HALT PKD
(Halt Progression of Polycystic Kidney Disease)

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

Sponsored by
The National Institute of Diabetes & Digestive &
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1. INTRODUCTION

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

2. METHODS

2.1. Overview of Study Design

The efficacy of interruption of the renin-angiotensin-aldosterone system (RAAS) on the progression of cystic disease and on the decline in renal function in autosomal dominant kidney disease (ADPKD) will be assessed in two multicenter randomized clinical trials targeting different levels of kidney function: (1) early disease defined by GFR >60 mL/min/1.73 m^2 (Study A) and moderately advanced disease defined by GFR 30-60 mL/min/1.73 m^2 (Study B). Participants will be recruited and enrolled to each study over the first two years and followed for an average of five years. The two concurrent randomized clinical trials differ by eligibility criteria, interventions and outcomes to be studied.

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

Study B will assess the efficacy of intensive RAAS blockade using ACE-I/ARB combination compared to ACE-I monotherapy on the time to doubling of serum creatinine, ESRD or death. All participants will be treated to standard levels of blood pressure control (systolic 120-130 and diastolic 70-80 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 six months thereafter. Participants will be followed by telephone visits at least every three months.

2.2. Specific Aims and Main Hypotheses

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

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

Hypothesis to be tested in Study B
In hypertensive ADPKD individuals with moderate renal insufficiency (GFR 30-60 mL/min/1.73 m^2), intensive blockade of the RAAS using combination ACE-I/ARB therapy will slow the decline in kidney function over ACE-I monotherapy, independent of standard blood pressure control (systolic 120-130 and diastolic 70-80 mm Hg).

3. ORGANIZATION OF THE STUDY TEAM

3.1. The PKD-TN Steering Committee

The participating clinical centers (PCC) and principal investigators (PIs), responsible for recruiting and following 314 study participants each, are the University of Colorado (Dr. R. Schrier), Mayo Clinic Rochester (Dr. V. Torres), Emory University (Dr. A. Chapman), and Tufts-New England Medical Center (Dr. R. Perrone). The Data Coordinating Center, led by Professor J.P. Miller, is at Washington University. Dr. Schrier is the Chairman of the Steering Committee and each of the other members, as well as Dr. Cathy Meyers (NIH Program Director), has a vote.

3.2. Additional Study Sites

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

3.3. External Advisory Committee

An External Advisory Committee (EAC), consisting of nephrologists with an interest in PKD and/or past experience in randomized clinical trials and statisticians has been selected by the NIH to review the protocol. Once recruitment begins, members of the EAC will serve on the Data and Safety Monitoring Board (DSMB).

4. RECRUITMENT

The same recruitment strategies will be used for both studies.

Recruitment Goals

A total of 548 participants for Study A (GFR >60 mL/min/1.73 m2) and 470 for Study B (GFR 30-60 mL/min/1.73 m2) will provide 90% power to detect 25% differences in treatment arms of each study, as discussed further in Section 13. To meet this goal, 165 individuals with GFR >60 mL/min/1.73 m2 and 142 individuals with GFR 30-60 mL/ min/ 1.73 m2 will need to be screened at each PCC. The number of potential participants approached, the number enrolled and the reasons for non-participation at each stage of the screening period for each study will be recorded. The means by

which participants learned about the study will also be recorded to direct subsequent recruitment efforts to those that have been most effective.

5. ELIGIBILITY

5.1. Inclusion Criteria for Study A

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

5.2. Exclusion Criteria for Study A

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

Exclusions specific to MR imaging acquisition and measurement:

17. Partial or total nephrectomy or renal cyst reduction (including aspiration) performed percutaneously, laparoscopically, or by open surgical procedure.

18. Cardiac pacemaker.
19. Presence of MR incompatible metallic clips (e.g. clipped cerebral aneurysm). This exclusion may be center-specific as some institutions permit MR compatible metallic clips.
20. Body weight >159 kg (350 lbs) or untreatable claustrophobia.

5.3. Inclusion Criteria for Study B

Participants with moderate renal insufficiency (GFR 30-60 mL/min/1.73 m^2), who demonstrate a rapid GFR decline of at least 4 mL/min/1.73 m^2/year, are targeted for Study B. The most consistent indicators of progressive decline at this rate or higher are the presence of hypertension and reduced renal function at baseline. The following criteria will be used to establish eligibility for Study B:

1. A diagnosis of ADPKD as described in item 1 of Inclusion Criteria for Study A.
2. Age 18 - 64 Years.
3. GFR 30-60 mL/min/1.73 m^2, equated from serum creatinine using the 4-variable MDRD equation.
4. Hypertension or high-normal blood pressure, defined as systolic blood pressure $\geq$130 mm Hg and/or diastolic blood pressure $\geq$80 mm Hg [JNC VII, 2003] on three separate readings within the past year, or by current use of antihypertensive agents or diuretics for blood pressure control.
5. Informed Consent.

5.4. Exclusion Criteria for Study B

1. Currently pregnant or intention of becoming pregnant in the subsequent 5 years. For those who have been pregnant, a minimum of six months postpartum and not currently lactating is required.
2. Congenital absence of a kidney or history of a total nephrectomy. A history of cyst reduction or aspiration or partial nephrectomy will not preclude participation in Study B.
3. Documented renal vascular disease.
4. Spot urine albumin-to-creatinine ratio $\geq$1.0 and/or findings suggestive of kidney disease other than ADPKD.
5. Diabetes requiring insulin or oral hypoglycemic agents or a fasting serum glucose of $\geq$126 mg/dl or a random non-fasting glucose of $\geq$200 mg/dl (in accordance with ADA recommendations for diagnosis of diabetes).
6. Serum potassium >5.5 mEq/Lfor participants currently on ACE-I or ARB therapy; >5.0 mEq/L for participants *not* currently on ACE-I or ARB.
7. History of angioneurotic edema or other absolute contraindication for ACE-I or ARB. Intolerable cough associated with ACE-I as defined above.
8. Systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications.
9. Systemic illness with renal involvement.
10. Hospitalization for an acute illness in past 2 months (not including elective admissions).
11. Any serious comorbid condition for which life expectancy is <2 years.
12. History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance that would preclude successful completion of the study.
13. Known presence of unclipped cerebral aneurysm $\geq$7 mm in diameter.
14. Absolute indication (other than hypertension) for β-blocker or calcium channel blocker therapy (e.g. angina, past myocardial infarction, arrhythmia).
15. Treatment within the past 30 days (prior to starting HALT PKD study medication at baseline) on an interventional study that would, in the PI's opinion, interfere with the HALT-PKD study, or creatine supplements within three months prior to the screening visit.
16. Known allergy to sorbitol or sodium polystyrene sulfonate.

