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Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

Manual Of Procedures

July 22, 2003

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1 CRISP Study Synopsis

1.1 Study Background and History

Autosomal dominant polycystic kidney disease (ADPKD) is the most common heritable renal disorder and accounts for 4.7% of the End-Stage Renal Disease (ESRD) population in the United States (1). Approximately 600,000 Americans are affected and although only half progress to ESRD, cost for renal replacement therapy alone exceeds 1 billion dollars annually. Both the PKD1 and PKD2 genes have been identified and their structures determined. Currently, multiple strategies are being developed that may cure or significantly alter the course of ADPKD. Given that ADPKD slowly progresses with a mean age of diagnosis of 28.5 years and an average age of entry into ESRD of 57 years, determining the salutary effects of promising agents over a short period of time is difficult. Therefore the aim of CRISP is to develop novel imaging strategies that accurately determine disease progression in ADPKD in a timely fashion.

ADPKD is a systemic disorder characterized by cystic involvement in both kidneys leading to renal enlargement, progressive renal insufficiency and ultimately ESRD. Although not all ADPKD patients reach ESRD during their lifetime, risk factors for progression to ESRD are now known. These include but are not limited to early onset hypertension (before age 35), ADPKD diagnosed in utero or during the first year of life, excess of 300 mg of urinary protein excretion/day, and a history of gross hematuria before age 30 in men (2,3). If interventional strategies are going to be successfully implemented in clinical trials involving ADPKD patients, the most suitable patients to treat would be those at risk for progression to ESRD who are still early in the course of their disease, i.e. those with good renal function. To date, this high risk group of patient has not been well characterized with regard to renal volume-renal functional relationships over time. Structure-function relationships in ADPKD suggest that larger kidneys are associated with renal insufficiency (4,5). However most data are cross-sectional, have used ultrasonographic measurement of renal volume and serum creatinine concentration determinations for renal function. Potentially because of these limitations, the relationship between structure (renal volume) and function (glomerular filtration rate) have not been strong or consistent, particularly in those individuals with good renal function. The goal of the CRISP Full-Scale Study is to conduct a prospective, longitudinal study to evaluate the accuracy and validity of magnetic resonance imaging to assess disease progression in ADPKD, defined as a change in cyst and renal volume over time. The study considers the MR based measurements as the gold standard and intends to measure the accuracy of ultrasound relative to MR in determining the extent of cross-sectional cystic involvement.

1.2 The CRISP Multi-Center Study

The objective will be to conduct a multi-center, prospective, longitudinal study to determine if magnetic resonance imaging can detect small changes in renal structural involvement over a short period of time in ADPKD. Sites involved in this study include the Mayo Foundation and University of Alabama at Birmingham as a single center, Emory University and University of Kansas Medical Center. The Data Coordinating and Image Analysis Center (DCIAC) is at Washington University. The primary outcome variables to be measured are changes in renal volume, renal cystic volume and % cystic involvement measured by MR

over time. These will be measured in ADPKD individuals with relatively normal renal function. This study will assess the use of ultrasound to approximate the measurements made by MR with the estimation of % cross-sectional renal cystic involvement. The relationship between these structural changes and changes in renal function, risk stratification for progression to ESRD, or clinical events in PKD will also be determined.

1.3 Eligibility and Patient Recruitment

Participants who are diagnosed with ADPKD between the ages of 15 and 45 with risk factors (2/3 of the study population) or without risk factors (1/3 of the study population) for progression to ESRD with relatively normal renal function will be eligible for recruitment into study. The objective of the recruitment process is to identify ADPKD participants with the appropriate level of renal function who are either at high or low risk for progression to ESRD, who will be available for the entire follow-up period and who are likely to be compliant with the study protocols and visit schedules.

1.4 Imaging in ADPKD using MR

Magnetic resonance (MR) imaging has been used for morphological and functional analysis of various organs, notably brain, heart, kidney, and liver. In the CRISP study, MR will be used as the primary imaging modality to quantify total renal and cyst volumes, while the utility of US as a secondary imaging modality will be tested. Renal parenchyma and cysts will be segmented and quantified in T1- and T2-weighted MR images.

Prior to gadolinium administration, T1-weighted images without fat saturation will be acquired to identify and quantify hemorrhagic cysts that are presented as regions with high signal intensity in these MR images. T2-weighted images with fat saturation will be obtained. Renal and cyst volumes can be calculated from T2-weighted images alone without using T1-weighted images. Segmentation of cysts will be facilitated by means of heavy T2-weighted images in which simple cysts are delineated as very bright structures against dark background. Gadolinium contrast will be administered, and MRA will be performed to accurately localize and measure the renal arteries. Subsequently, T1-weighted images will be repeated where the renal parenchyma will be presented as high signal intensity structures, thereby facilitating the segmentation of whole kidney from surrounding anatomical structures. Segmentation of renal parenchyma and cysts may be performed using co-registered T1 and T2 weighted images. Finally, renal artery blood flow will be measured on each artery using a cardiac-gated phase contrast technique. All MR imaging and flow quantification will be performed during breath-hold to minimize motion or misregistration artifacts.

As part of Phase 1 of this project, the DCIAC has performed renal volume and cyst volume measurements of kidney phantoms. These simulations demonstrated high accuracy in volumetric measurement of total kidney and cysts by MR image acquisition compared to true total renal and cyst volume measurements by water fluid displacement techniques. As well, repeat and between measurement variability within and between observers was acceptably low. The variability of measurement did not significantly differ from site to site or from MR vendor to vendor. Measurement variability in human subjects are being tested during the standardization phase of the study that four subjects with ADPKD traveled to each site.

1.5 Imaging in ADPKD using Ultrasound

It is important to assess ultrasonographic measurement of ADPKD kidneys in conjunction with magnetic resonance imaging to provide correlative and supportive information. Ultrasound is currently the imaging modality of choice for obtaining a diagnosis of ADPKD. As well, ultrasound is currently the most frequently used modality to follow ADPKD patients clinically. Reasons for this are related to cost, patient accessibility and insurance approval for the study. Ultrasound has been used to determine total renal volume, using the formula for a modified ellipse. However, assumptions used when applying this formula may have limitations. Reniform structures are assumed when using this formula and it is expected that all dimensions obtained to measure renal volume obtained in a single view. At present, in ADPKD patients with significant disease involvement as those currently proposed for study, ultrasound does not have the ability to detect and separate all cysts. However, single cyst detection and follow-up is possible. Although accurate and reliable ultrasonographic measurements of renal and cyst volume is difficult, due to increased operator dependency of the measurement and that maximal cross-sectional and longitudinal dimensions can be variable, representative cross-sectional measurements of upper, mid and lower poles of the kidneys and determination of percent non-cystic parenchymal cross-sectional area by ultrasound may provide a useful marker of disease progression in ADPKD

1.6 General Description of the Course of ADPKD

ADPKD is the most common inherited renal disease occurring in approximately 1 in 700 -1,000 individuals and accounts for approximately 4.7 % of the ESRD population in the United States (1). ADPKD is a systemic disorder characterized by the presence of renal cysts as well as cardiovascular (hypertension, mitral valve prolapse, intracranial aneurysms and left ventricular hypertrophy) gastrointestinal (liver cysts and diverticular disease) and extracellular matrix (inguinal hernias) abnormalities (6,7). Renal involvement in ADPKD is characterized by the presence of cysts which develop and expand and result in extreme renal enlargement resulting in ESRD. The majority of ADPKD individuals will enter ESRD by the seventh decade of life (2). The cost of renal replacement therapy alone for ADPKD in the United States is greater than $ 1,000,000,000.00/year. Clearly, interventions successful at curing ADPKD or halting the progression to renal failure are important from both a patient care and health policy perspective and worthy of investigation.

Both PKD1 and PKD2 genes have been located and their structure defined (8,9). Much progress has been made with regard to both gene structure and function. Abnormal regulation of cell growth and replication appear to occur with mutation of these genes. The understanding of the function of the PKD1 and PKD2 genes is progressing so that rational therapeutic approaches to the treatment of ADPKD will soon be available. ADPKD individuals at risk for progressing to ESRD who would benefit from therapeutic interventions need to be identified and well characterized in a longitudinal fashion using the most sensitive markers of disease progression for maximal therapeutic benefit.

1.7 Factors related to End-Stage Renal Disease (ESRD)

ADPKD is a disease of slow renal progression where the majority of patients present with clinical symptoms in the third or fourth decade (6,10). The age of clinical presentation in

ADPKD usually predates entry into ESRD by more than 10 years (2). In addition, although the majority of ADPKD patients will enter ESRD by the seventh decade of life, there are individuals who remain oligosymptomatic and die of causes unrelated to ADPKD. Given the late age of presentation, the slow rate of progression to renal failure, and the uncertainty of eventual progression to ESRD, it is necessary to 1) target ADPKD individuals at greatest risk for progression to ESRD to demonstrate therapeutic efficacy of an intervention and 2) identify surrogate markers that can accurately detect progression of renal disease in ADPKD in relatively short period of time, early in the course of the disease.

In large clinical cohorts of ADPKD patients, specific risk factors for progression to ESRD have been identified. Those who have inherited the PKD1 as opposed to the PKD2 mutation have a more aggressive disease resulting in an earlier age of entry into ESRD (11). Male gender, hypertension diagnosed before the age of 35, gross hematuria before the age of 30 in men, the presence of the ACE DD polymorphism, a family history of essential hypertension, ADPKD diagnosed in utero or in the first year of life, more than three completed pregnancies, and greater than 300 mg/day of urinary protein excretion in both adults and children are associated with faster progression to ESRD (12,17,23). The scope of CRISP cannot possibly include all age groups with all risk factors and will focus on those where treatment may benefit and that are not limited to gene type or gender.

In ADPKD, renal structure has an inverse relationship with renal function where larger kidneys are associated with poorer renal function (18). However, the relationship between renal size or volume and function in ADPKD is not linear in all stages of ADPKD. Investigators (10,18) have suggested that no uniform relationship may exist between structure and function in ADPKD. Significant renal growth can occur with relatively stable renal function until a critical point where renal function begins to deteriorate. Following this point, the rate of change in renal function may correlate with change in renal size. At present, it is not clear if there is a critical renal volume where renal functional deterioration begins in ADPKD, or if small undetectable but significant changes in glomerular filtration rate (GFR) occur early in the disease when renal structural involvement is increasing. Therefore there may be a constant inverse relationship between GFR and volume, even early in the course of ADPKD particularly in those at greatest risk for progression to renal failure. Importantly, increases in renal volume over time may predict future loss of renal function and be a more sensitive marker of disease progression in ADPKD than change in GFR.

Clinical features associated with increased renal volume are also associated with a faster rate of progression to renal failure. Hypertensive ADPKD patients with normal renal function, demonstrate larger renal volumes than their normotensive counterparts matched for age and gender (20). Gross hematuria, another risk factor for progression to ESRD, is associated with larger renal size (5). ADPKD children demonstrate larger renal volumes when compared to their unaffected siblings and ADPKD hypertensive children have a threefold greater rate of increase in renal volume as compared to their normotensive age-matched ADPKD counterparts (20).

Recent studies indicate race (Afro-American) may be a risk factor for progression to ESRD in ADPKD (21-23). A cross-sectional report from Network 8 of the USRDS suggests that Afro-Americans with ADPKD have a more severe form of renal disease with an earlier age of onset of hypertension and renal insufficiency. This is consistent with other renal diseases such as diabetic nephropathy, hypertensive renal disease, chronic transplant rejection and systemic lupus erythematosis (24-26) where Afro-Americans demonstrate a more

aggressive course of renal disease. At present, the potential mechanisms for differences in disease progression across race in ADPKD are not clear. Types of PKD mutation may differ across race, however, the relative incidence of ESRD in the Afro-American and Caucasian ADPKD populations mirrors the relative frequencies of the two populations in the United States (27).

