

  - ◊ Brief review of all research charts by study, including informed consent
  - ◊ Page−by−page review of specific charts identified in general review

- ***Tour of Facility***
  - ◊ GCRC, patient rooms, lab
  - ◊ Clinic area, waiting room, exam rooms, BP procedure if possible
  - ◊ Clinic Coordinator's work area
  - ◊ Storage of HALT participant data, forms and Manual of Procedures
  - ◊ Data entry work space, computer security
  - ◊ Department of Radiology
- ***Working Lunch and Review of Regulatory Documents***
  - ◊ IRB submissions, correspondence, approvals, renewals
  - ◊ Notices from NIDDK regarding DSMB, IND, etc.
  - ◊ Prepare summary of site visit findings
- ***Discussion with Principal Investigator and Study Personnel***
  - ◊ Staffing
  - ◊ Informed consent procedures
  - ◊ IRB approval
  - ◊ Review recruitment goals
  - ◊ Review any participant problems − retention, missed visits, other
  - ◊ Review results of audit of participant charts
  - ◊ Review site visit report
- ***Conclusion of Site Visit***

The site visit will typically start in a conference room with brief introductions of the site staff and site visitors. An outline of the purpose of the site visit will be presented (about 10 minutes).

The principal investigator (PI) and study coordinator will then give a presentation on their site's organization for the study, to include study personnel and their training, a description of the storage location for data, charts, drugs, files, etc., and a description of institutional support for the study. The PI may prepare a brief slide presentation to facilitate this aspect of the visit (about 15 minutes).

Review of participant−specific information for each study will follow the site presentation. This is usually the most labor−intensive part of the visit and is probably best to do early in the visit. The strategy will be to conduct a brief review of all enrolled participants, via a comprehensive table for each study that lists all participants at the site and the forms that should have been submitted for each visit, etc., thus far. The DCC will generate this table a day or two before the site visit. The site visitors will briefly walk through the information on each participant to verify that the DCC has received all relevant forms. In the course of this brief review, the site visit team will select a subset of participant charts from each study and then conduct a page−by−page review of the selected charts (consents, data forms, AE reports, relevant source documents, etc.) (about 1.5 to 2 hours).

The PCC staff will then take the site visitors on a tour of its GCRC, clinic, coordinator offices, locked storage

spaces, etc., and will show the site visitors their procedures regarding participants, study documents and sample collections (1 hour). A working lunch will allow the site visitors to review all regulatory documents, including IRB submissions, correspondence, approvals, renewals, notices from NIDDK regarding the DSMB and INDs, etc. It will also allow the site visitors to discuss any particular issues that came up during the morning session.

16.3.6.3. Touring Facility and Reviewing Study Procedures

Auditors will observe and report on the quality of each site's facilities and equipment. Waiting rooms, examination rooms, coordinator offices, as well as storage of study data, samples and supplies, will be viewed and evaluated. Blood pressure monitors and freezers, in particular, will be assessed during the site visit. The site's procedures for collecting, reporting and storing study data will be reviewed. Consent procedures will, specifically, be discussed with study personnel, as will study enrollment, participant satisfaction, and retention. Auditors may also request the opportunity to observe certain key procedures conducted at the site (e.g., blood pressure measurement and BP monitor calibration, sample collection and processing).

16.3.6.4. Review of Study Documents

- ***Regulatory Audit***

Auditors will review each site's IRB approvals of the study protocol and all necessary informed consent documents. Amendments to the protocol and any memoranda issued by NIDDK or the study chair should also be on file at the site. The consents will undergo two forms of review, a primary audit conducted by the DCC site auditors, and a secondary audit completed by the PCC personnel.

- ***Primary Audit of Consent Forms***

The primary audit of PCC study consents will be completed by the DCC site auditors. All randomly selected research charts identified for review during the site audit will be screened and the participant consent(s) will be examined for completeness. The review will confirm the presence of

- Study A or B current consents
- Genetic Study A or B addendum consents (if applicable)
- Consents (for participants documented as submitting genetic samples)
- Endpoint consents (for those participants meeting Study B endpoint)

- ***Secondary Audit of Consent Forms***

It is the responsibility of the PCC to maintain copies of all consents. For additional internal study audit purposes, a secondary audit of consents will be completed by the PCC staff. The DCC will circulate a site specific excel spreadsheet facilitating the PCC staff audit and documentation of the consent review. The PCC staff will verify the presence of the appropriate Study A or B main consents, addendum consents (if applicable), genetic consents (for participants documented as submitting genetic samples), and endpoint consents (for those participants meeting endpoint). The PCC staff completing the local audit will list their initials on the excel spreadsheet next to each HALT ID indicating the consent is accounted for. When completed, the excel document will be submitted to the DCC. Any PCCs failing to comply with the secondary consent review will be reported to the DSMB.

- ***Additional Site Visit Reviews***

The study Manual of Procedures should be current and accessible to site personnel. Research charts will be reviewed for up to a random 10% of all participants enrolled at each site. Auditors will compare research charts to data reported to the DCC and will report their findings to the clinical staff and other appropriate bodies. Key components of the study, listed below, will be given particular attention, with any problems being reported in detail.

Primary Endpoint − Study A: Total Kidney Volume (MRI).
Primary Endpoint − Study B: Composite Time to Event (reduction of eGFR, ESRD, death).
Secondary Outcomes − Study A: Rate of Decline of Renal Function: GFR, renal blood flow (MRA), albuminuria/proteinuria, cardiac MR (LVH).

- Specific Aims − Studies A and B: 24−hour urine aldosterone in all participants, home blood pressure in all participants (over seven consecutive days), quality−of−life and pain assessments.
- Other Key Issues: Security of study data (physical and electronic), drug logs and pill counts for returned medications, sample storage and shipment.

Auditors may review additional charts if the following events have been reported: endpoint reached, serious adverse events (including death), dose modification, or modified participation. As deemed necessary over the course of the study, the DSMB, or other bodies, may require that additional information be audited.

16.3.6.5. Consulting with PCC Staff

During the site visit, auditors will prepare a summary report, which will be reviewed with the PI and coordinator at the conclusion of the site visit. Specific topics to be discussed include staffing, informed consent procedures, IRB approvals, review of recruitment goals and participant retention, and audit findings. Special attention will be given to safety, drug accountability, and key study components, as described above. Auditors will highlight significant issues found at the site and make recommendations. Site personnel will be asked to create and implement measures to correct or avoid problems in the future and to suggest ways in which the DCC might be helpful in improving communication and facilitating resolution of issues.

16.3.6.6. Reporting Findings and PCC Response

Within one month after the site visit, auditors will complete a visit report of the audit findings, and will send a copy of the summary to the appropriate PI and study coordinator, Steering Committee Chair, NIDDK Project Director, and DSMB Chair, as well as to any other individuals for whom the findings of a site visit necessitate their receiving copies of the summary. The PI will be asked to formally respond with a plan for resolution of any issues raised in the audit report for his/her site.

16.3.7. HALT Reports

The HALT Steering Committee and subcommittees, and the DCC, have created numerous reports designed to help monitor safety, blood pressure control, and separation, dose levels of study medications, PCC performance, and quality control of data, images and samples. PCC−specific versions of these reports are reviewed with PCC personnel as part of each PCC site visit.

1. **Recruitment − These reports were provided during the enrollment period**
    - ◊ *Weekly Recruitment Report*: includes total number of participants enrolled to date by PCC and percent of expected rate of recruitment by PCC for the following periods: cumulative, past 6 months, past 3 months, past 30 days. Also includes total number of participants whose current status is registered, screened, excluded, started washout, randomized, or on study medication. Information is provided in graph and table format for Study A, Study B and overall. Report is cumulative and forwarded weekly to all study investigators and coordinators.
    - ◊ *Monthly Prescreening Report*: Includes total number of prescreening interviews performed per month by PCC. For a given month, gender by PCC is shown in graph and table format. Report is cumulative and forwarded monthly to all study investigators and coordinators.
    - ◊ *Screen Failure Report*: Includes total number of registered participants who fail screening, by reason for failure including frequency and percentage across PCCs, and specific information, including PCC, about "other" reasons for failure and GFR values when selected. Cumulative report forwarded to DSMB and all study investigators for each SC or DSMB meeting.
2. **Demographics and Baseline Characteristics**
    - ◊ *Demographics and Baseline Characteristics Report*: Includes total number of participants, mean and standard deviation for age, race, gender, and baseline lab values such as serum creatinine and eGFR. Also included are weight, body mass index, body surface area, and blood pressure values. Cumulative report, for Study A (standard and low BP goals) and Study B, forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
3. **Performance and Data Quality Control**
    - ◊ *Participants per Visit Report*: Includes total number of participants by PCC who have completed each study visit. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
    - ◊ *Visit and Forms Completeness Report*: Includes total number of expected and completed visits, and percent of expected visits completed, by study, visit and PCC. For completed visits, cumulative report includes total number of expected and completed forms, and percent of expected forms completed, by study, form and PCC. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
    - ◊ *At Risk Participant Report* utilizes the QC visit completeness report, compresses the data to refine the information reflect participants that have “at risk” attendance patterns. The report lists participants that miss their last PCC visit use a Quest Visit (Remote visit) within the last twelve months and complete a recent PCC visit out of window (attendance to visits before or after the target visit window)need immediate scheduling attention (expected). These site specific reports are generated monthly by the DCC and are emailed to the site coordinator team. The At Risk Participant Report is designed to reinforce the PCC efforts to track and schedule participants and

prevent the inadvertent misplacement of a participant on site tracking schedules.

- ◊ *Visit and Forms Timeliness Report*: Includes total number of visits completed within, before and after acceptable range, and average number of days and standard deviation for visits completed outside of acceptable range, by PCC and study visit, for Study A and Study B. Also includes total number of forms entered within and outside of acceptable range, and average number of days and standard deviation for forms entered outside of acceptable range, by PCC and study visit, for Study A and Study B. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
- ◊ *Data Completeness Report*: Includes percent of completed items and total number of items per form, for all forms entered, by PCC for Study A and Study B. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
- ◊ *Protocol Deviations Report*: Includes a chronological list of major protocol violations, participant IDs which reflect PCC, type of deviation and summary of each violation. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
- ◊ *Central Serum Creatinine Report*: Includes plots comparing serum creatinine values from PCC labs (at screening) to those from CCF central lab (at baseline), mean values to difference between duplicate samples at baseline and visit F5 (Bland Altman) by PCC, difference between samples over time by PCC, and cases where the differences is greater than 20% or 0.2mg/dL. Report is reviewed weekly by DCC staff. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
- ◊ *Data Quality Control Report*: Includes central lab values for serum creatinine when sample difference is >20% at baseline and visit F5, quality control samples for serum creatinine, urine aldosterone and 24−hour urine chemistry tests. Also includes participants taking BP meds for non−BP indications, listing participant ID, visit, drug name, start/stop dates and indications. Report distributed to Quality Control Committee for each monthly meeting. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.

4. **Blood Pressure Monitoring (Study Adherence)**

- ◊ *Blood Pressure Report*: Includes box plots for systolic, diastolic, and mean arterial pressure, by visit for Study A (standard and low BP goals) and B. Includes line graphs and bar graphs for systolic, diastolic, and mean arterial pressure, by PCC and visit, for Study A (standard and low BP) and B. Includes bar graphs for systolic, diastolic, and mean arterial pressure, by dose step, PCC and visit for Study A (standard and low BP goals) and B. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting. Report sent to Blood Pressure Committee monthly also includes participant−specific tables for Study A (standard and low BP goals) and B by PCC and visit, with mean systolic and diastolic pressures and heart rate (acceptability flagged) and suggested dosing actions for all, as well as listing complete dose histories for all participants whose BP was ever out of acceptable range.
- ◊ *Medication Levels Report*: Includes total number and percentage of participants per dose step across PCCs before visit F5 for Study A (standard and low BP goals) and Study B. Also includes total number and percentage of participants per strength of lisinopril, masked medication (ARB/placebo), and open−label drugs across PCCs before visit F5. Report is reviewed by BP Committee monthly. Report is cumulative and forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.