6. STUDY TIMELINE

Tables 1A and 1B summarize the study visits that will take place between screening and the end of the study,

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

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

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

Table 1A: Schedule of Assessments - PS-F5

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

A=At the B1 visit, K and BUN must be done at the PCC lab, but creatinine will be done centrally (see D and E).
B=Safety samples must be drawn for all participants at L2 and L4, and at L1 and L3 for Study B participants. (See Section 9.1.4)
C=May use outside lab during titration (L1-L4), if drawn at PI discretion, and after GFR <30 (potassium and serum creatinine required).
D=PCC lab must be used at S visit, Cleveland Clinic at all other visits. Confirm baseline results before starting randomized drugs.
E=TWO samples drawn at B1(≥2 hours apart), shipped same day to Cleveland Clinic. Repeat ASAP 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 DLF at Harvard.
I = Archival blood (serum and plasma), shipped on cold packs on the day of collection, and archival urine (freshly voided and 24-hour collection, with and without boric acid), batch-shipped to the NIDDK Biosample Repository.
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 8 weeks of randomization (B1). Typical washout period is 14-28 days before the start of masked drug (B2).
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.

Table 1B: Schedule of Assessments - (following F5 Visit)

Visit Code	F7	F10	F12	F15	F18	F21	F24~	F36~	F48~	F60~
Time Point	7 mo	10 mo	12 mo	15 mo	18 mo	21mo	24 mo	36 mo	48 mo	60 mo
Demographics										
Informed Consent										
Renal Disease History										
Family History										
Comorbid Conditions										
Hypertension History										
PCC Seated/Standing BP			x		x		x	x	x	x
Complete Physical Exam										
Symptom-directed Exam			x		x		x	x	x	x
Background Questionnaire										
QOL + Pain Questionnaires			x				x	x	x	x
MR/MRA (Study A Only)**							x		x**	
Interval History	x	x	x	x	x	x	x	x	x	x
Home BP Review	x	x	x	x	x	x	x	x	x	x
Review of Medications	x	x	x	x	x	x	x	x	x	x
Adverse Event History	x	x	x	x	x	x	x	x	x	x
Titrate Medication										
Serum Creatinine[D]			x		x		x	x	x	x
Total Electrolyte Panel: Na, K, Cl, CO^2, BUN			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
Glucose[M]			x				x	x	x	x
CBC with PLT			x		x		x	x	x	x
PCC Random/Spot Urine: Microalbumin + Creatinine										
β-HCG urine pregnancy[F]										
24-hr Urine Collection[H, #]			x		#		x	x	x	x
Genetic Sample[G]										
Specimen Banking[I]			x				x	x	x	x

C=May use outside lab if drawn at PI discretion and after GFR <30 (potassium and serum creatinine required).
D=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 DLF at Harvard.
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.

M=Glucose is random at all annual visits.

**Study A participants get MR/MRA at F24 (year two) + on or after F48 (year four), but before F60 (year five).

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

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

7. SCREENING

7.1. Pre-Screening Interview by Telephone and Registration

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

**Imaging reports must be reviewed for all individuals. In addition, the actual ultrasound films must be reviewed if an ultrasound report shows <20 cysts present in an individual without a family history of ADPKD.*

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

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

   For participants 15-64 years of age, GFR <30 mL / min/ 1.73 m^2
   OR
   For participants >49 years of age, GFR >60 mL/min/1.73 m^2

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

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

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

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

Study participants will be instructed to avoid medications with potential nephrotoxicity (NSAIDS, aspirin, antibiotics), or that alter serum creatinine independent of GFR (trimethoprim [Bactrim], cimetidine) for 1 week prior to all PCC visits. 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), drinking excessive fluids or undertaking vigorous exercise.

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

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

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

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

Past records, including laboratory results and imaging report(s), will be reviewed. A medical history and complete physical examination will follow, with blood pressure measured according to JNC VII guidelines [JNC VII, 2003]. A background questionnaire will be completed. A complete blood count, serum electrolytes (sodium, potassium, chloride, total carbon dioxide), liver function tests, serum BUN, albumin, calcium, phosphorus and creatinine, fasting glucose and spot urine albumin-to-creatinine ratio will be sent to the PCC laboratory. Serum creatinine will be sent to the PCC laboratory for analysis at the screening visit, but for the baseline and subsequent PCC visits serum creatinine will be measured centrally at the Cleveland Clinic Foundation Reference Laboratory. Women of childbearing potential will be screened for pregnancy with a qualitative urine β-HCG test.

If additional information is still required by the end of the screening visit or the participant wishes to discuss participation with friends and family, the study coordinator will follow up with the participant over the telephone to confirm eligibility. If the participant is eligible, drug washout may begin, with study medications being shipped to the participant as necessary. Consent for drug washout will have been obtained in person as part of the Screening Consent Form, and participants will have received an electronic blood pressure measuring device, as well as training for its use, at the screening visit. If there is a delay in obtaining the necessary information from which to establish eligibility (>6 weeks after the S visit for drug washout, >8weeks after the S visit for randomization), the potential participant will be required to repeat the screening visit.

Participants excluded after the S Visit will have the reason(s) for exlusion explained to them, and will

be informed of any concerning lab results. Participants will be encouraged to follow up with their primary care physician and/or nephrologist. If authorized, PCCs may inform physicians directly.

7.2.1. *Standardization of Serum Creatinine Measurements*

Serum creatinine will be measured at the PCC laboratory during the Screening Visit and equated to GFR using the 4-variable MDRD prediction equation, with the result being used to determine study assignment (Study A vs. B). Participants treated with ACE-I or ARBs will still be taking their respective therapies at the time the screening measurement is drawn; thus the true estimated GFR by MDRD will be, if anything, higher than that measured. In addition, PCC laboratories, though of high-quality, will not be calibrated to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) or to each other. It is recognized that this will lead to differences in study assignment at one PCC vs. another for participants with a GFR close to the cutoff (GFR 60 mL/min/1.73 m^2). However, the cutoff for study assignment is arbitrary; and a center-specific difference in study assignment for the few individuals with GFRs close to 60 mL/min/1.73 m^2 will not affect the internal validity of the study. The expense and time required to avoid this misclassification in study assignment for a small number of patients, which would require central measurements or calibration of PCC laboratories, is not felt to be justified.

If the screening GFR value is lower than 30 ml/min/1.73 m^2, the participant will be contacted immediately, informed of ineligibility status and instructed to resume the antihypertensive agents used prior to drug washout.