Racial differences in response to renal injury may also play an important role in differences in renal outcome between Afro-Americans and Caucasians. In contrast to previous observations that age of entry into ESRD in Afro-Americans with ADPKD is significantly earlier representing a more aggressive form of disease, there are reports that both Afro-American men and women with ADPKD enter ESRD at a similar age to their Caucasian counterparts. The average age of entry into ESRD was 63.8 and 66.3 years in Afro-Americans with and without a family history of ESRD and 60.8 and 62.8 years in Caucasians with and without a family history of ESRD (28). Why study results differ may be due to different study population size, cross-sectional as opposed to prospective data acquisition, and the presence of sickle cell disease in Afro-Americans in some reports (21-23). Conversely, ESRD registry data is limited with regard to assessing many confounding variables that can impact disease progression and may not represent the entire spectrum of ADPKD within a given population. It is important to determine if Afro-American race is a risk factor for progression to ESRD so that if differences exist, those high risk individuals can be targeted for interventional therapy. As well, if differences across race exist with regard to progression of renal disease it is important to determine potential mechanisms responsible for the differences seen.

1.8 Treatment of PKD

Previous clinical studies assessing interventions aimed at halting or slowing the progression of renal disease in ADPKD have not been successful (29-31). Reasons for the lack of benefit found are not related to the treatment applied but more related to study design, particularly the late stage of disease of the ADPKD subjects studied. The use of multiple interventions within study groups and short study duration have been problematic. Interventional studies in ADPKD patients have enrolled individuals with massive cystic involvement and chronic renal insufficiency (29,30) where potentially helpful treatment may have been instituted too late to be of benefit. Importantly, therapeutic interventions that target mechanisms responsible for disease progression specific to ADPKD may not have been used. In contrast to human clinical trials in ADPKD, non-gene modulating interventional studies in both genetic and acquired renal cystic models in non-human experimental animals have been successful in slowing the rate of renal progression particularly when administered early in the course of the disease. Factors which have shown structural or functional benefit include blockade of the renin-angiotensin-aldosterone system (32), dietary protein restriction (33), soy protein based diet (34,37), dietary supplementation with sodium bicarbonate and potassium citrate (35), administration of HmGCoA reductase inhibitors (36), dietary supplementation with flaxseed (35). In contrast, factors which accelerate the disease in the rat include exposure to growth promoting stimuli including increased protein intake, ammonium chloride and decreased potassium intake (38). Given successful interventions in animal models of polycystic kidney disease, and the recent advances in understanding the molecular mechanisms responsible for the development of renal cystic disease in ADPKD,

it is likely that interventional studies aimed at a cure or halting progression of renal disease in ADPKD could be tested in humans. In order to perform such studies, it is necessary to identify appropriate ADPKD subjects and to characterize these subjects with regard to the most accurate and reliable markers of disease progression.

1.9 Specific Aims

1. To determine the rate of change in measured renal volume, cystic volume and non-cystic renal parenchymal volume using magnetic resonance imaging over 3 years in a selected cohort of ADPKD individuals.
2. To determine if ultrasound measurement of cross-sectional cyst area based on representative cross-sectional images is similar to percent cyst volume based on total renal volume and cyst volume measurements obtained by MR.
3. To determine if changes in renal volume, cystic volume and non-cystic renal parenchymal volume will correlate with changes in renal function in ADPKD individuals.
4. To determine which factors predict disease progression defined as an increase in total renal volume, cyst volume and percent cyst volume over time.
5. To determine if changes in renal volume, cystic volume and non-cystic volume and decline in glomerular filtration rate will be greater in ADPKD individuals categorized as high risk in comparison to ADPKD individuals categorized as low risk for progression to renal failure.
6. To determine if correlation between changes in renal volume, cystic volume, non-cystic renal parenchymal volume exists with the occurrence of signs, symptoms and complication of ADPKD including but not limited to, the development of hypertension, frequency and severity of pain, and frequency and duration of hematuria.

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2 Study Organization

The Steering Committee has appointed a number of committees in order to more efficiently administer the study. These sections describe their roles.

2.1 Office of the Chair

The chair of the Steering Committee oversees the planning phases of the study and coordinates its smooth functioning. Specifically, the chair will officiate at the meetings of the Steering Committee during phase I of the study and participate in the conference calls of the study's Executive Committee. He coordinates the design of the validation protocols, the final study protocol, the Manual of Procedures and forms developed by the Steering Committee. The chair will coordinate recommendations from subcommittees and their chairs and will serve as a liaison with the program office. The chair of the Steering Committee will also participate in evaluation of study progress and recruitment activities. He will act as a spokesperson for the study to various scientific functions including discussion of the study to the press and outside organizations. Finally, the chair of the Steering Committee will represent the study at meetings and conference calls with the External Advisory Committee. The chair of the Steering Committee is William M. Bennett, MD[1].

2.2 Steering Committee

The Steering Committee will be charged with the development of study procedures and protocols and will include the principal investigators at the clinical sites, representatives of the data-coordinating center and the study central administration, the study statistical core and data analysis facility and the chief radiology investigator at each of the study sites. There will also be representation on the Steering Committee from the staff of NIDDK. The Steering Committee will have face-to-face meetings during phase I of the study. They will design the collaborative protocols, the standardization and validation studies, the final study protocol, the Manual of Procedures and forms and they will charge various subcommittees with specific tasks such as publications, quality control, intellectual property forms, imaging data management and data safety and monitoring board and be a liaison with the NIDDK program office. The members of the Steering Committee are shown in the CRISP Directory[2].

2.3 Publications Committee

2.3.1 Introduction

The policy of the CRISP study concerning publications and presentations is designed to achieve five objectives:

1. To assure timely publication of the results of the CRISP Study to the appropriate professional audiences,
2. To avoid premature publication of results that might compromise the performance of the study (such as by publishing trends before they become statistically convincing) or

[1] See URL `http://www.pkd.wustl.edu/pkd/Directory/chair.html`
[2] See URL `http://www.pkd.wustl.edu/pkd/Directory/steering.html`

that might compromise the ability to publish the results in high quality peer reviewed journals (as by premature release to the lay press),
3. To maintain high standards of quality of all material published by the CRISP Study,
4. To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees, and
5. To assure attribution of credit to all of the professionals participating in the CRISP Study.

To accomplish these ends, it is the policy of the CRISP Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Study Chairman to specifically appointed writing committees, and that all such materials must be reviewed and approved by the Publication Committee and/or the Steering Committee before publication.

The membership of the Publications Committee is listed in the CRISP Directory[3].

2.3.2 Scope of Policy, and Exception for Local Publicity Materials

All materials to be presented orally or submitted for publication or dissemination by individuals associated with CRISP Study and dealing with any aspect of the CRISP Study must receive prior review and approval by the Publications Committee and/or Steering Committee with the following exception:

> Material prepared for publicity purposes either nationally or within the recruitment region of a CRISP Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the CRISP Study and its objectives need not be reviewed by the Publications Committee. Such material must be limited to a background discussion of the scope of the Study and a description of the CRISP Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously unpresented and unpublished CRISP outcomes or generate a citable professional reference.

2.3.3 Source of Suggestions for Publications of the CRISP Study

All participants in the CRISP Study are invited to suggest topics appropriate for preparation as abstracts, paper reviewed papers, or chapters and reviews from the CRISP Study. Such suggestions should be made in writing to the Study Chair (cf. Section 2.1), with copies forwarded to the Chair of the Publications Committee, who shall review the request to be certain that there is no overlap with material previously assigned to other writing committees. Where such overlap exists, the Chair of the Publications Committee may make recommendations to the Study Chair that the suggestion be referred to an existing writing committee, that additional study participant be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter rests with the Study Chair.

[3]See URL `http://www.pkd.wustl.edu/pkd/Directory/steering.html`

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

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

2.3.4 Assignment of Writing Committees

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

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

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

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

2.3.5 Classes of Reports of the CRISP Study

There are four classes of report of the CRISP Study:

Class A: Reports of the major outcomes of the Study. It is assumed that there will generally be only one or two such all over reports derived from each Phase of the Study. Generally these reports will be prepared by the Executive Committee serving as the writing committee, with the Study Chair as the Chair of the writing committee.

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

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

Class D: Reports of investigations initiated outside of the CRISP Study, but using data or samples collected by the CRISP Study. The investigators may be CRISP or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the CRISP Study itself.

2.3.6 Authorship

The authorship policy of the CRISP Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports (cf. Section 2.3.5), are derived from the efforts of the entire CRISP professional staff. Thus, all reports, of whatever Type, must give recognition to all the participants of the CRISP study, and reports of Types A and B must give primary recognition to the entire study professional staff. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of the results of the CRISP Study. The CRISP authorship policy attempts to recognize each of these goals. The authors of CRISP publications will be listed as detailed below for each type of publication.

Type A Publications:

abstracts: "From the CRISP Study, presented by XXXX" (This will usually be by the Study Chair).

papers: "from the CRISP Study"

The CRISP participant box (cf. Section 2.3.7), detailed below, must be included in these papers.

Type B Publications:

abstracts and papers: "from the CRISP Study[1], prepared by [Chair of the writing committee, other members of the writing committee listed alphabetically]"

The CRISP Participant Box (cf. Section 2.3.7) will be included in all papers if this can be arranged with publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

It will be stated in a footnote that the names of the writing committee are listed alphabetically after the name of the committees chair.

Type C and D Publications:

> **abstracts and papers:** "by [members of the writing committee in any order acceptable to them] and the CRISP Study"
>
> The Participant Box (cf. Section 2.3.7) will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. In type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

2.3.7 Listing of Professional Participants in the CRISP Participant Box

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

- NIH
- Study Chair
- Image and Statistics Coordinating Center
- Clinical Centers (in alphabetical order)
- Central Laboratories (in alphabetical order)

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

2.3.8 Acknowledgment of Support and Reprint Addresses

Acknowledgment of grant support to be used in all papers reporting results of the CRISP Study (in the case of ancillary studies, additional sources of support should be cited as appropriate):

> The CRISP Study is supported by the Division of Kidney, Urologic and Hematologic Disease of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, through cooperative agreements.

The following information regarding reprint requests should be included in all papers prepared by the CRISP Study. The NKUD Clearing House will maintain an inventory of all CRISP Studies and will actually mail out the reprints:

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

2.3.9 Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

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

2.3.10 Review of Abstracts and Presentations by the Publications Committee

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

1. The writing committee wanting to submit an abstract, give a talk, or submit other material for which there is an explicit submission deadline shall contact the Chair of the Publications Committee. In the event that the Chair is unavailable, the Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of three members of the Publications Committee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be mailed by the submitter directly to the subcommittee.
2. The members of the subcommittee shall review the material and notify the Chair solely of the approval or disapproval. If there is unanimous approval, the Publications Committee Chair (or Alternate Chair) shall inform the submitter that he/she has CRISP Study approval for the submission. In the event of a split vote for approval, the issue will be reviewed by the Publications Committee Chair (or Alternate Chair) with the Chair of the CRISP Steering Committee (or in his/her unavailability with the Chair of the Operations Committee) whose decision will be binding.
3. All materials submitted for approval in this fashion will be distributed by mail, together with notice of the disposition, to all members of the Publications Committee and to the Chair of the Steering Committee. All approved materials will also be forwarded to the NIH Trial Coordinator, and for record purposes to the Principal Investigator of the Image and Statistics Coordinating Center, and will be distributed to the entire membership of the Steering Committee at the next meeting of that Committee as an Appendix to the report of the Publications Committee.
4. In the case of abstracts or other similar written material, the entire material to be submitted must be sent by the submitter for review by the appointed subcommittee.
5. In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.