5. **Safety Data**

- ◊ *Serious Adverse Events Report*: Includes total number of events, pre− and post− ACE+ARB therapy by PCC, expectedness and relatedness to study participation by event type. Includes total number of post−ACE+ARB events by PCC, expectedness and degree of study relatedness in event type tables. Also includes all events by PCC, participant ID, gender, age at time of event, dates of enrollment and randomization, event start/stop dates and a narrative of each event. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting. Report forwarded to Quality Control Committee monthly.
- ◊ *Medication Error Report*: Includes all medication errors (a subset of protocol violations), participant ID, date of event and a brief narrative of each event. Cumulative report reviewed monthly by Quality Control Committee, and forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting.
- ◊ *Quality Control Committee Report*: Includes total number and percent of other symptoms by visit across PCCs (non−serious adverse events). Includes participants who have modified study

participation by level of continued participation (continue/discontinue masked drug, frequency of follow−up). Includes participant ID, visit and date of modified participation, a brief narrative of each case, as well as treatment start/stop dates and duration of therapy for each participant. Includes Kaplan−Meier Curves of modified participation by PCC. Includes participant ID, age, race, gender, visit and date of all elevated/reduced serum potassium values as well as subsequent values to ensure control of hyper− and hypokalemia. Also includes all pregnancies, date reported, ACE+ARB status, and pregnancy outcome. Cumulative report forwarded to DSMB and all study investigators and coordinators for each SC or DSMB meeting. Report forwarded to Quality Control Committee monthly.

6. **Kidney and Cardiac Imaging**
   - ◊ *Image Quality Repor*t: Includes bar graphs reflecting graded image quality by PCC for kidney, cardiac and renal blood flow for study A (standard and low BP goals) and study B. Cumulative report forwarded to DSMB and study investigators for each SC or DSMB meeting.
   - ◊ *MRI Completion Report*: Includes total number of scans, by PCC for study A (by BP goal) and B, performed, received, evaluated, as well as those measured by image type. Cumulative report forwarded to DSMB, imaging committee, and study investigators for each SC or DSMB meeting.
   - ◊ *Kidney Size Distribution Report*: Includes box plots, total scans, mean kidney size by PCC and study. Cumulative report forwarded to DSMB and investigators for each SC or DSMB meeting.
7. **Central Laboratories and NIDDK Repositories**
   - ◊ *Timeliness of Central Serum Creatinine Sample Results*: Includes total samples by PCC per visit and days from visit to results report (mean, maximum and standard deviation). Cumulative report forwarded to DSMB, investigators and coordinators for each SC or DSMB meeting.
   - ◊ *CCF Central Laboratory Urine Samples Count*: Includes total number of samples collected and results received by visit, sample type and PCC. Also includes total number of samples stored at each PCC, shipped to CCF, and lost, damaged or destroyed. Report is cumulative and forwarded to DSMB, study investigators and coordinators for each SC or DSMB meeting.
   - ◊ *NIDDK Blood Samples Report*: Includes total number of samples collected and received at Fisher Biosciences (NIDDK repository) by visit and PCC. Cumulative report forwarded to DSMB, investigators and coordinators for each SC or DSMB meeting.
   - ◊ *NIDDK Urine Samples Report*: Includes total number of samples collected and received at Fisher Biosciences (NIDDK repository) by visit and PCC. Cumulative report forwarded to DSMB, investigators and coordinators for each SC or DSMB meeting.
   - ◊ *NIDDK Genetic Sample Consent Report*: Includes total number participants by PCC who have signed HALT genetic consent Cumulative report forwarded to DSMB, investigators and coordinators for each SC or DSMB meeting.
   - ◊ *NIDDK Genetic Samples Report*: Includes total number of samples collected and the number of samples received at Rutgers (NIDDK repository), with and without permission, by PCC. Also includes total number of CRISP genetic samples already in inventory. Cumulative report forwarded to DSMB, investigators and coordinators for each SC or DSMB meeting.
8. **Ancillary Studies and Publications**
   - ◊ *Ancillary Studies Report*: Includes all ancillary studies, PCC, investigators, approval, funding and status. Cumulative report forwarded to DSMB and investigators for each SC or DSMB meeting.
   - ◊ *Publications Report*: Includes list of all publications, PCC, authors, submission dates and status. Cumulative report forwarded to DSMB and investigators for each SC or DSMB meeting.
9. **Web−based Reports − N/A no longer in use**

   The following online reports are available via the HALT website:
   - *Blood Pressure Report (updated nightly):* As above, PCC−specific reports also available.
   - *Cumulative Randomization Report (updated hourly):* Line graphs reflect enrollment over time for Study A and B by PCC.
   - *Participant Status Report (updated hourly):* Lists all participant IDs by PCC, includes study (A or B), current status and visit dates, confirmed and anticipated
   - *Prescreening Report (updated monthly):* As above.
   - *Protocol Deviations Report (updated daily):* As above
   - *Quality Control Committee Report (updated monthly):* As above, monthly and cumulative reports

available. Includes Serious Adverse Events Report, Central Serum Creatinine Report, Data Quality Control Report, Protocol Deviations Report, as well as participant ID, age, race, gender, visit and date of all reduced serum potassium values to ensure control of hypokalemia.

- *Serum Creatinine Report (updated weekly):* As above.
- *Visit Completeness Report (updated nightly):* As above, PCC−specific reports.

16.4. Statistical Design and Analysis

The HALT study is designed as a double−blind clinical trial. There are two distinct components to the trial, Study A and Study B. These components are well−described in Chapter 2 of the MOP, and will not be repeated here.

Study A is a 2x2x2 "split−plot" design. The BP factor and masked medication (MM) factors are completely randomized factors, while the visit factor is a within−subjects factor. The data will be analyzed using a mixed−models approach, such as is found in the SAS procedures MIXED and GENMOD. These will be used depending on the specific variable being analyzed. In using these methods, the specific structure of the covariance structure for the repeated measures must be stated. In this experiment, either the unstructured method (in which all covariance's are estimated) or a more restrictive method, possibly AR(1) or a factor structure method, will be employed. The primary points of data for analysis will be the assessments made at the 2−year periods (baseline, 2 year, 4 year). These are assessments scheduled at equally spaced intervals, and are thus quite amenable to the AR(1) assumption.

For Study B, the primary endpoint is the time to reach an endpoint of ESRD, a terminal physical outcome, or the reduction of eGFR to 50 % of entry eGFR. These outcomes are thus examined using a survival method or other such time−to−event data analysis method.

16.5. Access to Study Data

Investigators

Access to study data by HALT PKD investigators is governed by the Publications/Ancillary Studies Subcommittee and will be provided to investigators by only the Data Coordinating Center (DCC).

Requests for specific reports and/or data analysis may be made to the DCC by sending an e−mail to the Project Manager.

Non−Study Investigators

Access to study data by non−study investigators is also governed by the Publications/Ancillary Studies Subcommittee. If a request for data by a non−study investigator has been approved, such data is to be provided by only the DCC. Requests for reports and/or data analysis may be made to the DCC via Request Tracker, as noted above.

Copies of the HALT PKD protocol, as well as all other study documents, cannot be provided to non−study investigators (or corporate entities) unless prior approval from the Steering Committee has been granted. To make such a request to the Steering Committee, send an e−mail to the HALT PKD Project Manager, who will distribute the request to the Committee members for consideration. Once the Steering Committee has either approved or disapproved the request, the Project Manager will inform the requestor of the Committee's decision.

General Public

Publications in professional journals will provide the general public with access to HALT PKD data and results. These publications will not contain any private health information (PHI).

Complete instructions on using Request Tracker may be found in Section 3.14.4.

Chapter 17. Study Closeout Procedures

The objective of the closeout visit is to insure a safe, organized and timely closeout at all levels of the HALT PKD clinical trial that includes the participant, PCC and DCC. The closeout procedures are primarily aiming to insure patient safety through adequate communication with the PCP/Nephrologist and also to maintain the integrity of the clinical trial.

17.1. Participant Closeout

17.1.1. Penultimate (next to the last) Visit

This visit is designed to prepare the participant for the end of the clinical trial and lay the groundwork for the last PCC visit, the "Closeout Visit".

17.1.1.1. Prior to Penultimate Visit

It is suggested that coordinators discuss the penultimate visit with the participant at the 3 month visit telephone call preceding the penultimate visit date to facilitate scheduling and to underscore the importance of the visit.

- Schedule the Penultimate visit with participant
- Discussion with participant at scheduling
    - Importance of Penultimate visit
    - Plan for transition of care to local PCP or nephrologist and for Telmisartan/placebo study medications to be discontinued at the closeout visit.
    - The plan is for Telmisartan/Placebo study medications to be discontinued at the closeout visit.

17.1.1.2. Penultimate Visit Form Completion

The following forms must be completed during the PCC visit prior to the last visit:

Form 2 - Contact Information Form

- Coordinators are to confirm the participant's most recent contact information.
- It is essential that contact information for the participant's local PCP or nephrologist be obtained at this time.

Form 5 - Symptoms Checklist Form
Form 6 - Concomitant Medication Form
Form 8 - Background Questionnaire F
Form 9 - Required Lab Results Form
Form 12 -Home Blood Pressure Form
Form 15 -Current Physical Findings
Form 16 - Urine Sample Collection Form (if annual visit)
Form 18 -Archived Blood Sample Collection Form (if annual visit)
Form 19 - Central Serum Creatinine Sample Collection Form
Form 21 - MRI Session Form

- For all Study A participants that require an F60 or Redo MRI

Form 22 - Renal Blood Flow (MRA) Form

- For all Study A participants that require an F60 or Redo MRI

Form 36 - Home Blood Pressure Calibration Form
Form 38 - Quality of Life Questionnaire (SF-36 36v2 Health Survey) *(if annual visit)*
Form 39 - HALT PKD Pain Questionnaire *(if annual visit)*
Form 40 - HALT PKD Visit Tracking Form

- The DCC will provide sites with a list of their participant's projected date of last visit Form 62 - Drug Card Assignment Form

Form 63 - Study Medication Form
Form 81 - Shipping Manifest Central Lab (CCF)
Form 82 - Shipping Manifest Central Lab (UPCI)
Form 130 or Form 131 *will be used depending on the investigator preference*
Form 130 – Participant Penultimate visit questionnaire options

- A checklist for capturing key information regarding the transitioning care at the final visit, insurance status, interest in knowing study assignment (telmisartan/placebo), and final contact information.
- Coordinators will ask the participant the list of questions and complete the form. The participant signature is to be placed on the form when completed.
- If Form 130 was not completed at the penultimate visit, it is to be completed at the final visit
- This form informs the participant that the investigator will be disseminating their study
  results and treatment allocation to the participant and his/her providers at the completion of the study.

The following forms are to be completed at the Penultimate visit, if applicable:

Form 13 - Serious Adverse Events
Form 17 - Genetic Sample Collection Form
- If obtained, complete Form 83 - Shipping Manifest Repository Genetic Sample

Form 25 - Missed Visit Form
- Rescheduling participants

Refer to 17.1.1.3 - Rescheduled or Missed Penultimate visit

Form 28 - Modified Participation Form
Form 30 - Hospitalization Form
Form 31 - Death Notification Form
- Request certificate of death within1 week of visit.

Form 32 - End Stage Renal Disease Form (ESRD)
Form 33 - eGFR Reduction Form and Kidney Function Endpoint
Form 35 - Post Closeout Follow up Form (Study B)
Form 52 - Post-Closeout Follow up (Study A)
Form 84 - Shipping Manifest Repository Serum Plasma
Form 85 - Shipping Manifest Repository Urine
Form 90 - Quest Visit Form
- Closeout considerations if Penultimate visit is completed remotely.
  - Coordinators will contact the participant and obtain PCP/Nephrologist contact information and review plan for closeout visit stressing the importance of closeout visit attendance.

