

Major Kidney Clinical Research Studies and Projects Inventory

Halt Progression of Polycystic Kidney Disease (HALT PKD).

1. Administrative Data

(a) Name of study/research project and acronym:

Polycystic Kidney Disease-Treatment Network (PKD-TN): Halt Progression of Polycystic Kidney Disease (HALT PKD).

(b) Type of study/research project:

Randomized clinical trial.

(c) Funding status:

Currently funded.

(d) Recruitment status:

Recruitment has not yet been initiated.

(e) For studies/projects currently recruiting, indicate total sample size or number currently enrolled and anticipated period of recruitment:

Anticipate recruiting approximately 1,150 subjects over a period of two years.

(f) Data coordinating center principal investigator contact information:

Professor J. Philip Miller
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(g) Number of recruiting sites, list of principal investigators at recruiting sites, and contact information:

Kidney Disease Clinical Studies Initiative, Major Kidney Clinical Research Studies and Projects Inventory,* Halt Progression of Polycystic Kidney Disease (HALT PKD).

Seven (7) recruiting sites as listed below.

Theodore Steinman, M.D.
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(h) List of principal investigators at central laboratories/facilities (identify type of central facility) and contact information:

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The Cleveland Clinic Foundation
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E-mail: vanlenf@ccf.org

(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

External Advisory Committee:

William Henrich, Chair, University of Maryland
William Bennett, Oregon Health Science University
Tom Greene, Cleveland Clinic
Dan Larson, PKD Foundation

Peter McCullough, William Beaumont Hospital
Sharon Moe, Indiana University
Michael Rocco, Wake Forest University
James Shayman, University of Michigan
Samy Suissa, McGill University
Robert Toto, UT Southwestern Medical Center
David Wendler, NIH, Clinical Center

(j) Private sector support (type of support, e.g., financial, donation of drugs/placebo, etc.):

Pharmaceutical companies will be asked to donate drugs and/or to provide additional funding for HALT PKD.

2. Study Design

(a) Objective:

This randomized clinical trial will test the primary hypothesis that intensive blockade of the renin-angiotensin-aldosterone system (RAAS) using an ACE inhibitor (ACE-I) together with an angiotensin receptor blocker (ARB) in hypertensive individuals with autosomal dominant PKD (ADPKD) has a statistically significant advantage over other currently used antihypertensive agents in delaying the renal and possibly cardiac complications associated with this disease, independent of the level of blood pressure control.

In addition, a second hypothesis to be tested is that a lower blood pressure target (MAP \leq 83 mm Hg) in the setting of intensive RAAS blockade will delay renal progression early in the course of ADPKD over standard blood pressure control. Clinical studies of progression in humans with ADPKD are few in number and have not shown consistent outcomes. There is substantial clinical data to implicate the RAS in the pathogenesis of hypertension in ADPKD, in the progression of the structural changes such as renal cyst growth and renal interstitial fibrosis, and in the development of left ventricular hypertrophy (LVH) as an important cardiovascular manifestation. The question we plan to answer is whether complete interruption of the RAAS impacts the clinical course. To date, this question has not been addressed in a large randomized study.

(b) Study design:

The efficacy of interruption of the RAAS on the progression of cystic disease and on the decline in renal function in ADPKD will be assessed in two multicenter randomized clinical trials targeting different levels of kidney function: (1) early disease defined by a GFR >60 ml/min/1.73 m² (Study A) and (2) more advanced disease defined by a GFR 30-60 ml/min/1.73 m² (Study B). Subjects will be recruited and enrolled to each study over the first two years and followed for an average of 5 years. The two concurrent randomized clinical trials differ by eligibility criteria, interventions, and outcomes to be studied.

Study A will assess the effects of ACE-I/ARB combination therapy compared with β -blockers on structural progression and the effects of two blood pressure targets in the setting of combination ACE-I/ARB therapy. Subjects will be randomized to one of three study arms:

- Combination ACE-I/ ARB with standard blood pressure control (MAP \leq 100 mm Hg)
- β -blocker with standard BP control
- Combination ACE-I/ARB treated to a low BP target (MAP \leq 83 mm Hg).

Open-label antihypertensive agents will be added from an ordered protocol to achieve the targeted blood pressure. Blood pressure will be monitored at the clinical center at 4 months and 12 months in the first year and also via review of home blood pressure records over the telephone at defined intervals for the length of the study. Study visits will occur every six months. The primary outcome of Study A is the percent change in total kidney volume measured by Magnetic Resonance Imaging (MRI).