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

2.3.11 Review of Papers by the Publications Committee

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

1. The Chair, Publications Committee, shall appoint a panel of three primary reviewers, two of whom must be Publications Committee members, and one of whom may be any professional member of the CRISP Study Group with appropriate expertise. The Chair shall distribute the material to all members of the Publications Committee and to the Principal Investigator of each center participating in the CRISP Study. The three members of the review panel shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire Publications Committee. The PI's of the various clinical centers will be given a deadline by which any comments or critiques that study participants at their center may wish to make to the Chair, Publications Committee. This mechanism will assure that each professional participating in the CRISP Study will have an opportunity to review any materials that will be submitted for publication bearing his/her name as a participant and co-author.
2. The Chair, Publications Committee shall schedule a meeting of the Committee (generally by conference call), including review of papers and other non-time critical materials as Agenda items. The reviews of the panel members and any comments received from the center PI's will be distributed to the committee with the agenda.
3. While discussion of the submitted papers and other materials will be led by the three appointed reviewers, all members of the Committee will be invited to participate and all shall vote on final disposition.
4. In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.
5. The Chair, Publications Committee shall be responsible for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non-acceptance of the material as submitted but with suggestions for revision and resubmission, he or she and the writing committee may agree not to proceed with a report to the Steering Committees at that time, pending revision and resubmission.

6. If there is a recommendation for approval or final approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the chair, Publications Committee shall report this outcome in writing to the Steering Committee for final action. In the case of a dispute between the Publications Committee and the author(s), the Chair, Publications Committee shall provide a copy of the submitted material and a summary critique to the Steering Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.
7. The authority to grant final approval for a formal scientific paper of the CRISP Study rests with the Steering Committee.
8. All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the Steering Committee. All materials receiving final approval by the Steering Committee will also be forwarded to the NIH Trial Coordinator, and for record purposes to the Principal Investigator of the DCIAC.
9. In the event that editors of a scientific journal to which an approved CRISP scientific manuscript is submitted request a revision to a paper, the revisions should be submitted to the Publications Committee to review the revision, and every effort will be made to expedite such repeat reviews.

2.3.12 Criteria for Review of Materials by the Publications Committee

All materials submitted to the Publications Committee will be reviewed for acceptability on two grounds:

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

2.3.13 Maintenance of Records of Publications and Presentations

The DCIAC will maintain a record of all official publications and presentations of the CRISP Study, separated into the following categories:

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

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

2.3.14 Acknowledgment and Acceptance of CRISP Policies on Publications and Presentations by the Professional Participants in the CRISP Study

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

2.4 Clinical Committee

The Clinical Committee is charged with developing and dealing with all issues relating to the clinical examination of the participants.

2.5 Data Management and Quality Control Committee

Purpose:

The purpose of this committee is to assure that data logistics are provided as appropriate for all CRISP studies in a uniform manner, that the recruitment of participants and transfer of information to the DCIAC proceeds in a timely manner and that the research data are adequately verified.

Procedure:

The DCIAC Project Coordinator should schedule the Data Management and Quality Control Committee meeting immediately before or after the meetings of the Steering Committee. Membership should consist of:

- Chair of the Steering Committee
- Chair of the Data Management and Quality Control Committee
- Chair of the Forms Committee
- Chair of the Clinical Committee
- Chair of the Imaging Committee
- Study Statistician
- DCIAC Data Coordinator
- DCIAC Project Coordinator

Review the following items at the meeting:

- Current participant accrual rate
- Verification of research data (deviations from protocol and missing data)
- Review of quality editing procedures
- Data needed for analysis
- Data management and quality control concerns
- Reporting of Adverse Effects

Document the results of the meeting and forward concerns to the Steering Committee.

2.5.1 Ancillary Protocol Development and Approval

Purpose:

This standard operating procedure (SOP) provides an overview of the development and approval process for studies.

Process of Review of Crisp Ancillary Studies

Who	What
Investigator	Develops concept
Steering Committee	Reviews concept, determines development track
Investigator	Develop full written protocol
Ancillary Studies Committee	Reviews study
Steering Committee	Approves protocol
External Advisory Committee	Approves protocol
IRB	Approves protocol (if necessary)
Investigator	Protocol Implemented

2.5.2 Data Logistics Development Process: Coordination Process

Purpose: The purpose of this procedure is to assure development of data logistics for all studies conducted by CRISP. Data logistics are coordinated at various stages of the protocol development process.

Procedure:

First draft of protocol

Who	What
Project Coordinator Database Specialist Ancillary Studies Committee	Review first draft of protocol for consistency between Protocol sections; review stratification and descriptive factors, grouping factors appropriate to the goals of the Study.
Forms Committee	Develop Participant-completed forms (see Development of Participant-completed Forms Procedures).
Investigators	Develop descriptive factors to be included on the Eligibility Checklist.
Project Coordinator	Forward concerns to the Steering Committee.

Final Protocol Review

Who	What
Project Coordinator	Arrange the protocol review meeting and e-mail each committee member with the details.
Database Specialist	Forward a copy of the current protocol and forms to all meeting participants
Steering Committee EAC	Review Protocol and forms.
Steering Committee EAC	Approve or disapprove protocol.

2.5.3 Study Conduct Management

Purpose: To ensure that the goals and objectives of the protocol are carried out following Protocol and NIH guidelines. Study conduct management consists of:

- Identification of potential Study participants.
- Registration of Study participants.
- Management of patients according to the protocol.
- Data management.

Procedure:

Participant identification. Identify potential Study patients.

- Facilitation is aided by Eligibility Criteria Checklist.
- Identification of potential participants can occur through physician referrals, patient inquiries, referrals by PKRF, etc.
- The Study Coordinators will maintain a list of potential participants.
- The Study Coordinators will schedule appropriate screening and enrollment tests.

2.5.4 Development of Participant-Completed Forms

Purpose: Participant-completed forms include any questionnaire, survey or diary that will be filled out by a participant and used in the analysis of the study or to document participant activities. The purpose of this procedure is to assure that forms are developed in a standardized format for all CRISP studies.

Applicable Policies: Copyrighted forms may be used only after permission has been obtained from the author by the DCIAC. If "blanket" permission exists for use of a form, no further permission is required.

Forms that must be purchased from the author may not be reformatted.

Participant-completed forms will be in the form of a booklet when a set number of forms can be supplied to all participants on a study. If forms will not be in booklet format, they will be in the standard page format.

Procedure:

Who	What
DCIAC	Supply participant-completed forms with the first draft of a protocol to the Steering Committee.
Database Specialist	Process and date the forms using the date of the protocol draft.
DCIAC	File a copy of the forms in DCIAC Files.
Forms Committee	Review and revise forms.
Project Coordinator	Forward original and revised forms to the Steering Committee.
Steering Committee	Review and revise forms at the data management meeting.

2.5.5 Development Of Data Collection Forms

Purpose: Data collection forms are forms used to collect data for use in the analysis of a study. The purpose of this procedure is to assure that all data collection forms are developed in a standardized format.

Applicable Policies: Only data items necessary for analysis and patient evaluation are included on data collection forms.

All forms will be study-specific.

Procedure:

Who	What
DCIAC Project Coordinator	Develop first draft of forms when the protocol is received for peer review
DCIAC Project Coordinator	Send forms to Database Specialist for word processing
Database Specialist	Process the forms, dating them
Forms Committee	Review and revise the forms
Database Specialist	Forward forms to Steering Committee for review.
Database Specialist	Forward final forms to the PCC.

2.5.6 Development Of An Eligibility Checklist

Purpose: The eligibility checklist is a physician-/R.N. Study Coordinator-completed form, signed and dated by Principal Investigator. It is used to confirm participant eligibility for a specific protocol. This is to assure a participant is eligible for the protocol and all tests and procedures have been met and confirmed.

Applicable Policies: All Inclusion and Exclusion Eligibility criteria must be met as is written in the Manual of Procedures for a participant to be eligible.

If, according to the eligibility criteria, an "ineligible participant" is felt to be a suitable Study Participant by the Principal Investigator, that Principal Investigator has the right to seek the advice and approval from the Steering Committee regarding the participant's deviation from eligibility.

Approval for a participant to enroll, who does not meet the eligibility criteria in a study, must be obtained from the CRISP Steering Committee on an individual and case by case basis.

Documentation from the CRISP Steering Committee of that approval must be obtained and that record filed with the participant's file, the PCC IRB as well as the PCC Study Binder and the Project Coordinator.

Procedure:

Who	What
DCIAC	Create the Eligibility Checklist form using the protocol.
Project Coordinator Forms Committee	Review the form and return completed form to the Steering Committee.
Steering Committee	Make any necessary changes prior to activation.
Database Specialist	Process the Eligibility Checklist form and forward to the PCC
DCIAC	Process any Deviation from Eligibility forms.

2.5.7 Forms Revision Process

Purpose: The purpose of this procedure is to assure uniform revision of all data collection and participant-completed forms.

Procedure:

Who	What
Anyone	Send any proposed forms revisions to the Project Coordinator and/or Database Specialist
Project Coordinator Forms Committee Database Specialist	Review proposed revision for data collection and analysis implications.
Project Coordinator	Discuss revisions with the Study Statistician and Steering Committee as necessary.
Database Specialist	If all approve, send the forms to Database Specialist for processing, including changing revision number and date.
Project Coordinator	File a copy of the forms in the Project Coordinator's Study File.
Database Specialist	Forward a copy of the revised electronic forms to the PCC Study Coordinators and the Steering Committee.

2.5.8 Electronic Forms Development Process

Purpose: The Electronic Forms are developed for data entry and are study-specific. Using the WDES, the original paper forms remain at the PCC and the data entry/correction is done by personell familiar with the data collection process. The purpose for electronic form documentation is to facilitate data retrieval for a specific purpose.

Applicable Policies: Electronic forms must be created for all forms developed for data collection where the data is to become part of the CRISP study data base.

If data collection forms are incomplete, or answers are not within limits set for a specific protocol (or form), an error will show on screen notifying the Database Specialist that something is incorrect and needs to be verified.

Procedure:

Who	What
Database Specialist	Following approval of a form, create HTML version of the form.
Database Specialist	Process HTML code with WDES preprocessor to produce the shell of SAS code.
Database Specialist	Revise SAS code until all elements functioning correctly to add and edit data from form.
Database Specialist	Create JavaScript code to provide validity checks during data entry procedure.
Study coordinators	Pretest data entry.
Database Specialist	Put into production.
Database Specialist	Produce annotated form with SAS variable names, etc.

2.5.9 Data Monitoring

Purpose: The data monitoring process is designed to insure the highest possible quality of the CRISP data base.

Applicable Policies: The DCIAC will generate reports to the study coordinators about missing data, questionable data values, missing forms, apparent missed visits, etc. on a periodic basis. These reports will primarily be available on the CRISP website[4] and e-mail notifications will also be sent.

Under direction from the Steering Committee performance reports will be created on at least a monthly basis outlining the current status of recruitment, characteristics of participants enrolled, promptness of data entry, missed visits, missing forms, etc.

Procedure:

Who	What
DCIAC	Create reports about missing data, questionable data values, missing forms, apparent missed visits, etc.
DCIAC	Create a production schedule for the running of each of the reports and notify study coordinators about each newly generated report.
Study Coordinators	Resolve deficiencies noted on reports.
DCIAC	Draft performance reports.
Steering Committee	Approve performance reports.
Database Specialist	Implement performance reports.
Database Specialist	Create a production schedule for the running of each of the reports and notify Steering Committee about each newly generated report.

[4]See URL `http://www.pkd.wustl.edu`

2.6 Intellectual Property Committee

2.6.1 Mission statement and Function

The mission of the Intellectual property committee (IPC) is to ensure intellectual properties such as collected data and inventions that arise in the course of the CRISP study are appropriately protected and become available to the public. The functions of the IPC are:

1. Serve as the initial forum for decision and appeal of intellectual property issues. Decisions in this regard are to be recommended to the Steering Committee for final decision.
2. Develop and propose policies relating to ownership of intellectual property. These policies will require approval by the Steering Committee.
3. Evaluate and make recommendations for use of data by specific outside investigators (This duty may overlap with the Ancillary studies committee)
4. Evaluate if new knowledge gained in the CRISP study has commercial or patent potential.
5. All policies and recommendations need to be in accordance with NIH and federal guidelines, and when possible in accordance with individual institutional guidelines.