17.1.1.3. Rescheduled or Missed Penultimate Visit

a) PCC staff should proceed in earnest with attempts to reschedule the participant
b) Participants that miss a scheduled penultimate visit should be rescheduled within the visit window as soon as possible.
c) Missed Penultimate Visit Letter should be sent by certified mail to the participant, Letter #1.
d) If the participant utilizes email communication with the site, the letter may be sent as an email attachment. A copy of this communication should be maintained in the source document

17.1.2. Closeout Visit

When scheduling the participant for the Closeout Visit, PCC staff should remind the participant to bring all unused study drug cards with them to the PCC.

17.1.2.1. Prior to Closeout Visit

Scheduling the Closeout Visit:
- It is recommended that participants with target Closeout visit dates in June 2014 should be scheduled in the earliest portion of their target window and preferably attend the PCC closeout visit in May of 2014.
- Send participant Pre-Closeout Letter

#2 Discussion with Participant:
- Importance of Closeout visit
- Plan for transition of care to local PCP or nephrologist
- Information for discontinuance of study drug will be provided during the closeout visit by the study investigator.

17.1.2.2. Closeout Visit Forms

The following forms must be completed at the Closeout visit:

Form 2 - Contact Information Form
- Coordinators are to confirm the participant's most recent contact information. It is essential that contact information for the participant's local PCP or nephrologist be obtained at this time.

Form 5 - Symptoms Checklist Form
Form 6 - Concomitant Medication Form
Form 9 - Required Lab Results Form
Form 12 - Home Blood pressure Form

Form 15 - Current Physical Findings Form
Form 16 - Urine Sample Collection Form (if annual visit)
Form 18 - Archived Blood Sample Collection Form (if annual visit)
Form 19 - Central Serum Creatinine Sample Collection Form
Form 21 - MRI Session Form (Study A only)
Form 22 - Renal Blood Flow (MRA) Form (Study A only)
Form 36 - Home Blood Pressure Calibration Form
Form 38 - Quality of Life Questionnaire (SF-36 36v2 Health Survey) *(if annual visit)*
Form 39 – HALT PKD Pain Questionnaire *(if annual visit)*
Form 40 – HALT PKD Visit Tracking Form
- DCC will provide sites with a list of their participant's projected date of last visit

Form 62 - Drug Card Assignment Form
- Use for any participant that receives additional study drug for taper at closeout visit. Form 63 - Study Medication Form

Form 81 - Shipping Manifest Central Lab (CCF)
Form 82 - Shipping Manifest Central Lab (UPCI)
Form 130 or Form 131 *will be used depending on Investigator preference.*
Form 130 – Participant Penultimate Visit Questionnaire options
- A checklist for capturing key information regarding the transitioning care at the final visit, insurance status, interest in knowing study assignment (telmisartan/placebo), and final contact information.
- Coordinators will ask the participant the list of questions and complete the form. The participant signature is to be placed on the form when completed.
- If Form 130 was not completed at the Penultimate visit, it is to be completed at the final visit.
- This form permits the participant to choose what study information is received and disseminated to providers including study results and treatment allocation.

Form 131 – Participant Penultimate Visit Questionnaire mandated notice
- A checklist for capturing key information regarding the transitioning care at the final visit, insurance status, interest in knowing study assignment (telmisartan/placebo), and final contact information.
- Coordinators will ask the participant the list of questions and complete the form. The participant signature is to be placed on the form when completed.
- If form 131 was not completed at the Penultimate visit, it is to be completed at the final visit.
- This form informs the participant that the Investigator will be disseminating their study results and treatment allocation to the participant and his/her providers at the completion of the study.

The following forms are to be completed, if applicable:

Form 8 - Background Questionnaire (if not completed at the penultimate visit)
Form 13 - Serious Adverse Events
Form 17 - Genetic Sample Collection Form
- If obtained, complete Form 83 - Shipping Manifest Repository Genetic Sample

Form 25 - Missed Visit Form
Form 30 - Hospitalization Form
Form 31 - Death Notification Form
- Request certificate of death within one week of notification

Form 32 - End Stage Renal Disease Form (ESRD)
Form 33 - eGFR Reduction Form and Kidney Function Endpoint
Form 35 - Post Closeout Follow up Form (Study B)
Form 52 - Post-Closeout Follow up (Study A)
Form 84 - Shipping Manifest Repository Serum Plasma
Form 85 - Shipping Manifest Repository Urine
Form 90 - Quest Visit Form
- If participant misses closeout visit, perform Quest visit for final labs and close out per usual.

17.1.2.3. Discontinuance of Masked Study Drug

HALT Study Investigators are responsible for safely tapering blinded study medication & replacement as needed with open label medication or alternatives. Until study analysis completed, combination ACE-I/ARB therapy is not considered standard of care medication in hypertension management and blinded study medication can be substituted with other classes of anti-hypertensive agents appropriate for their comorbidities. ACE or ARB alone may be reasonable. The goal is to complete transition to conventional antihypertensive medications within 2-8 weeks of their closeout visit with stable blood pressures. If patient assistant program becomes available for study medication, staff will be notified.

- ARB withdrawal and/or replacement: The Investigator is responsible for tapering study drug with BP goal of < 130/80 with documentation of medications, dose, and frequency. The investigator will supply prescriptions for all BP medications to be continued after closeout. At discretion of the investigator, BP monitoring will continue and medications adjusted until target BP is reached within 2-8 weeks of their closeout visit.
    - 80mg of Telmisartan/Placebo
        - Decrease to 40mg once daily.
        - BP will be reported & open label antihypertensive therapies will be prescribed until target goal of < 130/80 is achieved.
        - Once BP controlled, discontinue 40mg dose.
        - BPs will continue to be reported and open label antihypertensive therapies will be prescribed until target goal of < 130/80 is achieved.
    - 40mg of Telmisartan/Placebo
        - Discontinue study drug.
        - BP will be reported and open label antihypertensive therapies will be prescribed until target goal of < 130 /80 is achieved.
- Supply prescriptions for other step antihypertensive therapies or manage their replacement (e.g. participants with no prescription coverage) deemed appropriate (by site investigator) to individual patient co-morbidities.
- Collect unused study drug and document drug destruction
- The Investigator is to use his/her discretion to determine the frequency and intensity of participant blood pressure monitoring and follow-up.
- Provide the participant with:
    - Closeout visit letter to participant – 80 mg taper (Letter #3)
    - Closeout visit letter to participant—40 mg taper (Letter #4)

17.1.2.4. At the Conclusion of the Closeout Visit

- Provide the participant with their current eGFR value and stage of kidney disease
- Unblinding: neither the participant or site staff will know the participant's allocation of placebo or telmisartan at closeout.

Additional information may be found in section 17.1.4 - Unblinding of the participant.

17.1.2.5. Participants Who Miss the Closeout Visit

- Perform Quest visit/remote visit for final labs and closeout per usual.

17.1.2.6. After the Closeout Visit

17.1.2.6.1. BP Control Post Closeout Visit

If BP is >140/90 mm Hg, symptoms of hypertension (e.g., headache, blurred vision) or hypotension (e.g., lightheadedness, fatigue) develop, or if there are intolerable side−effects of the new post closeout medications, participants will be instructed to contact their study coordinator or PI in case an immediate visit to the PCC for management is needed.

Ideally patients will remain on the same step medications as they were taking during the study, but:

- If clonidine needs to be stopped, (step 9 onwards) it should be tapered off slowly over the course of several days to weeks, depending on the dose, due to the risk of rebound hypertension associated with its taper.
- If beta blocker (labetalol or metoprolol- step 6 onwards) needs to be discontinued it should be tapered over several days.

17.1.2.6.2. Transition of Participant Care to Local PCP/Nephrologist

In order to insure a safe and smooth transition from study back to PCP/nephrologist's care, a formal letter will be drafted with all pertinent information about the patient's participation in the clinical trial and mailed to the local physician/Medical Provider identified by the participant on study Form 2. This letter will include date of enrollment, potential medication side effects during the study, the current medication list, lab results and latest office blood pressure readings. The investigator will use his/her own discretion to determine the letter content and level of detail with regard to

the participant's history and physical.

Send Closeout letter to the participant's local PCP/Nephrologist

- Letter 5 (Study A)
- Letter 6 (Study B)

17.1.2.7. Management of Modified, Endpoint, Withdrawal or Lost to Follow Up Participants

- Send certified letter to notify the participant that the study has come to an end (Letter 7) Letter is to be sent to modified and endpoint participants by August 30, 2014
- Those participants that are lost to follow up, withdrawal or indicate "refuses follow up" on the Modification Form 28 will not be contacted or sent additional study information.
- Unblinding and provision of study results to these participants will be completed at the discretion of the study investigator.
- If sufficient study data is available on the participant and no penultimate questionnaire information has been completed to aid staff in the participant unblinding decisions, a 'participant blinded maintained' letter will be sent.

17.1.3. Phone Contact 8 Weeks After Closeout Visit

The follow up call is designed to assess post treatment status. Coordinators will contact the participant eight weeks after the last study visit to investigate any serious adverse events that may have taken place during the process of study drug tapering. Coordinators are encouraged to find out if the participant has been seen by their local PCP or nephrologist. Record adverse events (symptoms and SAEs) during closeout up to 8 weeks post closeout. SAEs listed as "ongoing" at the time of the eight week call will be monitored until resolved or until the October 2014 final data lock occurs.

This visit is managed similar to the 3-month, between PCC visit calls. End of study participation occurs after the 8 week call is completed and/or letters 5 or 6 are sent to the Local PCP.

17.1.3.1. Forms to be Completed at this Call Include:

Form 5 - Symptoms Checklist

- AEs will be documented on Form 5 in the same manner they were captured during study participation.

Form 6 - Concomitant Medication Form

Form 63 - Study Medication Form

- Documents on the date on which the last dose of study medication was taken
- Provides documentation that the study drug has been stopped

The following forms are to be completed if applicable:

Form 13 - Serious Adverse Events

- Determine if any SAEs have occurred within eight weeks of the last PCC visit.
- SAEs will be submitted until participant has completed his/her final call eight weeks after the closeout visit at the PCC.
- Participants having an "ongoing" SAE at the eight week contact will be monitored until the participant is either recovered or final data lock occurs (October 1, 2014).
- No new SAEs will be submitted after the eight week phone follow up.

Form 25 - Missed Visit Form

Form 30 - Hospitalization Form

Form 31 - Death Notification Form

- Request certificate of death within1 week of visit?

Form 51 - Required Safety lab Results Form

- Investigators are to use their own discretion with regard to ordering labs.
- All ordered labs should be data entered into the system

17.1.4. Unblinding of Participant and Notification of Study Results

The Principal Investigator will use his/her discretion and determine the level of information to be disseminated based on discussions with his/her local IRB. The investigator will identify which algorithm will be followed at their site and communicate these site specific management strategies to the DCC prior to June 1, 2013.

Those PCCs and local IRBs mandating the dissemination of study results and treatment allocation to the participant and his/her local physician will inform the participant of the intent to provide this information during the PCC visit. Form 131 will be utilized at these centers.

Those PCCs who opt to protect the right of the participant *not* to know their study treatment allocation, will ask their

participants if they would like to receive assignment information after the study results are released and complete Form 130. Participants may then choose to be unblinded or retain their blind to treatment allocation. The participant will also be provided the option to share their study information with their local physician or have that data remain confidential. The form 130 will be used at these centers and will allow complete flexibility on unblinding at the participant and local physician levels.

The Data Coordinating Center will create a file that sites can access via the web to generate letters with fields detailing each participant's date of enrollment and last study contact date, treatment allocation, current kidney disease staging and specific lab and radiology values. Each center will be responsible for creating the hard copy letter, obtaining site investigator signatures and sending it to the participant, as he/she has indicated on Form 130/131, either by private email or by via certified mail. For those participants permitting the dissemination of study information, letters to the participant's designated physician will be sent via standard US Postal system. Copies of all letters, including all email communications, should be maintained in the source document. It is recommended that receipts from certified mailing are also filed. Physicians of participants wishing their local physician to be informed of their treatment allocation will receive Notification of Study Results (PCP/nephrologist unblinding) Letter 9.