Study B will assess the effects of ACE-I/ARB combination therapy as compared with ACE-I alone on the time to doubling of serum creatinine, ESRD or death. All subjects will be treated to standard levels of blood pressure control (MAP \leq 100 mm Hg). As in Study A, blood pressure will be monitored at 4 months and 12 months in the first year and also via telephone follow-up of home records at defined intervals for the length of the study. Study visits will occur every six months.

(c) Major inclusion criteria:

Study A	Study B
Diagnosis of ADPKD	Diagnosis of ADPKD
Age 15-50 years	Age 15-65
Glomerular Filtration Rate (GFR) \geq 60 ml/min/1.73 m ²	GFR 30-60 ml/min/1.73m ²
Hypertension or high-normal blood pressure as defined by \geq 130 mm Hg systolic and/or \geq 85 mm Hg diastolic on three separate readings, or by the current use of antihypertensive agents or diuretics for BP control. For subjects aged 15-17, hypertension or high normal blood pressure will be defined as blood pressure exceeding the 75 th percentile* for gender averaged across 15-17 year olds for the 50 th percentile of height or by the current use of antihypertensive agents. The values for females are a systolic and/or diastolic blood pressure \geq 120 / 74 mm Hg and for males, \geq 125/74 mm Hg. Percentiles are based on the Task Force on Blood Pressure Control in Children [62].	Presence of hypertension, defined as the current use of antihypertensive agents for BP control, or systolic blood pressure >140 mm Hg or diastolic blood pressure > 90 mm Hg on three separate readings. For children <18 years of age, hypertension will be defined as the current use of antihypertensive medications or blood pressure exceeding the 95 percentile matched for age, gender, and height
Informed consent.	Informed consent.

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(d) Major exclusion criteria:

See table below.

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Study A	Study B
Currently pregnant or intention of becoming pregnant in subsequent 5 years	Currently pregnant or intention of becoming pregnant in subsequent 5 years
Partial or total nephrectomy or renal cyst reduction	Documented renal vascular disease
Documented renal vascular disease	Spot urine albumin-to-creatinine ratio of > 0.5 and/or findings suggestive of kidney disease other than ADPKD
Congenital absence of one kidney	Diabetes requiring insulin or oral hypoglycemic agents or fasting glucose level of >126 if not receiving insulin or oral hypoglycemic agents
Spot urine albumin-to-creatinine ratio of > 0.5 and/or findings suggestive of kidney disease other than ADPKD	History of anigoneurotic edema or other hypersensitivity reaction with ACE-I or ARB
Diabetes requiring insulin or oral hypoglycemic agents or fasting glucose level of >126 if not receiving insulin or oral hypoglycemic agents	Absolute indications for ACE-I: a) Past history of symptomatic or asymptomatic heart failure diagnosed clinically or via cardiac imaging studies (ejection fraction <40%) b) >55 years of age with a history of coronary artery disease myocardial infarction/ PTCA/ CABG), stroke or peripheral vascular disease [64]
History of anigoneurotic edema or other hypersensitivity reaction with ACE-I or ARB	Absolute indication for β -blocker or calcium channel blocker – (e.g. angina, arrhythmia)
Past history of symptomatic or asymptomatic heart failure	Systemic illness necessitating NSAID use or immunosuppressant or immunomodulatory medications
Absolute indication other than hypertension for β -blocker or calcium channel blocker therapy	Systemic illness with renal involvement
Systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications	Hospitalization for an acute illness within past 2 months
Systemic illness with renal involvement	Any serious comorbid condition for which life expectancy is <2 years
Hospitalization for an acute illness within past 2 months	History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance
Any serious comorbid condition for which life expectancy is <2 years	Known presence of unclipped cerebral aneurysm >1 cm in diameter
History of non-compliance, drug or alcohol dependence within the past year or other psychiatric disturbance	
Body weight >350 lbs	
Cardiac pacemaker	
Presence of unclipped cerebral aneurysm >1 cm in diameter	
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	

(e) Description of intervention(s):

The intervention for Study A will consist of two arms with different blood pressure targets in the setting of ACE-I/ARB combination therapy and one arm for active control (standard BP). The two different blood pressure targets will be assessed to determine whether lower blood pressure confers additional benefit in slowing renal progression. It will be critical to maintain separation between the low MAP (≤ 83 mmHg) and the standard MAP (≤ 100 mmHg). The intervention for Study B will consist of ACE-I /ARB combination therapy versus either a one-arm (ACE-I) or two-arm (ACE-I and ARB) monotherapy, with blood pressure control to be monitored intensively, the target for all subjects being a MAP < 100 mmHg.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