The membership of the Intellectual Property Committee is shown in the CRISP Directory[5].

2.7 Forms Committee

2.7.1 Mission Statement and Function

To design, monitor and revise useful forms for the recording of the data that will be of central importance in the execution of this research. For membership in the committee see the the CRISP Directory[6].

2.8 Imaging Committee

2.8.1 Mission Statement and Function

The mission of the Imaging committee (IPC) is to develop and implement accurate and reproducible imaging techniques which will be used to monitor progression of ADPKD and early treatment interventions in ADPKD.

1. Serve as the initial forum for decision and appeal of imaging-related issues. Decisions in this regard are to be recommended to the Steering Committee for final decision.
2. Develop and propose the study protocols for the imaging studies
3. Establish standardization of the imaging data
4. Formulate strategies to improve image data acquisition, collection, transmission, storage, and analysis
5. Evaluate the training of imaging technologists and quality controls
6. Assist the members with imaging-related technical supports

[5]See URL `http://www.pkd.wustl.edu/pkd/Directory/intellectual.html`
[6]See URL `http://www.pkd.wustl.edu/pkd/Directory/steering.html`

For membership in the Imaging Committee see the CRISP Directory[7].

2.9 Ancillary Studies

2.9.1 Ancillary Studies Definition

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

2.9.2 Funding of Ancillary Studies

Funding will not be provided by the main study, but will require an independent source of funding.

2.9.3 Approval Procedures for Ancillary Studies

Proposals may be generated by a participating clinical center or by other interested investigators providing at least one center is includes a co-investigator. These applications are submitted to the DCIAC for Review by the Ancillary Studies Subcommittee.

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

- Hypothesis to be tested
- Specific outcome variables that will be assessed
- Need for data from the DCIAC
- Significance of the proposed ancillary study
- How will performance of this ancillary study affect the main CRISP study? Specifically: Will there be any deviations from the main CRISP study protocol? If so, what will they be?

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

- Hypothesis to be tested.
- Significance of the study
- Conduct and performance of the study including specifying the study population and the data to be collected.
- Sample size justification
- Quality control of the data
- Data analysis methods.

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

[7]See URL `http://www.pkd.wustl.edu/pkd/Directory/steering.html`

2.9.4 Guidelines for Genetic Ancillary Studies

Any genetic ancillary studies require submission to the Ancillary Studies Subcommittee similar to any other protocols. All submission for genetic grants must have either the principal or a co-investigator of a respective CRISP center intimately involved in the study.

2.9.5 Publication of Ancillary Study Results

The policies regarding publications and presentation of the results of ancillary studies are the same as those governing the publications and presentations of results of the main study (see Publications Committee (cf. Section 2.3)). Any potential publication needs to be reviewed by the Publications Committed prior to submission. These policies are designed to:

- Assure timely publication of the results to the appropriate professional audiences.
- Avoid premature publication of results that might compromise the performance of the main study or that might compromise the ability to publish the results in high quality peer reviewed journals.
- Maintain high standards of the published material.
- To guard against duplicate publication of results.
- Assure equitable attribution of credit to all of the professionals participating in the ancillary study and the CRISP study.

Membership of the Ancillary Studies Committees are shown in the CRISP Directory[8].

2.10 External Advisory Committee

An independent committee supported by the NIDDK and composed of experts in nephrology, biostatistics, radiology, clinical trials, and bioethics, who are not otherwise involved in the study, will be established to review periodically the progress of the study (described in detail under Terms and Conditions). This Committee will also be responsible for reviewing the acceptability of initial data-quality monitoring plans established by the Steering Committee and the subsequent monitoring of data quality by means of reports prepared by the DCIAC.

2.11 NIDDK Program Office

The NIDDK will appoint a Project Officer, within the Division of Kidney, Urologic and Hematologic Diseases, to assist the Steering Committee and External Advisory Committee in carrying out the study. The Project Officer will provide scientific support to awardees' activities, including protocol development, quality control, interim data monitoring, final data analysis and interpretation, preparation of publications, and overall performance monitoring.

[8]See URL `http://www.pkd.wustl.edu/pkd/Directory/ancillary.html`

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3 Study Design

3.1 Study Time Table

The anticipated duration of study is 37 months, beginning in November 2000 and completing in November 2004.

Month 1: Start enrollment

Month 11: Finish enrollment: Last baseline visit (September 15th, 2001)

Month 35: Finish last year 3 visit (September 15th, 2004)

Month 37: Finish data analysis and manuscript preparation (November 30th, 2004)

3.2 Study Calendar

Time Line	Visit Number	Form Name	Form Number
Screening Visit	SV01	Identification	1
		Exclusion/Inclusion Criteria	1a
Enrollment Visit	SV01 or SV02	Registration	2
		Informed Consent	Site-Specific
Baseline Visit	BV01	Initial Screening	3
		Baseline Visit	4
		OTC/Prescribed/Other Drugs	5
		Reproductive History	6
		MR Session	7
		US Session	8
		GFR Collection Study	9
		GFR Reporting	10
		Physical Findings	11
		Symptoms	12
		Blood Pressure	14
		Family History	16
		Renal Blood Flo	17
Interim Visits	IV0.3 (3 months)	Follow-up Study	13
	IV0.6 (6 months)		
	IV0.9 (9 months)		
Follow-up Visit	FV01	MR Session	7
		US Session	8
		GFR Collection Study	9
		GFR Reporting	10
		Physical Findings	11
		Blood Pressure	14
		Renal Blood Flo	17
		24 Hour Urine	21

Time Line	Visit Number	Form Name	Form Number
Interim Visits	IV1.3 (3 months) IV1.6 (6 months) IV1.9 (9 months)	Follow-up Study	13
Follow-up Visit	FV02	MR Session US Session GFR Collection Study GFR Reporting Physical Findings Blood Pressure Renal Blood Flo 24 Hour Urine	7 8 9 10 11 14 17 21
Interim Visits	IV2.3 (3 months) IV2.6 (6 months) IV2.9 (9 months)	Follow-up Study	13
Follow-up Visit	FV03	MR Session US Session GFR Collection Study GFR Reporting Physical Findings Blood Pressure Renal Blood Flo 24 Hour Urine	7 8 9 10 11 14 17 21
Special Events	When Needed	Death Notification Transfer 18 Missed Visits/Drops Event	15 19 20

3.2.1 Visit Windows

Visit or Contact	Time Window Limits
IV0.3 - Telephone Interview	12-14 weeks post BV01
IV0.6 - Telephone Interview	25-27 weeks post BV01
IV0.9 - Telephone Interview	38-40 weeks post BV01
FV01 - Clinic Visit	51-53 weeks post BV01
IV1.3 - Telephone Interview	64-66 weeks post BV01
IV1.6 - Telephone Interview	77-79 weeks post BV01
IV1.9 - Telephone Interview	90-92 weeks post BV01
FV02 - Clinic Visit	103-105 weeks post BV01
IV2.3 - Telephone Interview	116-118 weeks post BV01
IV2.6 - Telephone Interview	129-131 weeks post BV01
IV2.9 - Telephone Interview	142-144 weeks post BV01
FV03 - Clinic Visit	155-157 weeks post BV01

3.3 Participant Eligibility

3.3.1 Inclusion Criteria:

ADPKD participants including no less than 20% Afro-American (self identified). Equal numbers of males and females between the ages of 15 and 45 years of age with relatively normal renal function will be recruited. Participants will be recruited based on their risk for progression to ESRD in a 2:1 ratio of high:low risk individuals. These targets will be monitored study-wide during recruitment and recruitment goals adjusted accordingly.

High risk:

- Hypertension diagnosed prior to age 35 years
- Gross hematuria in males with ADPKD prior to age 30 years
- Greater than 300 mg urinary protein excretion in 24 hours in an adequate urine collection, defined as $>$ 15 mg/kg/day and $<$ 25 mg/kg/day creatinine excretion
- Diagnosis of ADPKD in-utero or in the first year of life

Low Risk:

- Absence of all risk factors

Exclusion Criteria at screening:

1. Age at the time of enrollment: less than 15 years
2. Age at the time of enrollment greater than 45 years
3. Serum creatinine concentration greater than 1.4 mg/dl in ADPKD women
4. Serum creatinine concentration greater than 1.6 mg/dl in ADPKD men
5. Weight greater than 350 lbs.
6. Previous partial or total nephrectomy
7. Congenital absence of one kidney
8. Previous renal cyst reduction performed percutaneously, laparoscopically, or surgically
9. Documented presence of renal vascular disease
10. Presence of indwelling ureteric stents
11. Greater than 2.0 grams of urinary protein excretion in a 24 hour period
12. Renal parenchymal infection within six months of entry into study.
13. Recent (less than 6 months) hospitalization for an acute illness (not including elective admissions)
14. Recent (less than 6 months) myocardial infarction or cerebral vascular accident (including transient ischemic attack, cerebral infarction, subarachnoid hemorrhage, or intracranial aneurysm rupture)
15. Current unstable angina
16. Diagnosis of non-insulin dependent or insulin dependent diabetes mellitus
17. Presence of systemic illness with renal involvement (systemic lupus erythematosis)
18. ADPKD women who are pregnant, currently lactating or less than six months after delivery of a child
19. Significant pulmonary, cardiac, or liver disease not including polycystic liver disease

20. History or presence of malignancy
21. Significant anemia (Hemoglobin less than 10 mg/dl)
22. Significant thrombocytopenia (Platelet count less than 70,000)
23. Significant neutropenia (ANC less than 500)
24. Current psychological makeup of the potential subject that in the discretion of the principal investigator indicates that the subject will not successfully complete the study (eg: psychiatric illness precluding informed consent, unable to maintain compliance with study visits)
25. Unable to provide written informed consent
26. Presence of MR incompatible clips
27. Previous clipping for intracranial aneurysm
28. Presence of cardiac pacemaker
29. Known claustrophobia to MR scanners

Rationale for Criteria:

These criteria define a cohort of ADPKD participants who are early in the course of their disease but at risk for progression to ESRD. Hence, the rationale for age and renal function selection. A second small subset of participants at low risk for progression that are similar in age, race and gender distribution are included in the cohort so that differences in progression to renal failure can be detected. Given the nature of the study design and the specific aims being addressed, the participants considered for this study were not selected so that a natural history study of PKD could be performed but rather a radiological progression study. Exclusion criteria for this study were determined so that not only the correct participants would be recruited but that the integrity of the study would be maintained. The integrity of the study is ensured by recruiting reliable participants without other diseases (e. g. diabetes mellitus) that may modify progression in ADPKD and that can be safely studied (e. g. those without intracranial aneurysm clips).

Screening Log

All potential participants who are considered for recruitment for CRISP should be logged in the Screening Log which is kept at the PCC. The screening activity will be summarized on a Screening Summary data entry screen at the end of each month.

3.4 Primary Outcome Variables to be Measured

- Renal volume, cyst volume, % non-cystic renal volume by MR
- Change in renal volume, % non-cystic renal volume over time by MR
- % cross- sectional cyst volume by US
- Change in % cross-sectional cyst volume by US over time
- Relationships between changes in volumetric measures and changes in renal function by GFR
- Renal blood flow by MR

For the data collection protocols to support these objectives, see the Measurements (cf. Section 6.2) section.

3.5 Analysis Plans

In the CRISP study, the analysis plans are modeled very closely on the Specific Aims. The specific aims will be discussed separately below.

The general analysis approach will involve the use of mixed effects regression models (Laird and Ware, 1984; etc.) for the data obtained from the four yearly clinical appointments. In this modeling approach, a separate linear model is fit for values over time for each participant, and the regression coefficients (slope and intercept) are assumed to be normally distributed random variables. It is assumed that the change over time (slope) will be linear, and will vary from individual to individual.

Once such models are fit to the data, various models will be tested with both the fitted data and other values:

1. To determine if MR including gadolinium enhancement detects small changes in renal volume, cystic volume and non-cystic renal parenchymal volume over a short period of time (e.g. 1-2 years) in ADPKD individuals.