Participants indicating they do not want knowledge of their treatment assignment will be mailed a letter only containing the study findings of specific labs and radiology values (Notification of Study Results Letter #10). These letters will be generated in the same fashion as stated above and will be void of the treatment allocation information.
The local PCP/nephrologist caring for the participants that wish for the local PCP/nephrologist to remain blinded will receive a letter containing the participant's study findings with information. Notification of Study Results-(PCP/nephrologist of participant maintaining blind) Letter 11.

Information detailing the study outcomes will be summarized by the PKD Foundation in an effort to translate the scientific language into layman's terms. This summary will be included in the Notification of Study Results letters to participants and their local physicians.

17.2. PCC Personnel Closeout Responsibilities

The primary goal of the PCC study team centers on the safe transition of participant care back to the local PCP/nephrologist (designated Medical Provider). The secondary level of closure efforts involve the timely closure of research efforts within the study centers (research offices, clinics, pharmacies, radiology, laboratory areas) and the timely submission of all outstanding data to the DCC. Tertiary level closure efforts focus on the communication of clinical trial closeout to the local IRBs, providing all necessary closeout documentation to the study and pharmaceutical sponsors.

17.2.1. Principal Investigator and Co-Investigator

The primary goal of the Principal and Co-investigators is to work closely with the study team to keep patients' blood pressures under optimal control and communicate with patients' PCP/Nephrologist/Medical Provider (PA or CRNP) to insure that participants safely transition care during the closeout phase. It is the Principal Investigator's responsibility to assure study coordinator staffing during the closeout process to monitor the participant's study drug taper. It is imperative that adequate staffing levels are maintained throughout the closeout phase thereby assuring the DCC has a contact person available at the site to follow up with any final data queries and mailings.

17.2.1.1. Investigator Closeout Participant

1) Penultimate (next-to-last) Visit; R*efer to 17.1.1.1-17.1.1.3, Prior to Penultimate Visit*
2) Closeout visit-*refer to 17.1.2.2*
    a) Drug taper *refer to 17.1.2.3 Discontinuance of masked study drug*
3) Eight week phone follow up; *Refer to 17.1.3; Phone Contact 8 Weeks After Closeout Visit*
    a) AEs will be documented on Form #5 in the same manner they were captured during study participation.
    b) SAEs will be captured until the participant has completed his/her final call eight weeks after the closeout visit at the PCC.
        i. Participants documented as having an "ongoing" SAE at the eight week contact will be monitored until the participant is either "recovered" or final data lock occurs in October 2014.
        ii. No new SAEs will be submitted after the eight week phone follow up is completed as the centers will not be contacting the participants.
    c) Notification of study results
        i. Participant and PCP Notification of Study Results-letters are detailed in Chapter 17.1
        ii. With participant permission, the information regarding study drug allocation (telmisartan or placebo) will be included in the letters.
        iii. Recommended content of study letters is outlined in the Investigator Checklist. The document serves to guide the investigator's final dictation on the participant and is designed to promote consistency across all study sites with regard to letter content. It is up to the discretion of the

investigator to utilize the checklist.

17.2.1.2. Investigator Closeout of PCC Facilities

The PI responsibilities include the review and verification of documents that detail: closeout of the clinical trial activities within all PCC departments, final DCC site visit audit at closeout and the retention of all essential study documents.

- Research Offices
  - Subject Identification code list
    - Copy retained by PCC only
  - Final PI review of all PCC SAEs during the clinical trial

The DCC will provide each PCC with a cumulative list of SAEs reported through the 8 week follow up call. It is the responsibility of the PI to review the content of this list to ensure the completeness of the study database.

  - Assure the security and retention of source documentation
    - The study recommends retention of source documents for a period of at least three years after the first publication of study results or, for the time period in accordance with FDA guidance determined by the local IRB, whichever time period is the longest.
    - On site storage of source documents will be needed until transfer to long term storage is completed.
    - When it is determined that the hard copy of source documents is no longer needed, the documents must be destroyed in a manner that protects the participant's confidentially.
  - Insure proper and prompt data collection and data transfer to the DCC.
  - Collaborate with the DCC to resolve any pending inquiries from the DCC to maintain the integrity of the data and facilitate data analysis.
- Research Pharmacy
  - Study drug destruction will be completed in keeping with the institution's drug destruction protocol.
  - Assure authentication of drug destruction logs
  - Confirm no study drug remains on site at closure of the clinical trial.
- Clinic Area
  - Confirm removal of all HALT related documents or study related material from the research clinic setting.
- Research Labs
  - Insure proper and prompt transfer of the last biological specimen to the NIDDK bio-repository.
  - Confirm all lab samples have been shipped and resulted.
  - Confirm destruction of all back up samples.
- Radiology Department
  - Confirm all study images have been transferred to the Imaging Center and resulted.
- Closeout Site Visit
  - DCC closeout site visit audit report
  - Copy to be retained by the Investigator and the NIDDK

17.2.1.3. Investigator Regulatory Responsibilities at Closeout

Please refer to the detailed description of regulatory requirements please see regulatory section in chapter 17 of the MOP. The following list of documents will need to be submitted:

1) Local IRB
   a) The PI is to notify the local IRBs of the study termination and follow all local IRB reporting policies.
   b) Principal Investigators will adhere to local IRB reporting guidelines for the content of the final clinical study report.
   c) Suggested content of the final clinical study report for the local IRB may include the following information:
      i. Study title, name of drug, indication, sponsor & contact information, clinical trial number, phase, IND number, study start date, study end date, principal investigators and sites, DSMB monitoring team, report date, publications, objectives, methodology, number of subjects, diagnosis and main inclusion criteria, duration of treatment, study drug, criteria for evaluation, statistical methods, summary results, efficacy results, safety results, complete listing of PCC SAEs, outcome measure results, conclusion.

2) NIH/NIDDK
   a) Report of Grant Closeout CFR Title 21 document due 90 days after the expiration or termination of the grant and includes:
      i. Final federal financial report
      ii. Final progress report
   b) IND 1572—The Principal Investigator is responsible for generating a letter to the DCC confirming that all remaining excess study drug has been destroyed per FDA guidelines.
      i. Target date for all letters to be received by the DCC is August 31, 2014.
      ii. Study drug destruction will be completed in keeping with the institution's drug destruction protocol.
      iii. Documentation of investigational product destruction
         * PI approves the final accounting of investigational products received at the site, dispensed to participants and those returned to the PCC by participants.
         * Proof of destruction of unused products; the DCC will provide drug destruction, templates to document date of destruction, quantity, and dosage for any telmisartan/placebo drug card and open label drug that has to be destroyed. PCC staff completing drug destruction will sign the form.
         * Copy to be retained by the Investigator/Institution and sponsor.
   c) Certificate of Confidentiality
      iv. Expires on date the IND is terminated
   d) Documentation that closeout audit has occurred
      v. DCC letter documenting completion of audit
      vi. Copy to be retained by the Investigator/Institution and sponsor

17.2.2. Study Coordinator Closeout Responsibilities

The primary level of the site coordinator closeout responsibility is to collaborate with the site PI and Co-I to conduct the participant closeout as outlined in chapter 17.1. Secondary level responsibilities include the monitoring of all data entry to assure the timely completion of forms as outlined in the protocol. This is especially crucial after the eight week follow up phone contact which signals the official participant closeout of study participation.

17.2.2.1. Study Coordinator Closeout of Participant

1) Penultimate Visit
   a) Penultimate (next-to-last) Visit; *Refer to 17.1.1.1-17.1.1.3, Penultimate Visit*
2) For those participants receiving study drug please refer to 10.3.1.1 Drug card validation prior to dispensing study drug.
3) For each penultimate visit, the coordinator will assure all forms are data entered within two weeks, in keeping with window outlined in the protocol.
4) Coordinators will monitor any necessary rescheduling of participants that miss the penultimate visit and will aggressively pursue and identify new visit dates and reschedule.
5) Form 2-Contact Information Form
   a) This is a compulsory form for all participants to complete. *See Notification of Study Results in section 17.2.2.1. for more information.*
6) Form 130 or Form 131
   a) The DCC will program either Form #130 or Form #131 for each PCC based on the Principal Investigator and local IRB determination of what information will be disseminated to participants and their local provider.
   a) Form 130 - Participant Next to Last Visit Questionnaire options. This form has been developed to gather important information from participants pertaining to their transition of care to the PCP/nephrologist. The Form #130 also determines the data that will be provided to the PCC for inclusion in Notification of Study Results letters 8-11.
      i. This is a compulsory form. The coordinators will complete this form during their discussion with the participant during the penultimate visit.
      ii. This form permits the participant to choose what study information is received and disseminated to providers including study results and treatment allocation.
      iii. This form will be data entered, along with all other study visit forms, into the web based system.

iv. PCCs that do not comply with submission of the Form 130 will not have access to the DCC computer generated letter templates.

v. The Form 130 has an area for the participant's name and signature. These are required fields for completion. In order to maintain confidentiality, this web based form will be programmed so that this identifiable information *is not* entered.

vi. If for some reason the participant does not complete the Form 130 at the penultimate visit, the form must be completed at the closeout visit. *See Notification of Study Results in section 17.2.2.1 for more information.*

vii. Those participants who are modified or have met endpoint may complete Form 130 with coordinators during the follow up contact and may receive the notification of study result letters. The investigator should access the participant's level of study participation and use his/her discretion with regard to what participants receive the letters. (ex: a participant that modifies at F12 with limited study involvement may not have sufficient data to warrant a notification of study results letter to be generated)

viii. Participants that have refused all follow up, withdrawn participation or are lost to follow up will not receive any study communication beyond their documented withdrawal or lost to follow up.

7) Form 131 – Participant Next to Last Visit Questionnaire mandated notice

a) This is a compulsory form. Coordinators will complete this form during their discussion with the participant during the Penultimate visit.

b) This form informs the participant that the Investigator will be disseminating their study results and treatment allocation to the participant and his/her providers at the completion of the study.

c) This form will be data entered, along with all other study visit forms, into the web based system.

d) PCCs that do not comply with submission of the Form131 will not have access to the DCC computer generated letter templates.

e) Form 131 has an area for the participant's name and signature. These are required fields for completion. In order to maintain confidentiality, this web based form will be programmed so that this identifiable information *is not* entered.

f) If for some reason the participant does not complete the Form 131 at the penultimate visit, the form must be completed at the closeout visit. *See Notification of Study Results in section 17.2.2.1. for more information.*

g) Those participants who are modified or have met endpoint may complete FORM 131 with coordinators during follow up contact and may receive the Notification of Study results letters. The Investigator should assess the participant's level of study participation and use his discretion with regard to what participants receive the letters. (Ex: a participant that modifies at F12 with limited study involvement may not have sufficient data to warrant a Notification of Study Results letter to be generated.)

h) Participants that have refused all follow-up, withdrawn participation or are lost to follow up will not receive any further study communication beyond their documented withdrawal or lost to follow up date.

8) Closeout Visit

a) Closeout visit-*refer to 17.1.2.2*

b) Drug taper *refer to 17.1.2.3, Discontinuance of Masked Study Drug*

i. Study coordinators will work closely with the PCC investigators to taper participants off of study drug in keeping with documented protocol.

ii. It is essential that accurate documentation of all medication changes and participant reported blood pressure response is clearly recorded in the source document.

iii. Drug card validation, *refer to 10.3.1.1., Drug Card Validation Prior to Dispensing Study Drug*

c) For each closeout visit, the coordinator will assure all forms are data entered within two weeks, in keeping with window outlined in the protocol.

i. Coordinators should verify Form 2 and Form 130 were completed at the penultimate visit.

ii. Review the content with the participant to assure no changes have occurred.

d) Coordinators are encouraged to schedule participants in the early segment of their visit window. This is particularly important for those participants attending closeout visits:

i. in April - June 2014

ii. Requiring an F60 MRI.