Subjects will be screened over two visits, S and Bo. At the first visit, Screening (S), participants will be informed of the purpose and logistics of the study; consent for Screening and Drug Washout (Bo) will be obtained; participants will be trained to monitor blood pressure at home; eligibility questionnaires will be completed; and screening laboratory measurements will be obtained. After review of the labs drawn at S and not more than 2 months (Study B) or 6 months (Study A) after S, a study coordinator will contact the subject via telephone to initiate a 2-week drug washout period. At the Baseline (B1) visit, baseline lab measurements will be obtained, the participant will be enrolled and randomized, and study drug(s) will be initiated.

(g) Follow-up contact schedule (frequency, type of visit/phone, in-clinic, major assessments):

Study drugs will be incremented over three follow-up visits (F2-F4) two weeks apart to be conducted over the telephone. Serum potassium and creatinine will be checked between dose increments at the PCC or a local lab. Additional open-label therapies will be added to achieve the targeted blood pressure control by the F6 visit. Study visits at the PCC will occur at 4 months and 12 months during the first year, after which study visits will occur every 6 months. Blood pressure will be monitored at 4-month and 12-month study visits in the first year and by review of home records by telephone at defined intervals during the first year and every 3 months after the first year. Serum creatinine will be measured centrally every 6 months in participants of both studies. Study A participants will have magnetic resonance (MR) imaging at baseline, 24 months, and 48 months.

(h) Primary outcome, secondary outcomes:

Study A – The primary outcome measured in Study A is the percent change in kidney volume by MR over time. Secondary outcome measures include (1) rate of change in GFR over time; (2) rate of change in renal blood flow by MRA over time; (3) change in left ventricular mass; and (4) change in albuminuria.

Study B – The primary outcome measure in Study B is time to a composite of doubling serum creatinine, ESRD (initiation of dialysis or preemptive transplant), or death.

Secondary outcome measures include (1) rate of change in GFR and (2) change in albuminuria.

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates, or rate of change in outcome measure):

The statistical model for testing the treatment effect in Study A is the random coefficients model of Laird and Ware (82). 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 subjects, and the standard deviation of the noise (σ_n , deviations around the linear trajectories for each subject). 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 11/29/02), we have observed a mean change of .0182 or a 4.3% increase. Unfortunately with only two observations per person, we cannot separately estimate the standard deviation of true changes from the noise. We will be able to have such estimates after July 2003, when about half of the CRISP cohort will have had their 3rd imaging session. As an alternative approach, prior to starting CRISP, we conducted a standardization study where 4 subjects traveled to each of the 4 sites and were measured twice at each site. Each of the resulting 32 image series were then measured by two different analysts at the imaging center. Using a mixed model and REML estimates of the various variance components, we have estimated that the total noise standard deviation is about .017. Using the fact that the standard deviation of the difference between the baseline and annual measurement was observed to be .0303 and the identity that its square is equal to $\sigma_s^2 + 2\sigma_n^2$, we can estimate that σ_s is about .015.

Using the method of Lefonte 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 power of .80 and a significance level of .05 (2-tailed):

Proportion Slowing	% Change in Active Group	N-each Group
.20	3.4	277
.25	3.2	178
.30	3.0	124
.35	2.8	91
.40	2.5	70

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 20% (e.g., from 4.3% to 3.4%) with 277 in each group. If we assume no follow-up information for 15% of those recruited, then recruiting 978 ($=3*277/.85$)

would achieve a power of .8 for each of the hypotheses. The power calculations for Study B were based on an analysis of the serum creatinine values in 139 cases in from MDRD whose initial GFRs were in the same range as the proposed study (MDRD Study A). We fit the Laird and Ware model to this data with a mean intercept of 1.7 for females and 2.1 for males. The average slopes were .38 for the females and .53 for the males. The standard deviations for the intercepts were .42 and .47 for the slopes. The residual standard deviation was .21. We assumed that the probability of obtaining ESRD prior to a doubling of the serum creatinine was a function of the current serum creatinine level using rates of ESRD over 5 years as .005 for < 4, .05 for 4-4.5, .10 for 4-4.5 and .20 for > 5.0.