   The parameters from the mixed effects regression models, especially the average slope and the variance of the slopes across participants will be used to evaluate possible intervention trial designs following procedures similar to those used by Berg, et. al (1993).

2. To determine if ultrasound measurement of cross-sectional cyst area based on representative cross-sectional images is similar to percent cyst volume based on total renal volume and cyst volume measurements obtained by MRI.

   The protocol for CRISP involves image acquisition using both the US and MR modalities. After images are acquired and transferred to the DCIAC for measurement, relationships between the MR and US measures will be assessed. Correlational methods (to assess overall covariation in value) will be used for this comparison since US creates cross-sectional area values and MR produces volume estimates. The cost benefits of using US outcome measures for study designs considered in Specific Aim 1 will also be conducted.

3. To determine if change in renal volume, cystic volume and non-cystic renal parenchymal volume will correlate with change in renal function in ADPKD individuals.

   Over the CRISP study period, changes in the various characteristics of the kidney will be evaluated from the MR and US images. Additionally, renal function data will be obtained from the same patients. Using techniques currently under development in biostatistics (Zucker, Zerbe and Wu, 1995), mixed effects regression models will be fitted for both types of data. These techniques involve the simultaneous evaluation of several growth curves, which influence values in the other estimation.

4. To determine which factors predict disease progression defined as an increase in total renal volume, cyst volume and percent cyst volume over time.

Disease progression (as defined above) will be modeled as a function of both baseline covariates (race, sex, age, other demographic variables) and baseline values of relevant ADPKD variables (baseline kidney size, time since diagnosis, etc). Time-varying covariates, which can also be considered epiphenomena, will be not examined in this part of the analysis.

5. To determine if change in renal volume, cystic volume and non-cystic volume and decline in glomerular filtration rate will be greater in ADPKD individuals categorized as higher risk in comparison to ADPKD individuals categorized as lower risk for progression to renal failure.

   Changes in the various kidney parameters will be modeled using the mixed effects techniques. Using the slope estimates, the differences between the high-risk and low-risk groups will be examined. The main difference which will be tested will involve slope parameters. However, intercept values will be examined as well.

6. To determine if correlation between change in renal volume, cystic volume, non-cystic renal parenchymal volume exists with the occurrence of signs, symptoms and complication of ADPKD including but not limited to, the development of hypertension, frequency and severity of pain, and frequency and duration of hematuria.

   Following the estimation of several different types of growth curves in several different variables, the slope relationships will be examined using correlational methods. The slopes for different variables indicate the change over time for that variable. Thus, slopes which are highly correlated indicate variables which "change together" in a time-varying sense. Correlations between pairs of variables, and possibly regression of several slopes on others will indicate the relationships between the changes in variables. Time dependent covariates will also be included in these modeling efforts.

3.6 Power Considerations

In considering the sample size, we have chosen to focus on the hypothesis that the rate of progression in the high-risk cohort is greater than that in the lower risk cohort. By using prior experience of CRISP investigators with CT images over long followup periods, we have estimated that the average rate of growth in kidney volume for PKD patients is 48 ml/yr with a standard deviation of 44.5. From the analysis of the standardization study which included repeat scans at each site as well as the variability due to inter- and intra-observer variance in estimating total kidney size, we can estimate the residual error as 175. The error term was obtained from this confounded standard deviation because this represents the actual measurement process during the study.

We compute the power using the method of Lefante (Lefante JJ. The power to detect differences in average rates of change in longitudinal studies. **Stat Med** 9:437-46, 1990) to determine the necessary sample size to detect a 50% difference in the average slope (e.g. the average rate of change in the high risk cohort is 48 ml/yr with the average rate in the low risk cohort of 24 ml/yr. For a power of .90, and with twice as many high risk participants as low risk, we will need a total of 165 participants for the entire 3-year period of the

protocol. If we assume that 20% of those recruited will not complete the entire protocol with acceptable images, then we would need to recruit a total of 206 participants. Since the data from those subjects who do not provide all 4 images is still informative, this gives an added assurance that the study will have adequate power.

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4 Participant Enrollment

4.1 Screening Process

4.1.1 General Principles of Screening

The study is designed to test whether or not MR can detect changes in renal volume, cyst volume or change in % cystic involvement in ADPKD individuals over a short period of time. The study is also designed to determine if ultrasound can approximate % cystic involvement reliably in comparison to MR. It will be determined if the changes observed by MR and ultrasound imaging relate to decreases in renal function (glomerular filtration rate) in ADPKD individuals with relatively intact renal function. The objective of the recruitment process is to identify ADPKD participants with relatively normal renal function who are either at high or relatively low risk for progression to ESRD, who will be available for the entire follow-up period and who are likely to be compliant with the study protocols and visit schedules.

Recruitment strategies for the full-scale study include: referrals from local physicians, PKRF newsletters, surveys of local renal disease clinics, local PKRF friends groups, already identified patients known to the Principal Investigators, and local dialysis units. Contact questionnaires will help in determining eligibility of potential subjects. The majority of potential study participants will be identified at the local level, usually known to the Principal Investigator or referred by the National PKRF or the local friends PKRF groups. A chart review (Screening Form 1) can be used to assist in this process. When information is unavailable, clinic visits for the appropriate tests will be scheduled for the participant by the Study Coordinator. Included in this evaluation is obtaining a pedigree. The purposes of the pedigree are 1) to confirm the dominant nature of the inherited renal disease in these individuals, and 2) to identify other family members with ADPKD who may also be eligible for study or individuals helpful in determining PKD1 vs PKD2 gene status by gene linkage analysis. Participants will be asked to sign a consent form indicating their interest in the trial and their availability to undergo tests. Participants who meet all of the inclusion criteria and who are free from all of the exclusion criteria will be admitted to the Baseline Visit.

4.2 Implementation of Eligibility Criteria

Participants who are diagnosed with ADPKD between the ages of 15 and 45 either with risk factors (2/3 of the study population) or without any risk factors (1/3 of the study population) for progression to ESRD with relatively normal renal function will be eligible for screening.

4.2.1 Source Documents

All data used to determine eligibility requires source documentation. For example serum creatinine values used for the study require that the laboratory report be kept at the site. For an age of diagnosis of hypertension, a medical record stating the date of diagnosis of hypertension is necessary. For gross hematuria, a medical record noting the event is necessary. For urinary protein excretion greater than 300 mg/day, the original laboratory report

is necessary. For diagnosis in utero or the first year of life, a medical record note is necessary. Original radiographic images of ADPKD documenting a diagnosis of ADPKD is not required for the study, however, a medical record stating the diagnosis is required. Further support for the diagnosis will be provided by the pedigrees obtained. Other exclusionary criteria with regard to laboratory data are obtained at the time of screening or enrollment. Source documentation will be subject to review at regular site visits throughout the course of the study.

4.2.2 Creatinine Eligibility When Entering Baseline

Participants will be eligible for the baseline period if they meet all of the inclusion criteria listed above. Included in this is the estimation of GFR from the Cockcroft-Gault formula using a serum creatinine concentration. The estimate of GFR must be greater than 70 ml/min either by Cockcroft-Gault formula or by 24 hour creatinine clearance for potential subjects to qualify.

Cockcroft-Gault Formula:

$$\begin{aligned} \text{CC} &= \frac{(140 - AGE) \times W \times 0.85}{72 \times CR} female \\ &= \frac{(140 - AGE) \times W}{72 \times CR} male \end{aligned}$$

where:

$$\begin{aligned} \text{CC} &= \text{Creatinine clearance (ml/min)} \\ \text{AGE} &= \text{Age in years} \\ \text{W} &= \text{Weight in kilograms} \\ \text{CR} &= \text{Serum Cr in mg/dl} \end{aligned}$$

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

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

To calculate the BSA, use the following formula:

$$\text{BSA}(m^2) = \frac{\text{W}^{0.425} \times \text{H}^{0.725} \times 71.84}{10000}$$

where:

$$\text{H} = \text{height in centimeters}$$

4.3 Participant Identification Numbers

Subject ID numbers will be issued at the time of consent, whether that occurs at the screening or baseline visits. ID numbers will be generated randomly, as 6 digit numbers which are not allowed to be sequential. The first digit will identify the clinic ("1" for Kansas University, "2" for Mayo Clinic, "3" for Emory University and "4" for University of Alabama-Birmingham). The remaining digits will be random values. Participants who withdraw from the study will not have their numbers removed. All forms will be identified

by the CRISP ID number, and identifying information will be omitted, as per HIPAA regulations. Numbers which identify each scan will also be generated; these are termed "accession numbers" and serve to identify the scans so that they can be analyzed at the IAC without knowledge of their period of issue.

4.3.1 MR Accession numbers

An MR Accession number is required for each distinct MR session. The MR accession number is generated from the WDES system (cf. Section 12). At the time that the participant is registered for the MR session, the accession number will be generated, and used to label all studies during the session. Thus, the T1, T2 with HASTE, T2 with fat saturation and all other distinct studies will be labeled with the same accession number. This number is selected from a drop down list as part of transferring the image to the DCIAC (cf. Section 16.4.4). The accession number will also be used to generate and label the report about the MR session (Form 7[9]).

4.3.2 US Accession numbers

An US Accession number is required for each distinct US session. The US accession number is generated from the WDES system (cf. Section 12). At the time that the participant is registered for the US session, the accession number will be generated, and used to label all studies during the session. This number is selected from a drop down list as part of transferring the image to the DCIAC (cf. Section 16.4.4). The accession number will also be used to generate and label the report about the US session (Form 8[10]).

4.4 Participant Confidentiality

4.4.1 Privacy

At the beginning of the study, each participant is assigned an identification number. Participants are identified only by number in the study database and in generated reports, and, in general, only group data will be published. If individual participant data are published, no identifying information will be included. The data management system is highly secure with multiple levels of controls on access. The medical records of the participants in the CRISP Study will be confidential. Specific study related information may be made available to the Food and Drug Administration and the study sponsors, the National Institutes of Health or other regulatory agencies.

4.5 Recruitment

4.5.1 Recruitment Schedule

Recruitment will last 10 months. A total of 210 subjects will be recruited equally by the three participating clinical centers. The last patient will be enrolled September 15th, 2001. Given that each site will recruit 70 subjects, it is expected that recruitment goals will be reached every 3 months. It is expected that 1/3 of all subjects will be enrolled by February

[9] See URL `http://www.pkd.wustl.edu/pkd/test/formsforum/MRISession7.pdf`
[10] See URL `http://www.pkd.wustl.edu/pkd/test/formsforum/USSession8.pdf`

15th 2,001. It is expected that 2/3 of all subjects will be enrolled by June 15th, 2001 and that the entire study population will be enrolled by September 15th, 2001. Enrollment will be tracked continuously by the DCIAC. Those sites that are recruiting to less than 80% of their projected goal will be contacted by the DCIAC. Those sites who doe not recruit to within 80% of their projected goal two months in a row will be asked to provide an explanation as to why recruitment has declined.

4.5.2 Recruitment Monitoring

All successfully recruited participants, i.e. those who have signed informed consent and meet eligibility criteria will have a form submitted to the DCIAC who will track local recruitment rates. A monthly report of both successfully recruited individuals, and those who have entered the baseline phase of study will be sent to each of the PCC's and the NIH to assess progress of recruitment. Each local center will keep track of the number of participants contacted to enter into the study and the reasons why potentially eligible participants decline to participate in the study. As well, all participants who enroll in the study but who fail to qualify for the baseline visit will be accounted for and the reason for their ineligibility stated. These data will be kept in a log book at each site for future reference if necessary. This log book will be subject to review at designated site visits throughout the course of the study.