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

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

    a. PCC serum creatinine value (calculated GFR) out of range:
        Study A: $\leq$60 Study B: <30 or >60
    b. Albumin-creatinine ratio $\geq$0.5, or $\geq$1.0 for Study B
    c. Fasting serum glucose $\geq$126 mg/dl or random non-fasting serum glucose $\geq$200 mg/dl

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

3. Major abnormalities in parameters for routine (safety) labs (Na, K, Cl, CO2, BUN, transaminases, alkaline phosphatase, albumin, calcium, phosphorus, CBC w/ PLT) should be adjudicated based on the rubric of "serious comorbid conditions" no more than two 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 $\geq$4 month intervals.

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

7.3. **Standardized Blood Pressure Measurements**

7.3.1. *Selection of Home BP Monitor and Cuff*

At the Screening Visit, each participant will be provided with an autoinflation, electronic

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

7.3.2. ***Arm for BP Measurements***

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

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

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

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

At the B0 visit, the study coordinator will inform participants of their eligibility for Study A or B after review of the data from the Screening Visit (at the end of the visit or over the telephone within a few days of the visit). Participants will be enrolled within three business days after the B0 visit and instructed to stop taking existing antihypertensive medication and begin taking labetalol 100 mg po BID for two weeks or, for participants with a contraindication to β-blocker therapy, clonidine at a starting dose of 0.1 mg po BID. Higher doses of labetalol will be used for participants requiring more than one medication, to be decided on an individual basis by the PI. The two-week drug washout period will be followed by the baseline visit to the PCC for randomization.

Participants will be instructed to measure blood pressure at a minimum frequency of every other day during the two-week drug washout period. If blood pressure is >160/100 mm Hg or symptoms of hypertension (e.g., headache, blurred vision) or hypotension (e.g., lightheadedness, fatigue) develop, they will be instructed to contact the study coordinator or PI and an immediate visit to the PCC for randomization will be arranged. 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 than ACE-I or ARB), to be directed by the PI with close follow-up over the telephone until the next study visit. If, for some reason, the drug washout period is interrupted (i.e., the subject starts ACE-I or ARB), the drug washout may be restarted so long as the participant is able to be randomized within 8 weeks of the Screening Visit. After the Baseline Visit, labetalol/clonidine and/or other medications

will be tapered off and discontinued, as study drugs are initiated and increased according to a stepped protocol.

8. RANDOMIZATION AND BASELINE VISIT (B1)

8.1. Randomization

On completion of the two-week drug washout period, participants will return to the study center for randomization, based on lab values and assessments obtained during the screening visit, and a Baseline visit (B1). If no drug washout is required, randomization may take place the same day as the screening visit. Study coordinators and investigators will provide information and answer questions relating to the process of informed consent, randomization, interventions, subsequent study visits and risks/benefits of participation in the study. After informed consent has been obtained (if applicable), an interval history and symptom-directed physical examination will be performed; and participants will complete baseline questionnaires. Health status will be assessed at baseline using the Medical Outcomes Study Short-Form 36 Questionnaire (SF-36v2), a self-questionnaire that assesses physical, mental and social aspects of health-related quality of life. The HALT-PKD Pain Questionnaire will be used to measure pain and its impact on daily life. Blood will be drawn for potassium, BUN and creatinine and a 24-hour urine sample will be collected for aldosterone, creatinine, sodium, potassium, and albumin. Participants enrolled in Study A will undergo imaging exams at baseline: 1) MR to measure renal volume and liver cysts; 2) MRA to measure renal blood flow; and 3) cardiac MR to measure left ventricular mass.

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

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

8.1.1. *Home Blood Pressure below Limit for Eligibility*

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

8.2. Baseline Serum Creatinine Measurement

At the B1 visit, two serum creatinine measurements, drawn a minimum of two hours apart, will be sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for analysis. The rate Jaffe method for creatinine was used during the MDRD Study and continues to be used at Cleveland Clinic. The assay employs a Synchron CX3 analyzer and reagents obtained from Beckman Coulter Instruments (Brea, CA). Measurement of the picrate-creatinine complex formation was taken at 520 and 560 nm at 25.6 seconds after sample introduction. Total imprecision of this method ranged from 7.5% CV at 0.6 mg/dL to 1.1% CV at 8.6 mg/dL. Calibrator materials are aqueous-based.

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

A difference of 20% or less will be considered an acceptable level of agreement. If the two measurements differ by >20%, arrangements will be made for a second set of measurements to be drawn. For those individuals who live far from the PCC, the repeated blood samples will be drawn at a local laboratory and shipped by overnight mail to the central laboratory. Participants will remain on labetalol/clonidine and will not begin masked study medications until baseline creatinine has been remeasured according to the above procedure.

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

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

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

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

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

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

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

collected on a random 3% of all samples. Additional urine samples will be archived at the NIDDK Biosample Repository for future analysis.

8.4. Archived Samples/Specimen Banking

8.4.1. *Genetic Sample (whole blood)*

At the F5 visit, all 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. A separate, written, informed consent must be obtained from all participants who agree to provide blood specimens for genetic analysis. Participants will have the option to refuse to provide genetic samples. Genetic samples will **not** be obtained from participants who refuse cell immortalization. Briefly, three 8.5-mL Vacutainer tubes (ACD yellow-top) will be obtained from donors at the F5 visit. These will be coded and only the clinical center will have access to the names of participants. Whole blood samples will be sent to the Genetic Repository on the day of collection and, on receipt, will be stripped of identification codes and processed for future identification.

The NIDDK Repository will process whole blood samples. Samples will be stored in such a way as to allow retrieval of aliquots upon the desire of the HALT-PKD Steering Committee and subsequently that of NIDDK.

8.4.2. *Biological Samples (Serum and Plasma)*

On the morning of the visit (B1, then annually), a maximum of 38 ml of whole blood will be collected and processed for the NIDDK Biosample Repository. Twenty (20) ml will be collected in two SST tubes (tiger-top, 10 ml each) and 16 ml in two PST tubes (green/grey-top, 8 ml each). Samples will be centrifuged and shipped on cold packs to the NIDDK Biosample Repository 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. Samples will be re-drawn if there are problems with the collection or delivery of samples to the NIDDK Repository.