Early completion will permit the rescheduling of MRIs in the event a redo session is needed.

9) Eight Week Follow up Contact
    a. Refer to MOP Chapter 17.1.3 - Phone contact 8 weeks after Closeout visit
    b. For each eight week telephone contact, the coordinator will assure all forms are data entered within two weeks, as per protocol.
    c. Verification of current contact information should be completed during the call.
    d. Timely data entry is especially important for those calls being completed in between April 2014 and August 2014 in preparation for targeted data lock dates.
    e. SAEs will continue to be collected and submitted until the participant reaches the eight week follow up time point. At that time, he/she will have officially ended study participation.
    f. SAEs listed as "ongoing" at the time of the eight week call will be monitored with data entry being completed until the SAE is resolved or until the October 2014 final data lock occurs.
10) Notification of Study Results
    a. See 17.1.4 - Unblinding of the Participant and Notification of Study Results
    b. The HALT PKD web based program will utilize the information entered on Form 130 and 131 (Participant Next to the Last Visit Questionnaire) to guide the content letters 8-11.
    c. When study results are published and the Notification of Study Results letters 8-11 need to be generated, the PCC staff will access the DCC web based system, download the participant's study information into the appropriate MS Word letter template. Staff will use the most recent contact information provided by the participant on Form 2 to address the letter and mailing labels.
    d. Fields detailing each participant's date of enrollment and last study contact date, current kidney disease staging and specific lab and radiology values will populate the template. Subject treatment allocation will be provided based on Forms 130 and 131.

17.2.2.2. PCC Facility Closeout

The Study Coordinator's primary responsibility is the closeout of research activities throughout the study center under the guidance of the Principal Investigator.

1) Research Offices
    a) Source Documents
        i. The study recommends retention of source documents for a period of at least three years after the first publication of study results or, for the time period determined by the local IRB that is in accordance with FDA guidance, whichever time is the longest.
        ii. Develop plan for onsite storage until long term storage can be identified
        iii. The storage of documents should be consistent across all sites, the following file system is recommended:
            * Source documents are removed from their hard cover binders and secured with two ring-style binder clamps.
            * One ring clamp will be placed through the existing hole-punch at the top and the other at the base.
            * Two rubber bands will be placed around the source document to prevent destruction of source document pages
            * To decrease the burden of finding a specific set of documents, identifier tags should be attached to the top ring clip to indicate the source document ID and number of ringed components (i.e. 1 of 4, 2 of 4, 3 of 4 etc.)
        iv. Once this is completed, the documents will be placed in standard medical record boxes used by long term storage companies. If possible, all SUB ID's with multiple source documents (i.e. 1 of 4, 2 of 4, 3 of 4 etc.) should then be housed in the same container.
        v. Storage containers should have the SUB ID numbers of all documents within the box clearly documented on the outside panel.
        vi. It is suggested that PCCs retaining all source documents onsite until the release of study results to assure all queries are completed. It is recommended they remain on site in storage for three years post study.

3) Research Pharmacy
    a) Study drug destruction will be completed in keeping with the institution's drug destruction protocol.
    b) Study coordinators are responsible for assuring the study destruction logs are maintained and accurately reflect drug card disposal.
    c) All study drug destruction logs are to be scanned and emailed to the DCC. Faxed copies will be accepted. Each page of the log must be signed by the individual responsible for study drug destruction.
    d) No study drug is to remain on site at the completion of the clinical trial. Coordinators will have until August 31, 2014 to confirm that all study drug has been properly disposed of.
    e) All drug destruction logs will be submitted to the DCC by August 31, 2014.
4) Clinic Area
    a) Study coordinators are responsible for the removal of all HALT-PKD materials and participant related materials from the PCC clinic setting.
    b) Special care should be taken to assure that copies of the HALK-PKD study protocol and MOP are removed and either stored with source documents or disposed of in accordance to local research policy.
5) Research labs
    a) Study coordinators will contact the DCC and confirm that all remaining blood, urine and genetic samples have been received or resulted by the appropriate labs (CCF and NIDDK repositories).
    b) Once that the DCC has confirmed the sample results or receipt of genetic sample, the coordinator may direct research labs to discard/destroy all remaining back up samples of blood and urine.
6) Radiology Department
    a) It is recommended that participant MRI images remain within the medical record at the PCC in the event they are needed for continuing medical care. Sites will follow local IRB guidance on the management of imaging at closeout.
    b) Coordinators will contact the DCC and confirm that all MRI FORMS 21 and 22 have been submitted for all remaining images completed during closeout visits and that the transfer of all images have been successfully sent and received by the Data Imaging Center within the University of Pittsburgh.

17.2.3. PCC Support Staff

17.2.3.1. Regulatory Manager

The Regulatory Manager's primary role is to collaborate with the Principal Investigator to assure all local regulatory documents are submitted per local IRB guidelines within the required time frame.

17.3. PCC Facilities Closeout

17.4. Repositories at Closeout

17.5. HALT Subcommittees

17.6. DCC Closeout

Chapter 18. Appendices

Chapter 18.1. Bibliography

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18.2. HALT PKD Directory

1. National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)
    - □ Michael Flessner MD
    - □ Robert A. Star, MD
2. University of Pittsburgh
    - □ Data Coordinating Center (DCC)
        - ◊ Charity G. Moore, Ph.D., MSPH (Principal Investigator)
        - ◊ Kaleab Abebe, Ph.D. Co-Investigator
        - ◊ Patty Smith
        - ◊ Susan Spillane, RN
    - □ Imaging Analysis Center
        - ◊ Ty Bae, MD
        - ◊ Samuel Chang
        - ◊ Cheng Hong
        - ◊ Cheng Tao
3. Beth Israel Deaconess Medical Center [ww.bidmc.edu]
    - □ *Theodore Steinman, MD (Principal Investigator)*
    - □ Peter Czarnecki, MD
    - □ Alice Lee
    - □ Bonnie (Barbara) Maxwell, RN
    - □ Jesse L. Wei, MD
4. Cleveland Clinic Foundation [www.ccf.org]
    - □ *William Braun, MD (Principal Investigator)*
    - □ Martha Coleman
    - □ Cathy Jackman
    - □ Saul Nurko MD
    - □ Erick Remer, MD (Radiologist)
5. Emory University Medical Center [www.emoryhealthcare.org]
    - □ *Arlene Chapman, MD (Principal Investigator)*
    - □ Sabira Bacchus
    - □ Regina Bugrovsky
    - □ Frederic F. Rahbari−Oskoui, MD
    - □ Diane Watkins
6. Kansas University Medical Center [www.kumc.edu]
    - □ *Franz Winklhofer, MD (Principal Investigator)*
    - □ Jared Grantham, MD
    - □ Sheri Copeland
    - □ Beth Courtney
    - □ Cathy Creed
    - □ Louis Wetzel, MD (Radiologist)
7. Mayo Clinic [www.mayo.edu]
    - □ Vicente Torres, MD (Principal Investigator)
    - □ Mohamud Abdulahi
    - □ Kristin Cornwall, RN
    - □ James Glockner, MD, PhD (Radiologist)
    - □ Peter C. Harris, PhD
    - □ Marie Hogan, MD
    - □ Bernard King, MD, R−D (Radiologist)
    - □ Vickie Kubly
    - □ Troy Ofstie, RN
    - □ Kris Otto, RNC

- □ Heather Ondler
- □ Debra Smith

8. Tufts−New England Medical Center [www.tuftsmedicalcenter.org]
   - □ *Ronald Perrone, MD (Principal Investigator)*
   - □ Julie Pollick Driggs, BSN, RN
   - □ Neil Halin, MD (Radiologist)
   - □ Dana Miskulin, MD
   - □ Peachy Simon, BSN, RN, CNN
   - □ Veronika Testa
9. University of Colorado Health Sciences Center [www.ucdenver.edu]
   - □ *Robert Schrier, MD (Principal Investigator)*
   - □ Godela Brosnahan, MD
   - □ Michel Chonchol, MD
   - □ Elwaleed Elhassan, MD
   - □ Maria Fishman, BS
   - □ Diana George
   - □ Pamela Morgan, RN
   - □ Nayana Patel, MD (Radiologist)
10. HALT PKD Study Coordinators

18.3. Study−Start Checklists

Study coordinators may find these checklists helpful in preparing to begin the study. Note the two checklists must be completed and received by the DCC prior to starting recruitment.

- o Regulatory Checklist
- o Site Readiness Checklist
- o Certification and Clinical Performance
- o Pre−Screening Policy
- o Study Drug Information

18.4. Data Collection Forms

- □ Forms Dictionary
- □ Forms per Visit Table
- □ Time Frames for Forms Data Entry

Table 18−1. List of HALT PKD Data Collection Forms

Form	Form Name
1	Monthly Pre−Screening Activity Report Form
2	Contact Information Form (Optional)
3	Registration Form
4	Clinical History Form
5	Symptoms Checklist*
6	Concomitant Medications Form
7	Physical Findings−Screening Form
8	Background Questionnaire Form
9	Required Lab Results Form
10	Enrollment Form
12	Home BP Form*
13	Serious Adverse Event Form*
14	Screen Failure Form
15	Current Physical Findings Form
16	Urine Sample Collection Form

17	Genetic Sample Collection Form
18	Archived Blood Sample Collection Form
19	Central Serum Creatinine Form
20	Randomization Form
21	MRI Session (Renal) Information Form
22	Renal Blood Flow (MRA) Form
25	Missed Visit Form
26	Unmasking Drug Form
27	Transfer Form
28	Modified Participation Form
29	Major Protocol Violation Form
30	Hospitalization Form
31	Death Notification Form
32	End−Stage Renal Disease Form
33	eGFR Reduction Form
34	BP Monitor Calibration Log (PCC)
36	Home BP Calibration Log
37	24−Hour Urine Checklist
38	Quality of Life Questionnaire
39	Pain Questionnaire
40	PCC Visit Tracking Form
50	Hormonal Birth Control Worksheet
51	Required Safety Lab Results Form
55	Home BP Log (Deleted − Use Form 12)
56	Therapy Confirmation Form
62	Drug Card Assignment Form*
63	Study Medication Form*
65	Washout Home BP Log (Deleted − Use Form 12)
81	Shipping Manifest: Central Lab − CCF
82	Shipping Manifest: Central Lab − DLF
83	Shipping Manifest: Repository − Genetic Samples
84	Shipping Manifest: Repository − Serum/Plasma Samples
85	Shipping Manifest: Repository − Urine Samples
86	Relatedness Form
91	Pre−Screening Interview Worksheet (Optional)
92	Pre−Screening Log (Optional)
93	For Your Next Study Visit (Optional)
94	Per Visit Checklist (Computer−Generated)
95A	Home BP by Phone (Optional) (Deleted − Use Form 12)
95B	Home BP Report (Optional) (Deleted − Use Form 12)
95C	Home BP Frequency (optional) (Deleted − Use Form 12)
95D	Home BP Diary (Optional) (Deleted − Use Form 12)
96	Modified Participation Checklist (Optional)

- *Symptoms Checklist Instructions (Form 5)
- *Home BP Form Instructions (Form12)
- *SAE Form Instructions (Form 13)
- *Drug Card Assignment (Form 62)
- *Study Medication Form Instructions (Form 63)

18.5. Model Consent/Assent Forms

The DCC has developed model consent and model assent forms for each PCC to refer to in developing their own site−specific consents. Minors will not be enrolled in HALT PKD Study B, so the model assent forms apply to Study A only.

18.5.1. Model Consents (Studies A and B)

- Screening and Drug
- Washout Baseline and
- Beyond Genetic

18.5.2. Model Assents (Study A)

- Study A − Screening and Drug Washout
- Study A − Baseline and Beyond
- Study A – Genetic

A Site Consent Checklist has been developed to assist each site in making sure that site−specific consent forms include all of the required information.