5 Informed Consent Procedures

5.1 General Principles of Consent

In order to be eligible for the study, each participant must be willing to sign 1) a statement of informed consent consenting to baseline, year 1, 2 and 3 visits and interim contact visits. This will document the agreement of the participant to participate in study activities. Participants will have DNA obtained for lymphoblastoid transformation; depending on the site recruiting patients, a second consent form may be required. The participant will be queried in a sincere discussion prior to enrollment to insure continued willingness to be involved in the study and comply with the study protocol and follow up visit schedule. Copies of the signature of the signed informed consent forms will be kept at the Study Sites and the date that the consent was signed will be kept at the DCIAC. These will be stored apart from the other study forms since they contain confidential information, i.e., the participants' names.

5.2 Sequence of Consent Procedures

It is recognized that Clinical Center Institutional Review Boards (IRBs) have official responsibility for determining informed consent procedures. Prototype informed consent forms have been developed for the study, and each Clinical Center's IRB-approved consent form will be reviewed to make sure the essential material is included. Copies of all IRB approvals (including amendments and renewals) must be promptly sent to the DCIAC.

Consent occurs at the initial stage of study. Consent should be obtained at the time of the first visit whether it is the Screening, Enrollment or Baseline Visit, and will include description of the interaction with members of the study team, a complete medical history, a complete physical examination, blood and urine tests to be obtained, DNA to be obtained, GFR's obtained annually, follow-up visits, annual MR and ultrasound procedures. If a second genetics consent form is to be used, it will be obtained at one of the above mentioned visits.

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6 The Participant Examination Process

Although this is not an interventional or therapeutic trial, this is an observational patient study, where findings obtained throughout the study may provide important information for maintaining the standard of care for the participants in the study. All physical examinations must be performed by a physician, nurse practitioner, physician assistant or by a nurse coordinator supervised by a physician. Any abnormal findings by imaging, blood work or physical examination are required to be reported to the patients primary treating physician within 3 weeks. Should subjects become acutely symptomatic during their annual or baseline visits or should medical conditions requiring immediate attention be identified, it is necessary that the primary treating physician be contacted immediately. Followup letters to treating physicians after patients have completed their baseline and annual visits including certain findings such as blood chemistries, and blood pressure levels are recommended. This not only improves the chances of successful subject retention but maintains an awareness of the CRISP study in the medical community. All documents pertaining to these evaluations need to be kept at each PCC site for review at site visits throughout the study.

See the Visit Schedule (cf. Section 6.1) and Study Calendar (cf. Section 3.2) for more details about when various measurements are made and the Measurements (cf. Section 6.2) section which outlines the protocols for obtaining study measures.

6.1 Schedule of Visits for CRISP

Successfully enrolled participants who meet inclusion and exclusion criteria and who have signed informed consent will undergo four study visits, Baseline, Year 1, Year 2, and Year 3. These visits will be performed in a standardized format in as identical fashion as possible. Between each study visit, participants will be contacted no less than 3 times at 3-month intervals to determine interim events including doctor visits, emergency department visits, hospitalizations, and medication changes.

See Study Calendar (cf. Section 3.2) for more details.

6.2 Measurements

The purpose of this section is to describe the procedures to be used for measurements critical to the goals of this study and which must, therefore, be carefully standardized across the clinical centers. These will be taken during the screening, the enrollment, baseline and follow up visits. They include the measurement of the glomerular filtration rate, collection of 24-hour urine samples and the measurement of 24 hour electrolyte excretion, measurement of blood pressure using the oscillometric method, measurement of biochemical profiles at individual and central sites, and the collection of MR and US data for image analysis. Included in this section are the questionnaire data to be obtained at each annual visit.

6.2.1 Magnetic Resonance Imaging

The purpose of MR imaging is to determine total renal volume, cyst volume and renal artery blood flow in participating subjects. MR images are obtained at each clinical site by a trained MR technologist or imaging specialist using protocols developing by the Imaging

Committee. After images are acquired, the data is transferred in appropriate format to the DCIAC for further image analysis.

6.2.2 Ultrasonographic Imaging

The purpose of US imaging is to measure multiple sampled cross-sectional areas and cyst areas of each kidney. If the kidney size is not much larger than normal (in early disease stage or in pediatric population), the entirety of the kidney can be captured in each cross-sectional image. The kidney, however, will be partially visualized in enlarged ADPKD kidney. In this case, the volumetric measurement by US imaging is limited to measuring % cross-sectional cyst area relative to the % cyst volume and to determining longitudinal and transaxial dimensions of the kidney. Ultrasound images will be obtained at each clinical site by a trained ultrasonographer or imaging physician using a protocol developed by the Imaging Committee. After images are acquired, the data is transferred in appropriate format to the DCIAC for further image analysis.

6.2.3 Glomerular Filtration Rate

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

1. To determine the rate of change in renal function in PKD individuals with relatively intact renal function.
2. To determine if change in renal function is associated with change in renal structural involvement

Glomerular filtration rate is measured by the renal clearance of iothalamate administered by subcutaneous injection at Baseline, Visit 1, Visit 2 and Visit 3 (annually, for four measurements) after enrollment. Ideally, GFR measurements should be performed within two weeks of the target visit date.

Guidelines regarding medications:

1. NSAIDS should be avoided for 7 days prior to enrollment and all return visits.
2. Bactrim, Pyridium, and Cimetidine should not be taken for 4 days prior to enrollment and all return visits as they can interfere with creatinine excretion. This may mean delaying enrollment or return visits for a couple of days for a select few patients.
3. HCTZ should not be started as new treatment for hypertension for 14 days prior to enrollment and return visits.
4. The participants' usual antihypertensive medications, including long-term diuretics, are not withheld prior to the study

The study may be postponed if, in the judgment of the investigator, there is a mitigating medical reason (such as a short term illness).

List of medications that should be avoided by CRISP PKD study participants (Extra-Strength Tylenol is acceptable for pain or discomfort):

1. Salicylates (Aspirin, Empirin, Midol)
2. Fioricet
3. FiorinaL
4. Phrenilin Forte

5. Ibuprofen/Excedrin/Advil
6. Motrin
7. Nuprin
8. Naproxen Sodium/Naprosyn/Anaprox/Aleve
9. Diclofenac
10. Indomethacin
11. Sulindac
12. Tolmetin
13. Meclofenamate
14. Mefanamic Acid
15. Nambumetone
16. Piroxicam
17. Fenoprofen
18. Ketaprofen (Extended Release)
19. Oxaprozin
20. Etodolac
21. Ketorolac
22. Toradol
23. Cox^2 Inhibitors
    - Celebrex (Celecoxib)
    - Vioxx (Rofecoxib)
24. *Note: Hydrochlorthiazide (and diuretics) should not be started as a NEW antihypertensive treatement less than 2 weeks prior to enrollment visit. If it is necessary for you to start this medication, enrollment should be delayed for 2 weeks.
25. The following medications also interfere with creatinine excretion and should not be used for 4 days prior to each visit:
    - Trimethoprim (Bactrim/Septra)
    - Cimetidine/Tagamet

The specific protocol for performing the GFR test is provided in the GFR Section (cf. Section 16.10).

6.2.4 Twenty-four Hour Urine Collections

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

1. Sodium, potassium, urea, calcium, phosphorus, uric acid and citrate: To determine dietary intake.
2. Creatinine: a) To estimate glomerular filtration rate (GFR).
3. Protein: a) To classify (as high risk) participants as high risk who have a urinary protein excretion of > 300 mg/day and b) To follow as a potential surrogate marker of disease during the study.
4. Albuminuria: To determine if subjects have excess amounts of albumin in the urine, a marker for risk for progression to ESRD in PKD. This test is performed at the Baseline and annual visits only and is not used for inclusion criteria for the study.
5. To estimate adequacy of urine collection.

If a 24 hour urine collection has not been obtained within six months of signing the informed consent, they are performed prior to the Baseline visit during the screening and enrollment phase. 24-hour urine collections are also obtained at the time of the Baseline, Visit 1, Visit 2 and Visit 3 of the study. Participants are provided with the urine receptacles containing 250 ml Boric Acid for preservation of oxalate.

Ideally the urine container is given to the participant on the visit immediately preceding the annual visits and the 24-hour urine collection is started the day prior to the GFR measurements. The participants receive specific instructions for obtaining a valid urine collection. The total volume of the urine is measured and the urine is aliquoted for determination of creatinine, sodium, potassium, urea, protein at the clinical center's labs. Drugs that interfere with creatinine excretion (e.g. pyridium, cephalosporins, bactrim/septra, H-2 blockers) are withheld for 4 days prior to the 24 hour urine collection; and NSAIDS are withheld for 7 days prior to urine collection.

6.2.5 Arterial Blood Pressure

Given that blood pressure is a major determination of progression of renal disease in ADPKD, it is essential that accurate blood pressures are obtained. Arm circumference will be determined during the Screening/Enrollment or Baseline Visit to determine the appropriate cuff size. During the screening physical examination, blood pressure will be determined by trained personnel using the oscillometric technique. Participants should be quietly seated for at least 5 minutes prior to the sitting pressures. Three pressures are obtained in each arm and then three pressures standing. During the baseline and annual visits, dominant arm determinations will be done (assessing the arm with the greater blood pressure) and no less than 9 blood pressure determinations no less than 3 minutes apart will be obtained in the seated position with the arm held comfortably at the level of the heart. All of these measurements will be done using Oscillometric measurements with machines calibrated no less than every 3 months at each clinical site.

The mean arterial pressure (MAP) is calculated for evaluation and monitoring purposes at: MAP = (systolic + (diastolic x 2)) / 3

6.2.6 Blood Tests

Blood tests are required for determining eligibility as well as an additional assessment of renal function. Certain substances that may be linked to progressive renal enlargement or loss of renal function in ADPKD are also of interest in this study and will be collected at some or all clinical sites based on the decisions of the Steering and the External Advisory Committee

Blood tests for inclusion into the study:

- CBC and platelets
- Serum chemistries (to be performed at local central laboratories) which include: Sodium, potassium, chloride, bicarbonate, urea nitrogen, uric acid, glucose, creatinine, total protein, albumin, aspartate transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, calcium, phosphorus, uric acid, magnesium and GGT.

- In addition, fasting total cholesterol, total triglyceride, LDL-cholesterol, and HDL-cholesterol are performed at Baseline and annually during the study. Serum creatinine is measured at baseline and annual visits. Qualitative urine HCG tests are done within 10 days before each GFR in women of childbearing potential (post-pubertal, pre-menopausal, not surgically sterilized).

Additional local blood work may be done as clinically indicated independent of the current study. These data are not sent to the DCIAC.

6.2.7 Baseline Evaluation

General Principles of Baseline This is the initial visit for obtaining baseline data that includes 24-hour urine collection, GFR, MR and ultrasound examinations. Medical and medication history, physical examination including standardized arterial blood pressure measurements will be performed. Biochemical and genetic markers will be obtained. Most important is that each center be internally consistent with baseline and subsequent annual visit measurements. At three sites: Mayo Foundation, University of Alabama at Birmingham and Emory University, subjects will be admitted to their respective General Clinical Research Centers (GCRC's). At the University of Kansas Medical Center, subjects will be seen in the outpatient clinic.

Magnetic Resonance Imaging Will be performed using a detailed protocol. All MR's will be obtained for each individual at approximately the same time at each site. The MR's at the Mayo Foundation, The University of Alabama at Birmingham and Emory University will be obtained in the morning of the second day of admission. MR's at University of Kansas Medical Center will be obtained in the afternoon following the GFR and ultrasound examination. These studies will be performed in the hydrated state at least six hours after food intake. All medications will be continued during this test.

Ultrasound examination Will be performed using a detailed protocol. All ultrasounds will be obtained for each individual at approximately the same time under standard conditions at each clinical center. The ultrasounds at all sites will be performed following the GFR determinations.

Glomerular Filtration Rate Will be performed in standardized format (see GFR Procedures (cf. Section 16.10)). All centers will perform the GFR measurement between 8:00 a.m. and 10:00 a.m. in the morning after an overnight fast with pre-test hydration. Iothalamate meglumine, which will be stored on site at each clinical center, will be administered subcutaneously. Two timed urine collections will be obtained and bladder ultrasound will be performed at the time of voiding to guarantee complete bladder emptying. All GFR kits (cf. Section 16.10) are provided by the Mayo Foundation and include shipping materials, tubes for urine and blood sample storage and FED EX billing slips to ship back to the Mayo Clinic for clearance determinations using capillary electrophoresis. All samples should be shipped the day of study (see shipping directions (cf. Section **??**)).