8.4.3. *24-Hour Urine Archived Sample*

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

8.4.4. *Fresh Urine Sample*

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

9. INTERVENTIONS

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

9.1.1. *Supply of Study Drugs*

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

9.1.2. *Masking Study Drugs*

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

9.1.3. *Dispensing Drugs*

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

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

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

9.1.4. *Titration of Study Drug*

Study medications will be initiated at the B2 visit and dose incremented every two weeks until the maximal dose is achieved, unless the participant

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

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

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

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

For individuals with difficult-to-control blood pressure, study medications (ACE plus ARB/placebo) may be started at a dose step higher than the first, at the discretion of the PI. It is clearly preferable to use more than one dose step to achieve the targeted BP goal, as opposed to starting with too high a dose step, as the latter may precipitate hypotension or hyperkalemia. The schedule of safety labs will be different for those participants who start at a dose higher than Step 1 if enrolled to Study A,

but will not change if enrolled to Study B. Labs are to be drawn one week after each dose increment whenever a step is skipped, regardless of enrollment to Study A or Study B. This is felt to be sufficient for the full therapeutic effect of the drugs to be apparent.

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

Study drugs and additional antihypertensive agents will be added in a stepped fashion according to the protocols shown in Table 6A (Study A) and Table 6B (Study B). The gray areas indicate masked study drugs, with all other medications being open-label. Study drugs will be maximized as tolerated while ensuring blood pressure does not fall below the lower limit of the targeted range. Home blood pressure records from the prior two-week period will be reviewed at each telephone visit to guide subsequent therapy. If blood pressure remains above the target after the study drug is maximized (8 weeks), open-label therapies will be added according to the protocol. For participants in whom any of the open-label medications (Steps 5-10) are contraindicated, the contraindicated medication may be skipped (e.g., metoprolol [generic] if contraindication to beta-blocker).

Table 2A: Protocol for Addition of Antihypertensive Agents in Study A

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

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

Table 2B: Protocol for Addition of Antihypertensive Agents in Study B

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

Gray indicates masked study drugs.

9.2. **Controlling Blood Pressure**

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

Maintaining separation between the standard and low blood pressure groups is critical for studying the effects of BP control on cystic progression (Study A). Thus, blood pressures will be monitored at home and at the PCC throughout the study. Home readings will be used to guide medication increments/additions because PCC blood pressure readings are likely to be systematically higher, and it will be difficult to obtain more frequent PCC readings for participants living long distances from the PCC. Precedence exists for using home blood pressure readings to achieve separation between blood pressure targets, similar to those in the present study, in ADPKD patients. The University of Colorado conducted an RCT to assess the effects of two different levels of blood pressure control on left ventricular hypertrophy and renal progression. Good separation between the blood pressure targets was achieved and maintained over a 7-year period through home BP monitoring. Participants were initially contacted weekly until control was achieved, after which contact was made monthly during the first year and every 2 months thereafter to the end of the 7-year study.

9.2.1.1. *Frequency of Home Monitoring*

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

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

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

Table 3: Blood Pressure Control over the Course of the Study

Time (visit #)	Phase of Study	Minimum Frequency of Home BP Readings	Minimum Follow-up with Study Personnel	Targeted BP (mm Hg)	BP at which Participant Calls Study Coordinator (mm Hg)	**Urgent Intervention Required**
-2 to 0 weeks (B0-B1)	Drug Washout	Every other day	At the B1 Visit.	≤160 / 100	>160 / 100 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	Study Drug Titration	Every four days	Every 2 weeks, or weekly if necessary	≤150 / 100; closer to target by F4 visit	>150 / 100, OR symptoms of hypertension or	***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

BP)					hypotension[#]	agents) ***If Symptomatic Hypotension or BP Below Targeted Range:*** Return to prior step
> 9 weeks **(F4 to the end of the study)**	Follow up	Weekly until at target, then Monthly	Every 3 months, or more often per PI discretion	See 9.2.4 for targeted standard or low BP ranges	2 out of 3 home BP readings in a single sitting outside accepted range (9.2.4)	***If Blood Pressure is Elevated:*** a. Add /increment agent(s), per next step of protocol, until target reached b. Close follow-up by PCC c. If BP does not respond to added agents, urgent visit to PCC may be necessary per discretion of PI ***If Symptomatic Hypotension or BP Below Targeted Range:*** Return to prior step

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

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

During the drug washout period and titration period, if a *single* BP reading exceeds 160/100 mm Hg or 150/100 mm Hg, respectively, blood pressure is considered to be out of control. For out of control BP during the drug washout period, participants will be instructed to increase the dose of labetolol (or clonidine) or add other medications, monitor BP daily, and arrange an immediate visit to the PCC for randomization. During the titration period, participants will be instructed to call the PCC, at which time medication will be increased ahead of the next scheduled titration. During the titration phase (B2 to F4), if BP remains above the targeted *goal* but <150/100 mm Hg, doses will be titrated at two-week intervals until the BP target is reached or the study drugs are maximized.

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

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

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

used for dosing at the PCC visit will be defined as the average of the readings for the week (last 2 out of 3, or last 4 out of 5) and will be computed for that individual at the specified visit.

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

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

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

In general, if either the systolic, diastolic or both readings are out of range for the average of the last two out of three readings (or four out of five) within a single sitting (at home), a dose adjustment will be made. A wider range of diastolic blood pressures may need to be accepted in order to keep the systolic blood pressure in the desired range, to be decided at the discretion of the PI on a case-by-case basis. Dose adjustments are ***not*** to be made if BP measurements at a PCC visit show elevated readings. Rather, the participant should be instructed to take BP readings at home, after the PCC visit to confirm or deny the need for dose adjustment. In some cases, BP levels in Study A participants may be above the desired range at one step and below the range on the next higher step. In other cases, systolic BP may be within or below the range but diastolic BP may be above the range.

Half-Step Dose Reduction – If a scheduled dose increase for a Study A participant results in a level of BP significantly below the lower limit of the targeted range, investigators will have the discretion to ***reduce*** the dose of open-label medication by a half step, as appropriate, to achieve a level of BP that is either within the targeted range or much closer to the lower limit of the targeted range than the previous dose increment allowed. As the goal for the low BP group in Study A is not only to get BP within target, but also to optimize blockade of the renin angiotensin system (RAAS); the investigator may increase study medication a step further once a participant in the low BP group reaches the targeted range (95-110/60-75 mm Hg), as long as BP stays within the targeted, or acceptable, range, study medications are well tolerated and symptoms of hypotension are not present.