History of Revisions to Model Consent/Assent Forms

18.6. Study Cheat Sheets

Table 18−2. List of HALT PKD Cheat Sheets

Cheat Sheet	Corresponding MOP Section(s)
Acceptable Visit Ranges and Missed Visits	8.16
Boric Acid Double Recipe	11.5.4.3 / 11.6.3.2.2
Cell Locations	11.6.3.5
Fisher − Blood Samples	11.6.2
Flow of Events PS−B2	8.1.3
GFR Table	8.2.3.1
Guidelines for PCC Visits	8.1.2
Imaging Procedures	12.2.6
Increase/Decrease Table (Dose modification guidelines)	10.2, 10.3.6.1
Informing Participants of Safety Concerns	8.1.4 / 11.1.8 / 13.4
Labels for Sample Collection	11.1.4
List of Central Lab and Repository Requirements	11.4 / 11.5 / 11.6
Missed and Out−of−Range Visits During Titration	8.16
Modified Participation Checklist (Optional Form 96)	5.5 / 8.18 / 18.2
Modified Participation Definition	8.18
Modified Follow−Up Due	8.18
NIDDK Phlebotomy Collection Form	11.6.1.2
PCC Checklist − Regulatory	3.15
PCC Checklist − Site Readiness	3.15
Pregnancy	14.2.2
Quest Fax Authorization (PI)	11.3.1.3
Regulatory Tracking	5.6

Required Tests Per Visit	Table 7−1 / Table 7−2
RUCDR Web Portal Instructions	11.6.1.2
SAE Definition/Reporting Guidelines	13.8
Safety Labs and Dose Increments	8.12.2.1
Sample Label Key	11.1.4
Sample Overview	11.1
Sidedoor Installation Instructions	3.14.6
Standardized Record Keeping	16.3.5.2.1
Strategies for Full Participation	4.7
Study Supplies Checklist	11.6.3.3
Study Visits Defined	8.1.1
Suggested Dosing Guidelines (Color)	10.2, 10.3.6.1
Suggested Dosing Guidelines (B/W)	
Table 5A − Assessments − PS−F5	7.1.3.1
Table 5B − Assessments − Following F5 Visit	7.1.3.1
Tables 6A and 6B − Stepped Protocols for Addition of Antihypertensive Agents	10.2.1, 10.2.2
Table 7 − Blood Pressure Control over the Course of the Study	9.2.2
Table 10 − Management of Adverse Effects of Medications	10.5
Tables 11−12 − Serious Adverse Events	13.8
Table 13 − Follow−Up After Primary Endpoints, Early Withdrawal or Modified Participation	14.2.1
Troubleshooting WDES	16.2

18.7. Training Aids

- Blood Pressure Training Manual

18.8. Recruitment Materials

- ◊ Catchment Map
- ◊ HALT PKD Study Brochure (Revised 2007)
- ◊ Information for Physicians Brochure
- ◊ HALT PKD Talking Points
- ◊ Letter to Physicians Informing them of HALT PKD
- ◊ Letter to Physicians Informing them of Patient's Enrollment
- ◊ Letter to Physicians Informing them of Patient's Enrollment (short version)

Notes

[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 SAEs 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.

[6] A "study procedure" is any test or procedure required for the study (e.g., MR for study A).

[7] 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.

[8] The "end of the study" is defined as the "stopping date" or "x date," and not the "end of data close−out."

[9] Data analysis will separate out any SAEs occurring before the start of study medication from those occurring after.

[10] For the HALT PKD study, all SAEs 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.

[11] 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.

[12] A "study procedure" is any test or procedure required for the study (e.g., MR for study A).

Chapter 19. Amendments

19.1. Study A – Examples of a Consent to Act as a Participant in a Research Study

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: HALT PKD (Halt Progression of Polycystic Kidney Disease): Efficacy of Renin-Angiotensive-Aldosterone Axis Blockade in Preventing/Slowing Renal Function Decline in ADPKD-Study B

PRINCIPAL INVESTIGATOR: _____
CO-INVESTIGATORS: _____

NEW INFORMATION:

You are currently a participant in the HALT PKD Study A protocol. The purpose of Study A is to find out the percent change in total kidney volume as assessed by MR at baseline, 24 and 48 months follow-up.

You are approaching your last designated follow up visit (Visit 48) for the study. This visit would conclude your participation in the HALT–PKD study. However, because of potentially valuable additional information that could still be obtained with a longer period of observation, if you agree, we are requesting that you to continue in the study until September of 2010 while continuing study medications in a blinded fashion. At that time, the NIH will review the data collected to date and make a decision as to whether or not it is important to allow a further extension of your participation until the entire study is completed in January of 2013. We would like you to continue in the study, until its total completion. You would continue to receive the same medications and treatment you presently receive. In addition, you would have an MRI at the 60 month follow up visit.

RIGHT TO WITHDRAW

You understand you can withdraw from this research study at any time. Your other care and benefits will be the same whether you participate in this research study or not.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my questions have been answered. I understand that, if not already done, I may request that my questions be answered by a physician involved in the research study. I also understand that any future questions I have about this research will be answered by the investigator(s) listed on the first page of this addendum to the consent document at the telephone number(s) listed. Any questions I have about my rights as a research subject will be answered by the Human Subject Protection Advocate of the IRB Office,_____.

By signing this form, I agree to the following participation:

_____Yes, I agree to continue in the study after my visit at 48 months and until the interim analysis has been completed.

_____Yes, I agree to continue in the study until its official end date of January 2013.

_____ _____
Patient/Subject Signature Date

INVESTIGATOR'S CERTIFICATION

I certify that I have explained this new information and its significance to the above individual and that any questions about this information have been answered.

_____ _____
Investigator's Signature Date

19.2. Study B – Consent for a Participant in a Research Study

(Department or School Letterhead)

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: HALT PKD (Halt Progression of Polycystic Kidney Disease): Efficacy of Renin-Angiotensive- Aldosterone Axis Blockade in Preventing/Slowing Renal Function Decline in ADPKD-Study B

PRINCIPAL INVESTIGATOR: _____

CO-INVESTIGATORS: _____

NEW INFORMATION:

You are currently a participant in the HALT PKD Study B protocol. The purpose of Study B is to find out: 1) the rate at which kidney function declines; and 2) if the study drugs lengthen the life expectancy for those with advanced polycystic kidney disease (PKD). You have met an endpoint of Study B because your kidney function (GFR) has had a 50% drop since your baseline visit , you have started dialysis or receiving a transplant. Therefore you are no longer required to participate in follow up visits or procedures. You will no longer receive study medications. However, we would like to continue to communicate with you annually to determine whether you have started dialysis or have received a kidney transplant and if not, to obtain your most recent serum creatinine. With your permission we will obtain an annual serum creatinine from your primary care physician or nephrologist.

The study medications you were taking must now be stopped. Dr._____will supervise the transition from the drugs that we were supplying over the next 1-2 months to assure that your blood pressure remains adequately controlled. It is important that the study medications are stopped under close supervision because there is the possibility that your blood pressure could become elevated. You are advised to make an appointment with your physician for continued follow up within 30 days of the medication transition and being notified that you have met a study endpoint. Dr._____has sent a letter to your physician updating him/her on your current status in the study and a copy of this letter will be sent to you.

The risk associated with collecting this information is the possibility of your private medical record being viewed by others who are not part of the research team. To prevent this, your information was given a special identification code. A master list linking the code number and your identity is being kept separate from the research data. The master list is kept in a locked file and only the principal investigator and designated members of the research team will have access to the master list. Every effort will be made to protect the confidentiality of your research data. There is, however, always the possibility of a breach of confidentiality. Your participation in this study, if it became known outside the research, could be damaging to your future financial standing, health care, employment, or employability.

RIGHT TO WITHDRAW

You understand you can withdraw from this research study at any time. Your other care and benefits will be the same whether you participate in this research study or not.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my questions have been answered. I understand that, if not already done, I may request that my questions be answered by a physician involved in the research study. I also understand that any future questions I have about this research will be answered by the investigator(s) listed on the first page of this addendum to the consent document at the telephone number(s) listed. Any questions I have about my rights as a research subject will be answered by the Human Subject Protection Advocate of the IRB

Office,_____. By signing this form, I agree to continue to participate in this research study.

_____ _____

Patient/Subject Signature Date

INVESTIGATOR'S CERTIFICATION

I certify that I have explained this new information and its significance to the above individual and that any questions about this information have been answered.

_____ _____

Investigator's Signature Date

19.3. Study B – Waver of Consent (Verbal Script)

Introduction: Hello (participant's name) this is (coordinator's name/MD name) from (PCC center). I'm calling to provide you with some new information about your participation in the HALT PKD Study.
As you are aware, you are enrolled in Study B. The purpose of Study B is to find out: 1) the rate at which your kidney function declines; and 2) if the study drugs lengthen your life expectancy because of your advanced polycystic kidney disease.

I'm calling because you have met an endpoint of Study B. (Select one of the options: A. your kidney function has had a 50% drop since your baseline visit, B. you have started dialysis, C. you are receiving a transplant.) Therefore, you are no longer required to participate in follow up visits or procedures. You will no longer receive study medications.
The study medications you were taking must now be stopped. Dr._____will supervise the transition from the drugs that we were supplying over the next 1-2 months to assure that your blood pressure remains adequately controlled. It is important that the study medications are stopped under close supervision because there is the possibility that your blood pressure could become elevated.

You are advised to make an appointment with your physician for continued follow up within 30 days of the medication transition and being notified that you have met a study endpoint. Dr._____has sent a letter to your physician informing him/her of your current status in the study. A copy of this letter will be sent to you.

We would like to continue to communicate with you annually to determine whether you have started dialysis or have received a kidney transplant, and if not, to obtain your most recent serum creatinine. With your permission we will obtain an annual serum creatinine from your primary care physician or nephrologist.

I wanted to mention the risk associated with collecting this information. There is the possibility of your private medical record being viewed by others who are not part of the research team. To prevent this, we will continue to use a special identification code (your HALT Study ID number) to store this information. A master list linking the code number and your identity is being kept separate from the research data. The master list is kept in a locked file and only the principal investigator (Dr.___) and designated members of the research team will have access to the master list.

Every effort will be made to protect the confidentiality of your research data. There is however, always the possibility of a breach of confidentiality. Your continued participation in this study, if it became known outside the research, could be damaging to your future financial standing, health care, employment, or employability. Remember, you can withdraw from the study at any time. Your medical care and benefits will be the same whether you continue to participate in the study or not.

Do I have your permission to contact you every year to find out how you are doing?	**YES**	**NO**
May we also contact your PCP or nephrologist for your latest serum creatinine results?	**YES**	**NO**

Research Staff:

All of the above was explained to_____and all of his/her questions have been answered. It was explained that he/she could speak to a physician directly involved in the study if so desired now or if any future questions arise. Dr._____ contact information was provided.

I certify that I have explained this new information and its significance to the above individual and that any questions about this information have been answered.

_____ _____
Research Representative Date

19.4. Form 130 - Participant Next to Last Visit Questionnaire

Attention - DO NOT enter patient data on this form if the header does not contain *preprinted* HALT PKD ID number, clinical center ID, and visit number.

Participant ID: _____ *haltid* **Clinical Center:** _____ *clinic* **Date of Report:** ___/___/___
month *dvm* day *dvd* year *dvy*

visit: ___**Form was not completed** *misfm*

PARTICIPANT NEXT TO LAST VISIT QUESTIONNAIRE_options **Form # 130**

Dear Participant,

During your visit today, we ask that you provide us with the answers to the questions below. This information will assist the HALT-PKD team to safely transition your clinical care back to your local physician when the study ends. Your study coordinator will assist you to complete this questionnaire.