24-hour Urine Collections Will be obtained at each site under standard conditions. At those sites where admission to the GCRC will take place, 24-hour urine collections will be obtained at the time of admission. At Kansas University Medical Center, subjects will provide a 24- hour urine collection at the time of evaluation that has been collected within 7 days of study date. For more details see the 24-hour Urine Collection (cf. Section 6.2.4) and Urine Handling (cf. Section 11) sections.

Laboratory Tests at Baseline visit Will include the following measurements at each site:

- CBC and platelets
- Serum chemistries (to be performed at local central laboratories) which include:
- Fasting total cholesterol, total triglyceride, LDL-cholesterol, and HDL-cholesterol
- Qualitative urine HCG tests are done within 10 days before each GFR in women of childbearing potential (post-pubertal, pre-menopausal, not surgically sterilized).
- Blood samples for lymphoblastoid transformation.

Specialized Tests performed at selected clinical centers or potentially all sites:

- Urine and serum MCP-1
- Urine and serum osteopontin
- Urine and serum IL-8
- Urine and serum cyst activating factor
- Urine and serum TGF-B
- Urine metalloproteinase
- Serum C-reactive protein

Screening medication status A thorough history with regard to prescription and non-prescription (over the counter) medication intake will be obtained at the time of the baseline visit.

History and Physical Examination A detailed history and physical examination will be obtained at the baseline visit that includes height and weight determination as well as systemic review of ADPKD related disease including inguinal and ventral hernias, liver cystic disease, intracranial aneurysms and mitral valve prolapse. In ADPKD women, a detailed obstetrical, birth control pill and estrogen use history will be obtained.

Blood Pressure Measurement Will be done in a standardized fashion at each site. See Blood Pressure (cf. Section 6.2.5) section for more details. Subjects will withhold morning blood pressure medication intake until blood pressure measurements are obtained.

Treatment during the Baseline Period This is an observational study with no ADPKD treatment component. However, should abnormalities in physical examination or laboratory work arise, the subjects primary care physician should be notified of all abnormalities identified.

Yearly Examination Will be performed in identical fashion to the baseline visits within two weeks of the date of the baseline visit.

6.2.8 Interim Examination

General Principles The purpose of this section is to describe the major time commitment of the study. Every attempt should be made to retain participants who have initially enrolled and completed the baseline portion of the study. Participants will be contacted by phone every three months for a detailed interview to review interim illnesses, hospitalizations, surgeries, changes in prescription and non-prescription medication intake. Specified forms will be filled out for these visits. At some PCC, the participants may be asked to come in for an examination based on the clinical stability of the subject or the reliability of the information given over the phone. Specified forms will be filled out should the participants be seen and examined. These opportunities for contact provide important medical information that is relevant to the study and also allows for continued contact with the participants that should improve the possibility of retainment during the study. Participants should be encouraged to contact the PCC about any intercurrent illness between the 3-month calls.

Telephone Followup Procedures Study coordinators should develop a standardized procedure for these calls.

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7 Magnetic Resonance Assessment Methods

7.1 Rationale

MR has been increasingly used because it provides high resolution 3D images with excellent tissue contrast and no need for ionizing radiation or iodinated contrast medium. MR limitations are relatively long image acquisition times and variability in the quality of images that can be produced from different MR scanners. Some of these limitations are being overcome by recent technical advances such as high-performance gradient systems, dedicated body phased array surface coils, and sequence development. With modern MR techniques, high-quality volumetric images of the kidneys can be generated. MR appears well-suited for our morphometric study to assess renal structures and changes.

7.2 MR Appearance of Cysts

On T1-weighted MR images, the kidneys in PKD patients would show multiple cysts with various signal intensities. Simple cysts appear dark on T1-weighted images and very bright on T2-weighted images. Hemorrhagic or proteinaceous cysts frequently have increased signal intensity on T1-weighted images and/or increased signal on T2-weighted images. Signal intensity also varies with the increasing complexity of cysts and with infection.

7.3 Preparation of MR Scan

Please refer to Certification of CRISP Study Personnel and Equipment section (cf. Section 13) for detailed description on MR Equipment and MR technologist certification.

7.4 MR Scanning Procedure

Our choice of MR sequences focus on those that do not require specially designed hardware systems and can be used to reproduce reliable, accurate volumetric measurements. MR sequences routinely available for clinical diagnostic studies will be used to measure renal structures. Some MR parameters will be adjusted to improve measurement accuracy and reliability. Gadolinium will be infused intravenously to enhance the contrast of the renal parenchyma and, for the renal blood flow measurement, to acquire a renal MRA.

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

1. An angiocatheter will be placed for Gadolinium study (20 cc or 0.1 mmole/kg). A slow-flow infusion with normal saline will be used to keep the vein open during the course of the study.
2. For MR scan with cardiac gating, EKG pads will be placed over the chest. If EKG gating is not available or functioning, it may be replaced with a peripheral pulse gating.
3. Subjects will be placed supine on the MR table with their arms to their side or over their shoulders.
4. A phased-array surface coil will be positioned with its center over the inferior costal margin, i.e. over the expected location of the kidneys. Breath-holding instruction will be coached prior to MR scanning.

5. Scout scan to locate the scan range of the entire kidneys. A stack of axial images to cover the most anterocaudal and posterocranial aspects of the kidneys are highly recommended.
6. The field-of-view (FOV) should be kept as small as possible (30-35 cm) without producing wrap-around artifacts.
7. Breath-hold coronal Regular T2 scan (SSFSE/HASTE T2 scan with fat saturation) with 9mm fixed slice thickness, usually achievable in a single breath-hold.
8. Breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat saturation) with 3mm fixed slice thickness, which would require 1-4 breath-holds depending on the kidney size. Use as few breath-holds as possible. The first scan should cover the posterior aspect of the kidney. Neighboring image groups should be overlapped by a single 3mm slice. To determine correct table position choose the "shift-mean (starting point in GE)" of the second scan, for example: the first shift-mean=-60mm, the number of slices in the first set = 23, (23-1)x3=66mm, new shift mean=-60 +66=6mm.
9. Breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat saturation) with adjusted slice thickness, 3-9mm, best attainable with a single breath-hold. The adjusted slice thickness may not remain the same in a follow-up MR scan if there is a change in the subject's breath-hold capacity or kidney size.
10. After shifting the field of view anteriorly to cover the liver for the liver cyst measurement, repeat breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat saturation) with adjusted slice thickness, 3-9mm. This repeat and initial adjusted MR image sets should share one overlapping slice.
11. Breath-hold coronal Heavy T2 scan (SSFSE/TSE with fat saturation) with the same adjusted slice thickness as Regular T2. Since Heavy T2 scan takes longer than Regular T2, this may require more than a single breath-hold.
12. Coronal PreT1 scan (3D VIBE/FMPSPGR without fat saturation) with 3mm fixed slice thickness.
13. (For renal blood flow measurement) MRA of renal arteries will be performed with Gadolinium injected at 1 cc/s for 20 cc. You have two minutes for the MRA acquisition from the start of the injection.
14. PostT1 scan: Repeat T1 scan (3D VIBE/FMPSPGR without fat saturation) with 3mm fixed slice thickness twice: 120 and 180 seconds after the start of the Gadolinium injection performed above.
15. Breath-hold, phase-contrast technique of renal blood flow measurement. From the MRA images, the renal arteries will be identified. To accurately measure velocity, it is important to choose the imaging slice perpendicular to a vessel. Velocity encoding (VENC) value of 100 cm/sec will be used. Small FOV (20-24 cm) and large matrix (256x192 or 512x512) are important for an accurate measurement of the vessel size. Segmented, prospectively cardiac-triggered phase contrast flow measurements will be obtained to compute the mean and peak velocities, as well as the total mean flow, during the cardiac cycle. Please, refer to Renal Blood Flow Assessment Methods section for detailed procedural description.

7.5 MR Image Quality Control and Image Transfer

Trained radiologists at each PCC will monitor the quality of images immediately after the acquisition of each sequence, while the patient is on the scanner. The adequacy of images will be determined by recognizing the presence of artifacts, respiratory motion, and incomplete coverage. When the quality of breath-hold images is in question, a set of repeat breath-hold images will be acquired and sent to the DCIAC along with proper documentation (Form 7[11])

[11] See URL `http://www.pkd.wustl.edu/pkd/test/formsforum/MRISession7.pdf`

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8 Ultrasound Assessment Methods

8.1 Equipment

Equipment will vary between sites but, provided that quality is standardized, this should not cause variability in the data. All scanners should have at least 128 channels and must have digital output capability in a DICOM format

8.2 Probe

All probes should be electronic, phased-array probes providing large near-field coverage. Probe frequency may vary between studies. A frequency of 5.0 MHz provides the best resolution in lean patients with kidneys that are moderately enlarged. Expansion of the kidney in PKD actually brings it closer to the abdominal surface but the posterior aspect of the kidney may be correspondingly deeper. In this case, a reduction in probe frequency to 3.0 - 3.5 MHz is likely to give the best overall resolution. A reduction to 2.0 MHz may be necessary in obese subjects. It is not possible to standardize probe frequency and it will be at the discretion of the sonographer to determine the probe frequency that gives the best overall resolution.

8.3 Scanning Procedure

All scans will be performed after an overnight fast approximately 45 min after completion of the GFR measurement. The patient will empty the bladder prior to the study.

8.3.1 Component #1: Kidney Volume

Place subject in the supine or lateral decubitus position and scan the kidney in its longitudinal axis. If possible, obtain a full longitudinal image with calipered measurement of the length and the depth. Each measurement is recorded on the session form. Then obtain a single transverse (perpendicular to the longitudinal axis of the kidney) image through the mid-kidney with calipered measurements. The maximum dimensions will be recorded as width and depth. The depth of this measurement should correspond to the depth measurement of the longitudinal image. Each measurement is recorded on the session form. If the kidney extends beyond the range of the probe in either the longitudinal or transverse axis, these views should be attempted in the prone position. All measurements must be obtained in the identical patient position. If the kidney still extends beyond the scanning sector on longitudinal scanning, then two overlapping images will be obtained in the identical plane and containing a common landmark that will be marked on each image. The first longitudinal scan will include the upper pole and the distance from the pole to the landmark will be recorded in the first row. The second longitudinal image will include the lower pole and the distance from the pole to the landmark will be recorded in second row. The two measurements will be added at the DCAIC to derive the full dimensions. If the midline transverse scan extends beyond the scanning sector, measurements will be extrapolated beyond the sector to the best approximation of the sonographer.

These images are labeled "Comp. 1, long" and "Comp. 1, trans". If two images are needed in either plane, then "#1" and "#2" are added to the end of the labels.

Label the kidney as right (R) or left (L).

8.3.2 Component #2: Measurement and Enumeration of Individual Cysts

When no more than 5 cysts are identified, they will each be imaged and measured in all three axes. Each cyst will be imaged in a longitudinal plane and orthogonal dimensions will be recorded as length and depth. The probe will be rotated 90 degrees to obtain the third dimension, which will be recorded as width.

These images are labeled "Comp 2, cyst #1", "Comp. 2, cyst #2, etc.".