Half-Step Dose Increase – In a case in which a participant's BP is not perfectly within range (e.g., systolic in range, diastolic a bit above

target), but may almost be there, investigators will have the flexibility to *increase* open-label study medication by a half-step in order to achieve the goal of getting participants within the correct BP range. The investigator will also have the discretion to use a half-dose as the first step for participants who, prior to enrolling in the study, were on only one anti-hypertensive medication at a low dose. In such a case the participant will start with a half-dose of lisinopril (2.5 mg); and if the participant's BP is then not in range, lisinopril will be increased to the full dose for Step 1. In Study B, more steps of the ordered protocol will be needed to achieve the targeted BP of 130/80 mm Hg. Blood pressure medications will be titrated up for Study B participants, per the stepped protocol for study medications, until BP is at target. Investigators will try to achieve the target for both systolic and diastolic BP, but the preference will be given to systolic. Once BP is at target (130/80 mm Hg) study medications will be stopped and not pushed further. A lower limit of 110 mm Hg for systolic BP will be in effect, so the acceptable range for BP in Study B will be 110-130 mm Hg systolic. For those with systolic BP below 110 mm Hg and diastolic BP in range (at or below 80 mm Hg), the investigator will cut study medications back so systolic stays above 110 mm Hg. If a participant has systolic BP at 110 mm Hg or above and diastolic BP above 80 mm Hg, the investigator may choose to push study medication further. These types of cases would likely be rare. In anticipation of greater difficulty and increased length of time to achieve the targeted level of blood pressure control, the frequency of home monitoring and study visits will be the same as in Study A.

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

9.2.5. ***Management of Hypotension***

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

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

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

9.2.6. ***Procedure for Measuring Office BP***

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

9.2.7. *Discrepancy between Home and Office BP Readings*

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

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

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

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

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

10. **FOLLOW-UP VISITS**

10.1. **Follow-up Study Visits**

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

PKD Pain Questionnaire will be used to measure pain and its impact on daily life. Blood pressure measurements and an interval physical examination will follow.

The following laboratory measurements will be obtained at study visits:

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

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

Pregnancy testing will be carried out in women of child-bearing potential only if there is a missed menstrual cycle. MR, MRA and cardiac MR studies will be obtained for Study A participants at the 24-month visit and at, or after, the 48-month visit. Participants will be instructed to hold a.m. doses of medications until MR images have been acquired, to reduce the hemodynamic effects of medications on renal blood flow measurement.

10.2. Blood Pressure Control

10.2.1. *Lifestyle Measures for Improving Blood Pressure Control*

Coordinators will regularly counsel participants regarding lifestyle measures to improve blood pressure control, as per guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [JNC VII, 2003]. Participants will be instructed to reduce salt intake to less than 100 mmol/day and participants with a BMI >27 kg/m^2 will be provided with dietary instructions to promote weight loss. Participants will be encouraged to participate in some form of exercise for at least 30 minutes for most days of the week.

10.2.2. *Long-term Blood Pressure Management*

Participants will be instructed to continue monitoring BP readings at least once a month after targeted control has been achieved and to continue reviewing BP records with the study coordinator by telephone every three months for the duration of the study. Additional antihypertensive agents will be added from the stepped protocols, as needed. The frequency of home blood pressure monitoring and of study visits may be increased, at the physician's discretion, for individuals whose blood pressure is 'out of control' at any point in the study.

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

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

11. MEASUREMENT OF PRIMARY AND SECONDARY OUTCOMES

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

The primary outcome of Study A is the percent change in total kidney volume as assessed by MR at baseline, 24 and 48 months follow-up. The MR techniques for imaging and interpretation of volumetric measurements established in the CRISP study will be employed in the present study, as early results from the CRISP study indicate that this MR protocol will provide an effective means for longitudinal evaluation of cyst volume and kidney volume in ADPKD patients. The imaging protocol for HALT PKD is simplified from the current MR imaging protocol used in the CRISP study. MR images will be obtained at each PCC. After the acquisition, MR images will be reviewed locally at each PCC site and securely transferred via secure internet connection to the Image Analysis Center (IAC). It is anticipated that the entire MR scanning session, including participant positioning and coil placement, will take less than 30 minutes.

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

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

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

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

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

quality control. Agreement between the radiologist and technician in the CRISP Study was very high (97%). The result from the radiologist's review of stereology measurements will be used to calculate the whole kidney volume.

11.2. Secondary Outcomes for Study A

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

11.2.1. *Rate of Change of GFR over Time*

GFR will be calculated from serum creatinine measurements using the MDRD or an alternate prediction equation, if a more accurate one becomes available during the course of the study. Serum creatinine measurements will be obtained at the baseline, F5, and F12 visits, and at every subsequent 6-month visit, and sent to the Cleveland Clinic Foundation Reference Laboratory for analysis.

11.2.2. *Measuring Renal Blood Flow*

Methods established in the CRISP Study, specifically, rapid image acquisition during a single breath-hold, will be employed in this study. Renal blood flow measurements will be obtained at baseline, 24 and 48 months in Study A participants. An Imaging Subcommittee, made up of radiologists who will be performing the studies at each center, will discuss a standardized method for measuring renal blood flow by MRA, as established in CRISP. 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. .

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

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

11.2.4. *Rate of Change in Albuminuria*

An aliquot of 24-hour urine will be analyzed for albumin and creatinine at baseline, 6 months,12 months and yearly thereafter. The change in albumin to creatinine ratio over time will be compared among intervention arms.

11.2.5. *Hospitalizations*

At each 3-month study visit (over the telephone or at the PCC), participants will be asked if they have been hospitalized since the last study visit. If hospitalized, participants will be asked to sign a consent form authorizing pertinent medical records to be released and forwarded to the PCC. The study coordinator will enter the date(s) and the primary reason(s) for admission on the Hospitalization Form. The primary reason for admission will be classified according to the Common Terminology Criteria for Adverse Events v3.0

(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.

11.2.6. *Adverse Event Reporting*

Differences in the frequency of adverse events will be compared across study arms.

11.2.7. *Quality of Life and Pain*

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

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

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

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

The primary outcome for Study B is a composite endpoint of time to the 50% reduction of baseleine eGFR, ESRD (initiation of dialysis or preemptive transplant), or death. Serum creatinine will be obtained on ths same schedule as those for Study A and will also be forwarded to Cleveland Clinic for analysis.

11.3.1. *Ascertainment of Doubling of Serum Creatinine, Death, or ESRD*

The outcome of time to the 50% reduction of baseline eGFR is based on measurements analyzed in the central lab every 6 months. The Recruitment and Retention Coordinator at each PCC will request supporting materials to document deaths, including hospital death summaries, death certificates, and/or an ESRD Death Notification Form (HCFA Form 2746) if appropriate. In case of death, study coordinators will request release of information from next of kin. To document ESRD, the run sheets of first dialysis treatments and/or ESRD Medical Evidence Report (HCFA Form 2728) will be obtained, and/or participants will be contacted directly if a kidney transplant was received.

11.3.2. *Secondary Outcome Measures for Study B*

Secondary outcome measures include: i) rate of change of 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; vi) quality of life and pain

measured using the SF-36v2 and HATL-PKD Pain Questionnaire, respectively and vii) adverse effects of medications.