1) During today's visit, did you complete the HALT-PKD study FORM #2- "Contact Information Form"? *form2*	1 ☐ Yes	0 ☐ No	
2) Do you have a PCP or nephrologist identified for the HALT-PKD team to transition your care to in six months? *pcpneph*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
2a) If no or unsure, do you have access to an alternative care center or clinic? Please provide that contact information to your coordinator. *clinic*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
3) When the study comes to an end, will you have established insurance, Medicaid or Medicare coverage? *insrnce*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
3a) If no or unsure, do you plan to apply for Medicaid or Medicare coverage? If so, please start the application process within the next two weeks. *applycovrg*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
4) Once the study results are released, your HALT PKD investigator, depending on your response below, will send you, and the physician you identified on Form #2, a letter containing your basic study information gathered over the course of the study. This letter will provide your lab results (kidney function-eGFR), radiology results (total kidney volume on MRI-Study A only), current stage of kidney disease, blood pressure measurement and your study treatment assignment (either telmisartan or placebo).	1 ☐ participant notified of planned release of study information. *ptnotified*		
4a) Do you want to receive your study results information? *receive*	1 ☐ Yes	0 ☐ No	
4b) Do you give the HALT PKD study permission to share your study results with your local physician(s)? *permitshare*	1 ☐ Yes	0 ☐ No	3 ☐ N/A (no provider identified)
5) Do you want to be told what study arm (telmisartan or placebo) you were assigned to during your participation? *studyarm*	1 ☐ Yes	0 ☐ No	
5a) Do you give the HALT PKD study permission to share your treatment allocation (telmisartan or placebo) with your local physician? *sharetrtmnt*	1 ☐ Yes	0 ☐ No	
6) Please identify the physician or designated provider that is to receive the final study letter. *provider* **Please contact the study staff if you change your local physician and provide updated contact information.	1 ☐ PCP/PA/CRNP (Form #2 item 10) ***OR*** 2 ☐ Nephrologist (Form #2 item 11) 3 ☐ N/A (declined release of results)		
7) How would you like us to send the final study letter to you? *mail* **Please contact the study staff if you relocate and provide updated contact information.	1 ☐ email account *identify primary email account on Form 2 only* 2 ☐ certified mail 3 ☐ N/A (declined release of results)		

HALT PKD, Participant Next to Last Visit Questionnaire, Form 130
Version 1, 2/1/2013

Page 1 of 2

Attention - DO NOT enter patient data on this form if the header does not contain *preprinted* HALT PKD ID number, clinical center ID, and visit number.

Participant ID: _____ *haltid* **Clinical Center:** _____ *clinic* **Date of Report:** ___/___/_____
month *dvm* day *dvd* year *dvy*

visit: ___**Form was not completed** *misfm*

PARTICIPANT NEXT TO LAST VISIT QUESTIONNAIRE_options Form # 130

COMMENTS: *cmmnt*

_____

_____

_____

_____

****PARTICIPANT NAME:** _____

****PARTICIPANT SIGNATURE:** _____

*****These form fields are excluded from entry into the HALT-PKD database to protect confidentiality.***

COORDINATOR NAME: _____

****

HALT PKD staff member completing this form: _____ **Date:** __ __/__ __/__ __ __ __
cmidnum Month *cdm* Day *cdd* Year *cdy*

Data Entry Status: Please check to indicate that the above information has been entered ☐

Primary Entered by: _____ Date: __ __/__ __/__ __ __ __
deidnum *dem* Month *ded* Day *dey* Year

19.5. Form 131 - Participant Next to Last Visit Questionnaire

Attention - DO NOT enter patient data on this form if the header does not contain *preprinted* HALT PKD ID number, clinical center ID, and visit number.

Participant ID: _____ *haltid* **Clinical Center:** _____ *clinic* **Date of Report:** ___/___/_____
month *dvm* day *dvd* year *dvy*

visit:

___Form was not completed *misfm*

PARTICIPANT NEXT TO LAST VISIT QUESTIONNAIRE_mandated notice Form # 131

Dear Participant,

During your visit today, we ask that you provide us with the answers to the questions below. This information will assist the HALT-PKD team to safely transition your clinical care back to your local physician when the study ends. Your study coordinator will assist you to complete this questionnaire.

1) During today's visit, did you complete the HALT-PKD study FORM #2- "Contact Information Form"? *form2*	1 ☐ Yes	0 ☐ No	
2) Do you have a PCP or nephrologist identified for the HALT-PKD team to transition your care to in six months? *pcpneph*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
2a) If no or unsure, do you have access to an alternative care center or clinic? Please provide that contact information to your coordinator. *clinic*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
3) When the study comes to an end, will you have established insurance, Medicaid or Medicare coverage? *insrnce*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
3a) If no or unsure, do you plan to apply for Medicaid or Medicare coverage? If so, please start the application process within the next two weeks. *applycovrg*	1 ☐ Yes	0 ☐ No	3 ☐ Unsure
4) Once the study results are released, your HALT PKD investigator will send you, and the physician you identified on Form #2, a letter containing your study information gathered over the course of the study. This letter will provide your lab results (kidney function-eGFR), radiology results (total kidney volume on MRI-Study A only), current stage of kidney disease, blood pressure measurement and your study treatment assignment (either telmisartan or placebo).	1 ☐ participant notified of planned release of study information. *ptnotified*		
5) Please identify the physician or designated provider that is to receive the final study letter. *provider* **Please contact the study staff if you change your local physician and provide updated contact information.	1 ☐ PCP/PA/CRNP (Form #2 item 10) *OR* 2 ☐ Nephrologist (Form #2 item 11)		
6) How would you like us to send the final study letter to you? *mail* **Please contact the study staff if you relocate and provide updated contact information.	1 ☐ email account *identify primary email account on Form 2 only* 2 ☐ certified mail		

COMMENTS: *cmmnt*

_____

_____

_____

**PARTICIPANT NAME: _____

**PARTICIPANT SIGNATURE: _____

***These form fields are excluded from entry into the HALT-PKD database to protect confidentiality.*

COORDINATOR NAME: _____

****

HALT PKD staff member completing this form: _____ *cmidnum* Date: __ __/__ __/__ __ __ __
Month *cdm* Day *cdd* Year *cdy*

Data Entry Status: Please check to indicate that the above information has been entered ☐

Primary Entered by: _____ *deidnum* Date: __ __/__ __/__ __ __
dem Month *ded* Day *dey* Year

HALT PKD, Participant Next to Last Visit Questionnaire, Form 131
Version 1, 2/1/2013

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19.6. Closeout Letters

19.6.1. Missed Penultimate Visit - Letter 1

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: LETTER #1 the MISSED next to last visit_participant

DATE:

Dear (Participant's Name),

The HALT-PKD clinical trial is approaching the final stages of the study. During the remaining visits, your physician will collect very important clinical information, adjust your medications and begin to transition your care to your local physician. Everything that you have contributed to HALT PKD over the past several years comes to fruition during these visits. The information and lab samples that you share with us provides key information that may influence the study outcomes. We are hopeful that the HALT PKD study results will be beneficial for millions of PKD patients worldwide. We sincerely value your continued participation, it is vital to the success of this important research.

Recently, the HALT-PKD team scheduled you for a visit on: _____.

Based on our records the visit was not completed. This is a very important study visit that is time sensitive to complete. We would like to resechedule the visit as soon as possible.

Please contact: _____*(staff member)*_____ at _____*(phone contact number)*__

Our goal is to complete this visit before: _____

During this visit, the HALT-PKD team will discuss the management of study medications and plans to transition your care to your local physician. It is very important that you provide the HALT-PKD team with contact information for your local physicians. Please bring the following information to the upcoming appointment detailed above.

- *Local MD Name*
- *Contact information*

Thank you for your continued commitment and participation in the HALT PKD clinical trial. Your contributions are invaluable and will impact the care of generations of Polycystic Kidney Disease patients worldwide.

Sincerely,

[Investigator]

[coordinator]

19.6.2. Pre-closeout Visit - Letter 2

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: LETTER #2 Pre-closeout visit_participant

DATE:

Dear (Participant's Name),

The HALT-PKD study has reached the final stages of the clinical trial. Your attendance of the last study visit with [enter PI/Co-I name] is vital to the success of this important research. We appreciate your ongoing commitment to this effort to identify improved treatment options for individuals diagnosed with Autosomal Dominant Polycystic Kidney Disease.

Your last study visit is designed to facilitate your transition of care back to your local physician. You are scheduled for your last HALT-PKD study appointment with Dr. [PI / Co-I] on:

- *Closeout visit date*]
- at *[time].*
- *Location*

At this time, Dr [PI/Co-I] and the study team will be discontinuing your study medication and will discuss plans to transition your care to your local physician. It is very important that you bring all remaining study medication cards along with your local physician's current contact information to this appointment. Please bring the following information to the upcoming appointment detailed above.

- *All study drug medication cards and bottles*
- *Local MD Name*
- *Contact information*

Thank you for your continued commitment and participation in the HALT-PKD clinical trial. Your contributions are invaluable and will impact the future care of Polycystic Kidney Disease patients worldwide.

Sincerely,

[Investigator]

[coordinator]

19.6.3. Participant Closeout Visit - Letter 3

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: LETTER #3
Participant Closeout visit letter_taper 80mg

DATE:

Dear (Participant's Name),

Today you completed your final visit within the HALT-PKD clinical trial. It is time to wean you off the study medication in the blister card, the Telmisartan/Placebo pill. Starting with your next dose, please start taking 40mg of the Telmisartan/Placebo medication. The number at the top of the card will start with a 40. Do not take the 80mg tablets anymore. Please check your blood pressure every day and record it. If at any time your blood pressure is greater than 140/90, contact your study coordinator. Your study coordinator will check in with you in 2 weeks to review your blood pressures. We may need to add additional blood pressure medications. The study investigator will discontinue your 40mg dose depending on your response to the use of traditional blood pressure medications.

We will transition your blood pressure management to your nephrologist or your primary care physician. Your doctor will be sent a letter containing your recent blood pressure readings obtained in the clinic and a list of the prescribed antihypertensive medications. It is important that you make an appointment to see your physician within the next thirty days to safely transition the management of your blood pressure. Please make an appointment as soon as possible. We will contact you in eight weeks to obtain a health status update.

The HALT-PKD study is one of the largest ADPKD studies ever done and the information that we learn will direct how ADPKD is treated for the next generation. Your contribution has been invaluable. We will send a letter to you as the study results become available.

Thank you for your dedication in helping us understand this disease and how best to treat it.

Sincerely,
[Investigator]

[coordinator]

19.6.4. Participant Closeout Visit - Letter 4

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: LETTER #4
Participant Closeout visit letter_taper 40mg

DATE:

Dear (Participant's Name),

Today you completed your final visit within the HALT-PKD clinical trial. It is time to wean you off the study medication in the blister card, the Telmisartan/Placebo pill. Starting with your next dose, please discontinue the blister cared medication. Please check your blood pressure every day and record it. If at any time your blood pressure is greater than 140/90, contact your study coordinator. Your study coordinator will check in with you in 2 weeks to review your blood pressures. We may need to add additional blood pressure medications.

We will transition your blood pressure management to your nephrologist or your primary care physician. Your doctor will be sent a letter containing your recent blood pressure readings obtained in the clinic and a list of the prescribed antihypertensive medications. It is important that you make an appointment to see your physician within the next thirty days to safely transition the management of your blood pressure. Please make an appointment as soon as possible.We will contact you in eight weeks to obtain a health status update.

The HALT-PKD study is one of the largest ADPKD studies ever done and the information that we learn will direct how ADPKD is treated for the next generation. Your contribution has been invaluable. We will send a letter to you as the study results become available.

Thank you for your dedication in helping us understand this disease and how best to treat it.

Sincerely,

[Investigator]

[coordinator]

19.6.5. Post Closeout Visit - Letter 5

HALT-PKD
Polycystic Kidney Disease Treatment Network

Template: LETTER #5
Post closeout visit PCP/Medical Provider letter_STUDY A

DATE:

Re: STUDY COMPLETION OF YOUR PATIENT FROM A RANDOMIZED CLINCIAL TRIAL

Dear (Physician's Name),

Your patient, _____, has been a participant in the HALT-PKD Study, a randomized clinical trial that is assessing the effects of combination ACE/ARB versus ACE alone on kidney function decline in Autosomal Dominant Polycystic Kidney Disease. Additionaly patients were assigned either to a "Standard blood pressure goal" or "Low blood pressure goal" We have been managing your patient's blood pressure since he/she was enrolled on _____.