We then conducted a Monte Carlo simulation of the trial where the serum creatinine values were generated according to the proposed protocol using the model fit from MDRD and assuming 50% males and 50% females. If a creatinine at any visit was greater than twice that for the baseline for that simulated subject, then a repeat creatinine was generated with the same expected value and a standard deviation of .15 (the standard deviation of the two baseline values in the MDRD data). If the mean of the triggering value and the repeat value were twice baseline, an endpoint was declared. Otherwise, a simulation was conducted for reaching ESRD. The study, with the specified sample size, was then repeated 250 times for each set of parameters and the empirical power calculated.

For the two group power calculations, the control group was assumed to have the rate of increase in serum creatinine values seen in MDRD and the ACE/ARB group to have varying slowing of that rate. The observe powers were:

n total	n per Group	Proportion slowing		
		.20	.25	.30
300	150-150	0.428	0.632	0.832
400	200-200	0.480	0.748	0.916
500	250-250	0.632	0.856	0.968
600	300-300	0.704	0.892	0.980
700	350-350	0.796	0.964	0.992
800	400-400	0.816	0.936	1.000
900	450-450	0.884	0.948	1.000
1000	500-500	0.896	0.984	1.000

For a slowing of the rate by 25%, a power of 80% can be achieved with about 225 (450 total) participants in each group. With a slowing of 30%, it can be achieved with about 140 (280 total) in each group.

For the three group power calculations, one group was assumed to have the MDRD slopes, the ACE/ARB group to have the specified slowing, and group two to have a slowing of one quarter of the amount of the ACE/ARB group. The ACE/ARB group was chosen to have more subjects allocated in a ration of 1:1:1.41 for maximum power for the

tests of monotherapy against combined therapy. The observed power for testing against group 1 (no slowing) was:

n total	n per Group	Proportion slowing			
		.20	.25	.30	.35
300	088-088-123	0.320	0.448	0.676	0.816
400	118-118-165	0.376	0.568	0.748	0.908
500	147-147-206	0.480	0.696	0.820	0.960
600	176-176-246	0.492	0.756	0.924	0.968
700	206-206-288	0.584	0.768	0.960	0.988
800	235-235-329	0.728	0.872	0.960	1.000
900	265-265-371	0.744	0.920	0.976	1.000
1000	294-294-412	0.748	0.924	0.984	1.000

With a slowing of 25%, a power of .8 could be achieved with a total of about 750 subjects and for a slowing of 30% with about 475 total subjects.

For the comparison of the ACE/ARB against the middle group, the observed powers were:

n total	n per Group	Proportion slowing			
		.20	.25	.30	.35
300	088-088-123	0.172	0.352	0.488	0.712
400	118-118-165	0.200	0.424	0.584	0.768
500	147-147-206	0.284	0.472	0.720	0.872
600	176-176-246	0.328	0.568	0.784	0.948
700	206-206-288	0.408	0.640	0.828	0.952
800	235-235-329	0.484	0.736	0.904	0.960
900	265-265-371	0.528	0.736	0.904	0.984
1000	294-294-412	0.592	0.772	0.936	0.984

(j) Web site:

The PKD-TN/HALT PKD web site was developed and is maintained by the Data Coordinating Center (DCC) at Washington University in St. Louis. The web site address is: <http://www.pkd.wustl.edu/pkdttn>. The home page for the HALT PKD web site contains content and links for public access, as well as a password-protected link to content, such as the Manual of Procedures, drafts of study documents, and archives, that have been restricted to access by only authorized study investigators. This user-restricted area will also contain the jumping off point to the web-based data entry system that is currently in development by the DCC.

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample, e.g., blood, urine, etc., the amount, and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry)

Serum creatinine levels will be obtained every 6 months throughout the study. What other assays and samples that will be collected is still under consideration.

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants sample was collected from, and physical location of where the samples are stored):

None yet.

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable (e.g., “use for other studies or not,” “allow genetic studies or not.”). Does consent include use of samples in other studies that are not part of the main study?

The model consent has not yet been finalized.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected, e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.):

Not finalized.

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

Under consideration.

4. Ancillary Studies

(a) Process and contact person for application to perform ancillary studies:

The process and contact person for application to perform ancillary studies has not yet been determined for HALT PKD.

(b) List of ancillary studies approved, completed, and ongoing (including source of funding and amount):

There are no ancillary studies in progress.

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5. List of Publications and Presentations (full citations, also note manuscripts in progress):

There are no publications or presentations to report at this time.