12. STUDY SAFETY

12.1. Data and Safety Monitoring Board

The NIH/NIDDK has appointed an independent Data and Safety Monitoring Board (DSMB), consisting of nephrologists with expertise in the areas of renal progression and clinical trials, statisticians, and experts in the treatment of hypertension. The DSMB meets at least annually to review the progress of the study and a summary of adverse events, as well as to review other interim results. All substantive changes to the protocol require approval by the DSMB.

12.2. Safety Monitoring

From the drug washout period through the first 6 weeks of the study, changes in medications and/or doses will be frequent. Participants will be asked to monitor their blood pressure every 2-4 days and to contact the study coordinator immediately if BP readings are out of the accepted range given the phase of the study. Participants will also be instructed to contact the study nurse if they develop symptoms of hypotension (lightheadedness, postural lightheadedness). The frequency of home BP monitoring and of study visits may be increased, at the physician's discretion, for individuals with 'out-of-control' blood pressure that is difficult to manage. Serum creatinine, potassium and BUN will be measured at the PCC or at participants' local laboratories one week after initiation and after each increment in study drugs. Serum potassium may be monitored more frequently in individuals with borderline hyperkalemia, at the discretion of the PI. Once the GFR falls to <30 mL/min/1.73 m^2, participants will have more frequent follow-up visits with their primary nephrologists than every 6 months (the HALT study visit frequency). For these participants, the study requires additional safety testing (serum creatinine and potassium) at three-month intervals.

At each PCC visit blood pressure will be measured using standardized, automated blood pressure equipment. This will calibrate the home blood pressure equipment. A panel of laboratory measurements will be obtained and reviewed for abnormal values. A computer routine at the DCC will scan laboratory values for alert conditions. The appropriate PCC will be alerted of such abnormalities by e-mail, with subsequent follow up by the DCC to verify that action was taken by the PCC. At each study visit, a systematic review of adverse events will be conducted.

12.3. Adverse Events

12.3.1. *Definitions and Reporting of Adverse Events*

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

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

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

12.3.2. ***Management of Adverse Events***

Adverse symptoms, or drug effects, will be recorded throughout the study. Due to a series of 8 episodes in 5 participants showing early acute renal insufficiency after introduction of ACE-I in ADPKD, we will particularly monitor these events. The following table outlines the management of participants that develop anticipated adverse effects of study drugs. PIs will manage hyperkalemia and increases in serum creatinine per the guidelines below, which reflect the current standard of clinical care. Per Table 9 below, all concerning lab values are to be reported within two weeks of collection, and all lab values defined as serious are to be reported within 24 hours, per section 12.4.2.

Table 9: Management of Adverse Effects of Medications

Event	Definition	Response	No Response to Prior Measures
Rise in serum creatinine (PCC to manage)	≤12 weeks of the start of ACE ± ARB: Serum creatinine increase ≥30% and <100%, or 1.0 mg/dl. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Hold ACE ± ARB. 3. Exclude unrelated causes such as volume depletion, infected urine, other drug effect, obstruction. 4. If serum creatinine falls <30% and no other cause found, re-challenge at lower dose per PI discretion. 5. Data-enter all such values within 2 weeks.	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.
	≤12 weeks of the start of ACE ± ARB: Serum creatinine increase ≥100% PI must be informed immediately (<24 hours)	1. Notify participant. 2. Hold ACE ± ARB. 3. Exclude unrelated causes such as volume depletion, infected urine, other drug effect, obstruction. 4. If serum creatinine falls <100% and no other cause found, re-challenge at lower dose per PI discretion. 5. All such occurences are 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 (within 6 months) 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 12. If no confirmation of doubling, no further action required.
Hyperkalemia	~~Potassium 5.6-6.0 mEq/l.~~	~~1. Notify participant.~~	~~Discontinue ACE ± ARB and proceed to~~

(PCC to manage)	PI must be informed immediately (<24 hours)	2. Exchange resins. 3. Repeat testing. 4. If <5.0, implement 2-gram potassium diet, and/or Loop diuretic, and/or chronic kayexalate. 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.	open-label therapy. Maintain blinding by intent-to-treat principle.
	Potassium >6.0 mEq/l. PI must be informed immediately (<24 hours)	1. Notify participant. 2. Exchange resin. 3. Hold ACE ± ARB. 4. Evaluate causes (admit to local ED if neccessary) 5. Repeat test after evaluation and treatment. If <5.0, implement 2-gram potassium diet, and/or Loop diuretic, and/or chronic kayexalate. 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. All K values >6.5 are reportable SAEs	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.

Table 9: Management of Adverse Effects of Medications (cont.)

Event	Definition	Response	No Response to Prior Measures
Angioneurotic edema	Periodically recurring episodes of non-inflammatory swelling of skin, mucous membranes, glottis, viscera of sudden onset lasting hours to days	Discontinue ACE ± ARB and proceed to open-label therapy. Maintain blinding by intent-to-treat principle.	N/A

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

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

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

12.4.1. ***Definition***

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

1. Resulting in death
2. Hospitalization- all hospitalizations, elective and non-elective, must be reported as SAEs. If a hospitalization is prolonged due to an event related to this study, this is also considered an SAE.
3. Life-threatening event- if the participant is at substantial risk of dying at the time of the event, or if continued use of a study medication[5] or study procedure[6] would result in the participant's death. Included in this definition are potassium levels of >6.5 mEq/L, and doubling of baseline serum creatinine within 12 weeks of beginning study medications.
4. Persistent or permanent harm or disability.
5. Exceeding the nature, severity or frequency of risk described in the protocol.
6. Congenital anomaly- if there is suspicion that exposure to a study medication[5] or procedure[6] prior to conception or during pregnancy resulted in an adverse outcome in the child.

7. Abuse of, or dependency on, study medication.
8. Any other important medical event, including new cancer diagnosis, which may jeopardize the participant, or may require intervention to prevent permanent impairment or damage or other outcome listed above.

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

12.4.2. ***Reporting Requirements***

All SAEs must be reported within 24 hours of study personnel learning of the event to the local PI and to the DCC. Information not available at the time of the initial report should be submitted to the DCC as a follow-up report within 5 business days. All SAEs will be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. Reporting requirements for the FDA differ depending on their relatedness to study interventions, as follows:

A. Drug-related and Unanticipated: The DCC will notify NIDDK of SAEs that are drug-related *and* unanticipated within one business day of receiving the report, and provide safety reports to all PIs and the DSMB within five business days. NIDDK will report drug-related and *unanticipated* SAEs to the FDA within seven days of initial knowledge of the event.

B. Drug-related and Anticipated: The DCC will report *anticipated* SAEs to the FDA, PIs and the DSMB 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 are responsible for fulfilling local IRB reporting requirements, which may vary by center.