Your patient was assigned to the

- Standard Blood Pressure Goal: BP: 120-130/70-80 mmHg
- Low Blood Pressure Goal: BP 95-110/60-75 mmHg.

We have provided your patient with the study medication (Telmisartan or placebo) as well as additional antihypertensive medications and potassium as needed, at no cost, throughout the course of the study. As your patient has reached the end of the study, the blinded study medication (Telmisartan/placebo) was stopped on the last day of participation in the study. We will no longer be providing medications or managing your patient's blood pressure.

Your patient was receiving the following antihypertensive medications:

- Telmisartan/Placebo ____mg/day
- Lisinopril __ mg per day
- Lasix ___ mg per day
- Metoprolol __ mg twice per day
- Diltiazem ____mg twice a day
- Amlodipine _____mg per day
- Other: _____

His/her latest blood pressure in the office was ---- / ----- and the average home blood pressures prior to the last visit was: ---- / -----.

Your patient is advised to continue all her/his antihypertensive medications with the following changes:

- StopTelmisartan/placebo
- Other: _____

HALT-PKD
Polycystic Kidney Disease Treatment Network

During the study, some of our participants experienced problems with antihypertensive therapies. Your patient:

☐ ***did not*** experience adverse symptoms or reactions

☐ had the following problems with antihypertensive medications that need to be captured in his/her medical records:

_____
_____
_____

Attached please find the latest laboratory test results (at baseline and the last visit) for your information.

In order to make a safe and smooth transition, we asked your patient to monitor his/her home blood pressures after termination of the study and to schedule a visit with you within the next 30 days to take over the management of his/her blood pressure. The participant's participation in the study will conclude on: _____ (*eight week end date)* _____ and will require pharmacotherapy management at that time.

We do not know yet whether combination ACE/ARB is superior to ACE alone, or whether the low blood pressure goal is superior to standard blood pressure control in slowing progression of ADPKD. These results will be made available upon publication of the study results, anticipated in December 2014. You may choose to continue or to modify the therapies that your patient has been receiving according to the current national or international guidelines. You will be notified of your patient's study drug assignment (ARB or placebo) at the conclusion of the study.

We appreciate your assistance in transitioning care from the HALT PKD Study to you and the other providers.

Please do not hesitate to contact us if you have further questions.

Sincerely,

Principal Investigator HALT PKD Study

Cc: participant

19.6.6. Post Closeout Visit Study A - Letter 6

HALT-PKD
Polycystic Kidney Disease Treatment Network

Template: LETTER #6
Post closeout visit PCP/Medical Provider letter_STUDY B

Re: STUDY COMPLETION OF YOUR PATIENT FROM A RANDOMIZED CLINCIAL TRIAL

Dear (Physician's Name),

Your patient, _____, has been a participant in the HALT-PKD Study, a randomized clinical trial that is assessing the effects of combination ACE/ARB versus ACE alone on kidney function decline in Autosomal Dominant Polycystic Kidney Disease. We have been managing your patient's blood pressure since he/she was enrolled on _____. We have provided your patient with the study medication (Telmisartan or placebo) as well as additional antihypertensive medications and potassium as needed, at no cost, throughout the course of the study. As your patient has reached the end of the study, the blinded study medication (Telmisartan/placebo) was stopped on the last day of participation in the study. We will no longer be providing medications or managing your patient's blood pressure.

Your patient was receiving the following antihypertensive medications:

- Telmisartan/Placebo ----mg/day
- Lisinopril __ mg per day
- Lasix ___ mg per day
- Metoprolol __ mg twice per day_
- Diltiazem ____mg twice a day
- Amlodipine _____mg per day
- Other: _____

His/her latest blood pressure in the office was ---- / ----- and the average home blood pressures prior to the last visit was: ---- / -----.

Your patient is advised to continue all her/his antihypertensive medications with the following changes:

- StopTelmisartan/placebo
- Other: _____

During the study, some of our participants experienced problems with antihypertensive therapies. Your patient:

☐ ***did not*** experience adverse symptoms or reactions

☐ had the following problems with antihypertensive medications that need to be captured in his/her medical records:

_____

_____

HALT-PKD
Polycystic Kidney Disease Treatment Network

Attached please find the latest laboratory test results (at baseline and the last visit) for your information.

In order to make a safe and smooth transition, we asked your patient to monitor his/her home blood pressures after termination of the study and to schedule a visit with you within the next 30 days to take over the management of his/her blood pressure. The participant's participation in the study will conclude on: _____ (*eight week end date)* _____ and will require pharmacotherapy management at that time.

We do not know yet whether combination ACE/ARB is superior to ACE alone in slowing progression of ADPKD. These results will be made available upon publication of the study results, anticipated in December 2014. You may choose to continue or to modify the therapies that your patient has been receiving. During the study your patient has been treated to a blood pressure goal of 110-130/70-80. You will be notified of your patient's study drug assignment (ARB or placebo) at the conclusion of the study.

We appreciate your assistance in transitioning care from the HALT PKD Study to you and the other providers.

Please do not hesitate to contact us if you have further questions.

Sincerely,

Principal Investigator HALT PKD Study

Cc: participant

19.6.7. Modified Participant and Endpoint Participant Closeout Letter - Letter 7

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: LETTER #7
Modified participant and endpoint participant Closeout letter

DATE:

Dear (Participant's Name),

The investigators of the HALT-PKD clinical trial wish to inform you that the study concluded on June 30, 2014. The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. We anticipate that study results will be available in late December 2014.

Thank you for your dedication to the HALT-PKD clinical trial. Your participation in this endeavor has been invaluable in assisting our understanding of this disease and how best to treat it.

Sincerely,

[Investigator]

[Coordinator]

19.6.8. Participant Notification of Study Results Unblinding - Letter 8

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: Letter #8 Participant Notification of Study results_unblinding letter

DATE:

Dear (Participant's Name),

The investigators of the HALT-PKD clinical trial wish to inform you that the study officially concluded June 30, 2014. Over the past several months the analysis of all study data has taken place and a summary of study results is now available.

During your last study visit, you indicated a desire to receive information on your treatment allocation during your participation in the study. The information supplied to you in this letter will also be shared with the local physician that you identified during your last study visit.

During you study participation you were assigned to the following treatment group:

Study arm assignment: _____

We have completed a review of your lab and radiology data obtained during your participation. The information below reflects those measures:

Date of study enrollment: _____

Date of final study contact: _____

Estimated GFR at enrollment: _____ Date: _____

Estimated GFR at last visit: _____ Date: _____

Total kidney volume MRI #1: _____ Date: _____

Total kidney volume final MRI: _____ Date: _____

Current Kidney disease staging: _____ Date: _____

Blood Pressure Measurement _____ / _____ Date: _____

Enclosed for your review, please find a copy of published study results recently provided to our sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). If you have questions or concerns with any of this information, please contact your study investigator, Dr. _____ at:_____

The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. Thank you for your dedication to the HALT-PKD clinical trial. Your participation in this endeavor has been invaluable in assisting our understanding of this disease and how best to treat it.

Sincerely,

[Investigator]

19.6.9. Designated Physician/Medical Provider Notification of Study Results Unblinding - Letter 9

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: Letter #9
Designated Physician/Medical Provider
Notification of Study results_unblinding letter

DATE:

Dear Dr. _____,

Your patient, _____ recently completed participation in the HALT-PKD clinical trial. This study was designed to assess the affects of combination ACE/ARB versus ACE alone on kidney function decline in Autosomal Dominant Polycystic Kidney Disease. The investigators of HALT-PKD wish to inform you that the study officially concluded June 30, 2014. Over the past several months the analysis of all study data has taken place. Enclosed please find a copy of published study results recently provided to our sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

During the last study visit, your patient requested that we share study related information with you. Listed below please find your patient's treatment allocation, a comparison of initial and final eGFR results, intial and final height adjusted total kidney volume and, finally, the patient's current stage of kidney disease documented at the last clinical evaluation.

Date of study enrollment:	_____	
Date of final study contact:	_____	
Patient study allocation:	_____	
Estimated GFR at enrollment:	_____	Date: _____
Estimated GFR at last visit:	_____	Date: _____
Total kidney volume MRI #1:	_____	Date: _____
Total kidney volume final MRI:	_____	Date: _____
Current Kidney disease staging:	_____	Date: _____
Blood Pressure Measurement:	_____ / _____	Date: _____

If you have questions or concerns with any of the enclosed information, please contact your patient's study investigator, Dr. _____ at:_____

The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. We appreciate the opportunity to care for your patient during the clinical trial. The participant's dedication to the HALT-PKD study has been invaluable in assisting our understanding of this disease and how best to treat it.

Sincerely,

[Investigator]

[coordinator]

19.6.10. Participant Notification of Study Results/Blind - Letter 10

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: Letter #10 Participant Notification of Study results_BLIND MAINTAINED

DATE:

Dear (Participant's Name),

The Investigators of the HALT-PKD clinical trial wish to inform you that the study officially concluded June 30, 2014. Over the past several months the analysis of all data has taken place and a summary of the study results is now available. Enclosed for your review, please find a copy of published study outcomes recently provided to our sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

We have completed a review of your lab and radiology data obtained during your participation in the HALT PKD study. The information shown below reflects some of those measures. This information will be shared with your local physician that you identified during your last study visit.

Date of study enrollment:	_____	
Date of final study contact:	_____	
Estimated GFR at enrollment:	_____	Date: _____
Estimated GFR at last visit:	_____	Date: _____
Total kidney volume MRI #1:	_____	Date: _____
Total kidney volume final MRI:	_____	Date: _____
Current Kidney disease staging:	_____	Date: _____
Blood Pressure Measurement:	_____ / _____	Date: _____

We are honoring your request to remain blinded to your treatment allocation (randomization to study drug or placebo) that information will remain confidential and will not be shared with your local physician. If you have questions or concerns with any of the information contained within this letter, please contact Dr. _____ at:_____.

The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. Thank you for your dedication to the HALT-PKD clinical trial. Your participation in this endeavor has been invaluable in assisting our understanding of this disease and how best to treat it.

Sincerely,

[Investigator]

19.6.11. Participant Notification of Study Results/Blind - Letter 11

HALT-PKD
Polycystic Kidney Disease Treatment Network

TEMPLATE: Letter #11
Designated Physician/Medical Provider
Notification of Study results_BLIND MAINTAINED

DATE:

Dear Dr. _____

Your patient, _____ recently completed participation in the HALT-PKD clinical trial. This study was designed to assess the affects of combination ACE/ARB versus ACE alone on kidney function decline in Autosomal Dominant Polycystic Kidney Disease. The investigators of HALT-PKD wish to inform you that the study officially concluded June 30, 2014. Over the past several months the analysis of all study data has taken place. Enclosed please find a copy of published study results recently provided to our sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

During the last study visit, we informed your patient that we would share study related information with you. Listed below please find your patient's initial and final eGFR results, initial and final height adjusted total kidney volume (Study A only) and, finally, the patient's current stage of kidney disease documented at the last clinical evaluation.

Date of study enrollment:	_____	
Date of final study contact:	_____	
Estimated GFR at enrollment:	_____	Date: _____
Estimated GFR at last visit:	_____	Date: _____
Total kidney volume MRI #1:	_____	Date: _____
Total kidney volume final MRI:	_____	Date: _____
Current Kidney disease staging:	_____	Date: _____
Blood Pressure Measurement:	_____ / _____	Date: _____

In honor of your patient's request to remain blinded to their treatment allocation, the HALT-PKD investigators will not disclose the patient's randomization to the study drug/placebo group.

The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. We appreciate the opportunity to care for your patient during this important clinical trial. The participant's dedication to the HALT-PKD has been invaluable in assisting our understanding of the disease and how best to treat it.

Sincerely,

[Investigator]