C. Unrelated to drugs and/or study participation: With the exception of death, hospitalization, and life-threatening events, the DCC will prepare summary annual reports for the clinical centers, NIDDK, DSMB and FDA. PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by center. *All deaths, hospitalizations, and life-threatening events*, whether related to study participation or not, must be reported as SAEs, as described above.

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

Table 11: Summary of FDA Reporting Requirements for SAE's

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

Study-Related **BUT** unrelated to drug	Anticipated/Expected	Annual Report
Study-Related **BUT** unrelated to drug	Unanticipated	Annual Report
Unrelated to Study		Annual Report

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

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

12.5. Drug Interaction of Telmisartan and Digoxin

Coadministration of Telmisartan and Digoxin, both metabolized by the liver, can lead to an increase in the peak concentration of Digoxin by up to 50%. Digoxin levels will be checked, along with potassium and BUN/ Creatinine (i.e., safety labs), between titration of ACE-I and Telmisartan/ placebo in the first 8 weeks of the study. Dose adjustments for digoxin will be made, if needed, by the PI. Digoxin levels should stabilize once a steady dose of telmisartan is reached, anticipated at the final titration step, L4 safety lab, but continued testing will be arranged if levels continue to flucuate. Digoxin levels will be followed every 6 months thereafter. If there are changes in telmisartan/placebo over the course of the study, digoxin levels will need to be rechecked within a week of the dose adjustment.

12.6. Modified Study Follow-up

Per the intent-to-treat principle, every effort must be made to follow each participant enrolled until the end of the study or death. Table 12 below outlines procedures to be followed for participants who meet primary endpoints, withdraw prematurely from the study, or in other circumstances where modified follow-up is anticipated. In cases for which follow-up must be modified, it is recommended that sites obtain the participant's consent for modified follow-up (per local policies). A checklist has been drafted to clarify participants' options and responsibilities.

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

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

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

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

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

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

Table 12: Follow-up After Primary Endpoints, Early Withdrawal or Modified Participation

Event	*Continue Masked Drugs?*	*Follow-up Visits*
Doubling Serum Creatinine and GFR $\geq$30 mLs/min/1.73 ^{2} (Study A and B)	Yes	As per full protocol of respective study. Study medications prescribed as per the investigative team.
GFR <30 mLs/min/1.73 ^{2} whether or *not* met doubling of serum creatinine (Study A and B)	Yes	As per full protocol of the respective study. Participant followed at more regular intervals by the primary nephrologist and modifications to study drugs may be required. [a] Participants will be followed with more frequent safety labs, at the discretion of the PI/ treating nephrologist.
ESRD (Study A)	No	Study drugs and BP goals are discontinued, but Q3 month telephone and Q6 PCC visits with completion of all forms and MR imaging as per protocol.
ESRD (Study B)	No	No; Vital Status Only [b]
Transplant (Study A or B)	No	No; Vital Status Only [b]
Cyst Reduction / Nephrectomy (Study A)	Yes	Study Protocol without renal MR/ MRA. Cardiac MR and other protocol continue.
Cyst Reduction / Nephrectomy (Study B)	Yes	Full protocol
Pregnancy	Resume 3 months postpartum and post lactation	Stop all study meds, transfer care to PCP, but continue to follow Q3 month (phone/clinic BP, all AEs, no imaging). Participants may re-enter study 3 months postpartum or immediately after lactation.
Serious Adverse Event	Yes	As per full protocol of respective study
Participant refuses home BP monitoring but agrees to study visits Q 6 months	Yes	All investigations scheduled for the respective PCC visit.
Participant refuses clinic visits	No	Participant to choose desired level of follow-up and provide written consent for such. Obtain local bloods, central serum creatinine and BP from PCP/nephrologist.
PI discontinues study drug for health/safety reasons	No	Continue 6 month PCC visits, completion of forms, labs and MRs per protocol
Participant moves to a different HALT region	Yes	Transfer care to the nearest HALT-PKD PCC. However, participant does have the option to continue follow-up with the original PCC.

Table 12: Follow-up After Primary Endpoints, Early Withdrawal or Modified Participation (Cont.)

Event	*Continue Masked Drugs?*	*Follow-up Visits*
Participant lost to follow-up without knowledge of study personnel	If participant reappears	1. Exhaustive efforts to contact the participant 2. Continued follow-up from point of reappearance 3. Check vital status with Vital Statistics via SS # and USRDS (via SS#) if all else fails

[a]Once the GFR falls to <30 mL/min/1.73 m^2, participants will have more frequent follow-up visits with their primary nephrologists than every 6 months (the HALT study visit frequency). For these participants, the study requires additional safety testing (serum creatinine and potassium) at three-month intervals. Dose modifications may be made by the treating nephrologist (e.g. for hyperkalemia/ fluid overload) and these will be tracked at the 3-month telephone or 6-month visits to

the HALT PCC. The HALT Study will continue to provide study medications until ESRD, transplant, death or another reason for termination of drugs ensues.
[b]Vital Status ascertained through 6-month telephone follow-up.

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

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

12.6.1.1. *Pregnancy Prior to Randomization*

If a female participant signs the study consent and completes all eligibility criteria at the screening visit, she may be enrolled to the study and start the drug washout period. If the participant becomes pregnant prior to the baseline visit, she will not be randomized but will be considered a screen failure, even if she has already been enrolled and/or intends to terminate the pregnancy. Study medications must be discontinued immediately and a Screen Failure Form (Form 14) must be completed and data-entered as soon as possible. The participant will be referred to her primary care physician (PCP) for management of the pregnancy and will not be followed under intent-to-treat. The participant will not be eligible for screening again until at least three 3 months after delivery or termination, or immediately after lactation.

12.6.1.2. *Pregnancy after Randomization*

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

<u>Required Modifications for Pregnant or Lactating Participants:</u>

1. Study drugs (ACE-I/ARB or ACE-I/placebo) therapy must be discontinued immediately.
2. All other study medications must be discontinued and participant care transferred to the PCP.
3. Pregnant or lactating participants will continue to be followed every three months by telephone (adverse events and medications only) and every six months at the PCC (for all required tests).
4. Pregnant or lactating participants will *not* be imaged (due to gadolinium). Home BP monitoring is not required.

5. Participants may reenter the study without being rescreened or reconsented: 3 months after termination of pregnancy or immediately after breastfeeding stops (whichever is later).

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

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

13. STATISTICAL ANALYSIS

13.1. Statistical Power and Sample Size Calculations for Study A

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

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

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

Proportion Slowing	% Change in Active Group	Total N Power=.80	Total N Power=.90
.20	4.3	544	726
.25	4.1	350	466
.30	3.8	244	324
.35	3.5	180	240
.40	3.2	138	184

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 4.1%) at a power of .90 with a total of 466 participants (233 in each group). If we assume no follow-up information for 15% of those recruited, then recruiting 548 (=466/.85) would achieve a power of .90

for each of the hypotheses. The same sample size would have a power of .80 to detect a proportion of slowing of about .22. Each cell in the design would have n = 116 or 117.

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

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

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

Analysis of these data will primarily utilize random regression methods. To improve the stability of the estimation process and reduce the impact of larger KVs on the overall assessment process, log (KV) will be examined. With three 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.

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

> **Hypothesis 1** (involving the ACE-I/ARB vs. ACE-I comparison) will be tested by random regression methods. The primary test of the hypothesis will involve a contrast comparison of the slopes of the random regression lines between these two conditions.
>
> **Hypothesis 2** (involving the normal vs. low BP comparison) will be tested by a contrast comparison of the slopes of the random regression lines between these two conditions.

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

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

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

To assess the association between treatment factors and adverse events of study medication, logistic regression will be used. 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. 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. 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 (changes of GFR, renal blood flow, left ventricular mass, albuminuria and quality of life), random regression methods of Laird and Ware will be used. 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 factors. Exploratory data analyses will be conducted first for each outcome to see whether data transformations are needed so that the appropriate statistical assumptions for the model are met. For example, a logarithm scale may be used.

13.4. **Effect Modification in Study A**

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

- **a)** Younger participants have lower absolute changes in kidney volume and interventions may not be as efficacious as in older participants. (Interaction: Age $\leq$30 vs. > 30*Intervention)
- **b)** Males have been noted to have larger kidneys than females at a given age Fick-Brosnahan, and may derive greater benefit. Results will be examined by gender and by gender for age (Interaction: gender *age <30 vs. $\geq$30)
- **c)** Interventions may be more efficacious in faster growing kidneys. (Interaction: baseline kidney volume to be categorized based on baseline distribution* Intervention)
- **d)** More aggressive growth in childhood may be associated with a greater response to the interventions (Interaction: In participants <30 y old, baseline kidney volume $\geq$75th percentile vs. <75th percentile *Intervention)
- **e)** Interventions may be more efficacious in kidneys with reduced function (Interaction: $\geq$80 mL/min/1.73 m^2 vs. <80 mL/min/1.73 m^2 * Intervention)

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

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

We then conducted a Monte Carlo simulation of the trial in which the eGFR values were generated according to the proposed protocol using the random components from model fit from the MDRD data. Because the mean eGFR in the MDRD cohort was

34.9 at the beginning of the study and Study B participants must have an eGFR in the range of 30-60, we assumed that the initial eGFR values were uniformly distributed over the allowable range. We used an average slope of -.35/month. Because of concern that the slope estimate from MDRD might be too aggressive, we also used mean slopes of .30 and -.25. We assumed that there were duplicate measures at baseline. We assumed that 400 participants would be recruited (200 in each treatment group) at a uniform rate over a period of 2 years. We assumed that followup would continue until the last participant had been enrolled for 4 years. Thus individual participants were followed for between 4 and 6 years, with an average of 5 years of followup. If an eGFR at any visit was less than 50% of that for the baseline for that simulated participant, then a repeat creatinine was generated with the same expected value. If the mean of the triggering value and the repeat value were less than 50% of baseline then an endpoint was declared. The rate of reaching endpoints was compared in the two groups using a log rank test. The study, with the specified sample size, was then repeated 1000 times for each set of parameters and the empirical power calculated. The average 6-year survival rate (life table method) was also calculated as was an average hazard rate.

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 40%. We also conducted sensitivity analyses and obtained similar results if we used either the log of creatinine or the reciprocal of creatinine as the parameter to be modeled. Results were also not different if we used a normal distribution of baseline eGFR with a mean of 45 (same as used above) with a standard deviation of the intercept of 8.57, corresponding to the variability seen in MDRD.

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

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

Each participant will be treated in one of two conditions:

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

The primary outcome variable for Study B is a composite endpoint of time to 50% reduction of baseline eGFR, ESRD or death. Participants will be followed until the end of the study (4-6 years). Participants who do not reach one of the three endpoints at the end of the study will be considered to be right-censored.

The analysis method for this arm will primarily involve survival methods. Proportional hazards (Cox) methods for comparison of survival times with censored observations will be used. Age, sex, and baseline GFR will be used as covariates. Clinic will be entered as a stratification variable.

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

Analytic methods for secondary outcomes in Study B will be the same as those for the secondary outcomes in Study A, except that Study B participants will be under a single standard BP control and the comparison will be made between ACE-I/ARB and ACE-I monotherapy

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

13.8. **Effect Modification in Study B**

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

13.9. **Randomization**

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

13.10. **Interim Analysis**

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

14. **DATA COLLECTION AND QUALITY CONTROL PROCEDURES**

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

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

As HALT-ID numbers and dates of registration are logged into the system, the master database will generate participant schedules and identify expected data collection forms and their associated due dates. Data collection forms will be programmed such that data-entry screens closely resemble the original paper forms. The data-entry clerk will enter data into the DMS from each data collection form. Fields will be set to exclude implausible entries. Missing values will generate queries requiring resolution. Queries will be tracked by the DMS. Even though the multiple steps described above reduce errors in data acquisition and entry, the data will undergo additional cleaning processes. A full database back-up will be performed daily using a network tape back-up system. The web application and databases will reside on different servers, with the databases behind a firewall. Access to the WDES from outside of the DCC will be restricted by both the use of Virtual Private Network (VPN) connections and the use of role-specific userid/passwords. The DCC staff will control all queries and reports from the database.

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

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

14.3. **Adherence**

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

14.4. **Training, Retraining and Certification**

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

14.5. **Site Visits**

DCC staff will conduct site visits at each PCC at least twice during the conduct of the study. The review will include examination of all study procedures (control and intervention group), verification

that the randomization system is being used correctly and that study group assignments are accurate, review of completed data collection forms, and review of procedures used to resolve queries. A specific site visit checklist will be used, and a report will be generated after the visit has been completed. The PI will be responsible for ensuring that any deficiencies noted during the site visit are corrected to the satisfaction of the Steering Committee.

14.6. **Laboratory Quality Control.**

All central laboratory measurements obtained by the DCC for HALT-PKD participants will undergo random quality control assessement, whereby duplicate samples for a small percentage of samples will be analyzed. This will be undertaken for serum samples sent to the Cleveland Clinica and for urine samples sent to the DLF at Harvard University.