8.3.3 Component #3: Transverse Scanning

With the probe maintained perpendicular to the longitudinal axis of the kidney, center the inferior renal border under the probe during deep inspiration and mark its location on the skin. Again maintaining the probe perpendicular to the longitudinal axis of the kidney, center the kidney at the costal margin during deep inspiration. Draw a line between the two marks and demarcate 2 cm intervals starting from the inferior end. Obtain a transverse image at each interval during deep inspiration. To continue this process superior to the costal margin, there are two options. The images may be obtained in the intercostal spaces with the understanding that it may not be possible to maintain the probe exactly perpendicular to the longitudinal axis. Alternatively, oblique transverse images may be obtained by pushing the probe under the costal margin and angling it superiorly. The sonographer must ensure that none of these images overlap. Only one of these options can be used for all images of a single kidney. The time-gain compensation must be adjusted to ensure that the lumens of near-field and far-field cysts are of equivalent darkness. Each image is stored twice, once before and once after the outline of the kidney is traced. When the kidney extends beyond the scanning sector, the border of the kidney is traced beyond the sector to the best approximation of the sonographer. This area will be used for calculation of renal volume. However, for determination of percent cyst area, only that portion of the kidney actually visualized will be used.

These images are labeled in ascending order from the inferior border of the kidney as "Comp. 3, trans 1, Comp. 3, trans 2."

8.3.4 Prominent Renal Veins or Collecting System

If the width of the renal vein or collecting system within the kidney is 1.0 cm or greater, record this value in the session form. In any subsequent transverse images, place a label within any fluid-filled areas that are vein "v" or collecting system "c".

8.4 Data Management

1. Print two hardcopies of each image. One set of prints is sent to the data coordinating center, the other is stored at the scanning site.
2. Download the study in DICOM format in a folder designated by the participant code and date. This folder is then sent to the data coordinating center via a DICOM transfer. Alternatively, this folder can be transferred via an FTP (file transfer protocol).
3. If not currently configured for DICOM, download images as TIF files. These files should be named acording to the following syntax:

[right/left]-[protocol component #]-[scan # or cyst # (not applicable to component #1)]-[scan type]

using the following symbols:

right: R; left: L; longitudinal: L; transverse: T; oblique: OB; intercostal: IC.

For instance, the transverse image of cyst #3 on the right, the file would be: R-2-3-T.tif. For the 6th scan of the left kidney obtained obliquely in the transverse scanning series: L-3-6-OB.tif.

4. The TIF files should be packaged in a folder with the participant identifier code.

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9 Renal Blood Flow Assessment Methods

Phase contrast MR angio techniques have been utilized to measure blood flow in the human body for approximately ten years. This technique has been applied to renal blood flow, portal vein blood flow, carotid blood flow, and CSF flow estimation. Early techniques utilized nonbreathold phase contrast MR flow evaluation. Within the last 5-6 years, faster breathold techniques have been developed improving the accuracy of MR blood flow analysis.

9.1 Concept

Moving protons within the body requires a phase shift during motion. This process is similar to moving structures that reflect sound and result in a Doppler shift in reflected sound waves. Phase contrast MR techniques utilize a method of MR estimation of phase shift in moving structures. Essentially, two images are acquired over a short period of time, and MR imaging systems are able to measure the phase shift within each pixel in areas of the body where movement occurs. When applied to blood vessels, phase shift measurements can be obtained within individual pixels within blood vessels. This phase shift is directly proportional to velocity and through a complex equation that is similar to the Doppler equation. Velocity estimates for each pixel within a blood vessel can be determined. This whole technique is called Phase Contrast MR Angiography.

From this phase shift or velocity information, images of blood vessels can be constructed using this velocity information much like color Doppler. Alternatively, actual measurements of average velocity within pixels can be estimated and, if the region of interest is drawn over the renal artery, blood flow can be calculated within the blood vessel (blood flow = cross sectional area x velocity).

9.2 Clinical Testing

Investigators utilized this phase contrast MR angiography to measure renal blood flow in a number of studies. Correlations were made to estimate renal plasma flow from PAH clearances. Estimated renal plasma blood flow was then converted into total renal blood flow using an hematocrit correction. Early estimates of renal blood flow correlated well with PAH estimates of renal plasma blood flow. However, estimates of renal blood flow usually took 3-6 minutes; and the respiratory excursion of the renal arteries resulted in a oval-shaped cross sectional area of the blood vessel and, therefore, resulted in overestimation of renal blood flow. Since then, techniques have been developed in which renal blood flow estimates of each renal artery can be obtained during a single breathold, which eliminates respiratory excursion of the renal artery and results in a more circular true cross section of the renal artery and more accurate blood flow estimations.

9.3 Technique

Based on gadolinium-enhanced MRA images of the renal artery and scout images of the abdomen in the axial and coronal plain, an oblique imaging plane is prescribed for the phase contrast blood flow study. The imaging plane must be perpendicular to the direction of the renal artery such that a circular cross sectional area of the renal artery can be evaluated. Once the appropriate plane is chosen, the following parameters are entered:

1. Pulse sequence 2D phase contrast (fast) breathold.
2. Torso coil
3. Minimum TR, minimum TE
4. Flip angle 20º
5. 18 second breathold
6. Peripheral gating
7. Trigger window and trigger delay - automatic or recommended
8. Reconstruction image type = phase difference
9. Velocity and coding value (VENC) - 100 cm/sec
10. Flow direction = slice direction
11. Matrix 256/128/1
12. Imaging field of view - 40 cm
13. Phase field-of-view - 0.5 cm (20 cm)
14. Frequency in coding direction - right/left

9.4 Blood Flow Phantom Devices

There are MR blood flow phantom devices that can be used to test the reliability of MR blood flow measurements. Many of these are built and designed locally by academic institutions. Shelley Medical Imaging Technologies, North York, Ontario, Canada, is the most commonly used commercial blood flow phantoms for ultrasound and for MR imaging systems. Shelley Medical Imaging has early prototypical flow devices that many institutions have utilized for ultrasound and MR systems quality control testing. Shelley Medical Imaging also has two new flow phantom devices (CompuFlow 1000 - $18,000 and CardioFlow 1000 MR systems - $22,000). These sophisticated phantom systems have pulsatile flow velocity patterns typical of carotid arteries, which also are similar to renal artery velocity flow patterns. These systems also have peripheral extremity arterial flow patterns as well as some cardiac flow techniques.

9.5 Blood Flow Quality Control Estimation for each PC Site

Each site should optimize blood flow MR estimating techniques utilizing phase contrast MR angiography. Each site should perform phantom testing on known flow rates to estimate a margin of error based on these flow phantoms.

There are essentially two options for the CRISP study:

First Option: Ask each investigating site (PCC) to acquire or utilize existing flow phantoms at their institutions for phantom blood flow measurements utilizing their MR system and their MR technique.

Second Option: The study group would need to purchase a Shelley blood flow MR phantom system and necessary cases for shipping and arrange for a technologist or individual to visit the various PCC sites to do blood flow estimates utilizing this phantom. The time it will take to order and receive a Shelly blood flow would be approximately 4-8 weeks. An individual or technologist will need to be recruited to travel around the various sites to test the blood flow estimations.

Because of fiscal constraints, the first option has been chosen for the CRISP study.

10 Blood Handling Methods

Each institution may collect the required lab tests by standard laboratory tubes and containers of the individual institution. Using aseptic technique, blood sampling may be drawn from any peripheral vein in either arm, under tourniquet occlusion.

10.1 Initial screening visit

Draw blood into one 7 ml "tiger-top"/SST tube for the following tests:

- serum creatinine
- serum electrolytes: Na, K, Cl, HCO3, Ca, PO4, Mg, glucose, uric acid and urea
- liver function tests: SGOT, SGPT, total bilirubin, alkaline phosphatase.

Draw blood into one 5 ml "purple-top" tube for the following tests:

- complete blood count (without differential), platelets

Total blood needed for testing: 12 ml

May draw blood for genetic linkage studies (cf. Section 10.6) during this visit, along with urine that is to be obtained under normal state of hydration. See below (cf. Section 10.4) for archived bloods for specialized tests.

10.2 Baseline visit

Draw blood into one 7 ml "tiger-top"/SST tube for the following tests:

- serum creatinine
- serum electrolytes : Na, K, CL, HCO3, Ca, PO4, Mg, glucose, uric acid and urea
- liver function tests: SGOT, SGPT, total bilirubin, alkaline phosphatase.
- fasting lipid panel : HDL, LDL, VLDL, and total cholesterol

Draw blood into 5 ml "purple-top" tube for the following tests:

- complete blood count (without differential), platelets

The following test may be done during the Initial screening visit when the urine collection is obtained, under normal state of hydration, for these same tests.

Draw blood into two 10 ml red-top tubes for the following test:

- centrifuge blood at 3000 rpm for 10 minutes, then aliquot 5 ml of serum from each red-top tube into the appropriate storage collection tube. Label each tube with the participant's study ID number, date of collection and storage site. This blood will be frozen at -20 C for "surrogate" marker to be explored in pilot studies in certain laboratories. Temporary storage at -80 C can be arranged for additional aliquots upon request. These samples will be sent to the laboratories where the assay will be performed.

Iothalamate clearance test with hydration. Blood collection and handling as described in the GFR Procedures Section (cf. Section 16.10). Additional 6 ml of blood is collected during this test.

Total blood needed for testing : 18 ml
Total blood needed for storage: 20 ml

10.3 Subsequent Visits

Draw blood into two 10 ml red-top tubes for the following test:

- centrifuge blood at 3000 rpm for 10 minutes, then aliquot 5 ml of serum from each red-top tube into the appropriate storage collection tube. Label each tube with the participant's study ID number, date of collection and storage site. This blood will be frozen at -20 C for "surrogate" marker to be explored in pilot studies in certain laboratories. Temporary storage at -80 C can be arranged for additional aliquots upon request. These samples will be sent to the laboratories where the assay will be performed.

Draw blood into one 7 ml "tiger-top/SST" tube for the following tests:

- serum creatinine
- fasting lipid panel (HDL, LDL, VLDL , and total cholesterol)

Iothalamate clearance test with hydration, at least once a year.

Blood collection and handling as described in the GFR Procedures Section (cf. Section 16.10). An additional 6 ml of blood will be collected during this test.

Total blood needed at each visit for testing : 13 ml
Total blood needed at each visit for storage:
two 5 ml aliquots/year (x4 years = 8 tubes or 80 ml blood)

10.4 Specialized Serum Collections Done on Demand for Archive

May be drawn during Initial screening visit when the same specialized urine collection is done under normal state of hydration.

Samples of blood for genetic linkage study will be drawn into appropriate tubes and sent immediately to the appropriate labs.

- blood sample for genetic linkage, mutation analysis and lymphoblastoid transformation collected according to protocol. (three- 5 ml purple-top tubes and one 5 ml green-top tube)
  Serum will be drawn and stored on demand. Blood will be drawn in a 10 ml red-top tube and centrifuged at 3000 rpm for 10 minutes. Serum will be decanted aseptically and placed in appropriate storage tube with screw-top cap. Each tube will be labeled with the participant's study ID number, date of collection and site of storage. In storage, the tubes will be kept frozen at -10 C. Lower temperature storage may be used as determined locally.
- serum MCP-1 (10 ml red-top tube)
- serum osteopontin (10 ml red-top tube)
- serum IL-8 (10 ml red-top tube)
- serum cyst activating factor (CAF) (10 ml red-top tube)
- serum TGFb (5 ml purple-top tube, spin immediately at 3000 rpm for 10 minutes in a <u>refrigerated</u> centrifuge, then aliquot 3 ml serum into appropriate storage tube and freeze at -80 C)
- serum metalloproteinase (MMP, TIMP) (10 ml red-top tube)

Total blood needed for storage: 75 ml

10.5 Local Blood Labs

Blood will be drawn aseptically from any peripheral vein in either arm, under tourniquet occlusion, into disposable vacuum tubes. Standard blood collection tubes may vary with each institution. Individual institutions may use the standard collection tubes designated by their lab.

7 ml "tiger-top"/SST tube

- serum creatinine
- serum electrolytes
- liver function tests
- fasting lipid panel

5 ml purple-top tube

- complete blood count (without differential)
- platelets

10.6 Genetic Bloods

10.6.1 Recruitment

All patients with ADPKD screened for eligibility in the CRISP Study will be invited to participate in the CRISP Study Genetic Repository by providing a blood specimen for EBV transformation. Inclusion criteria for patients screened and entered into the CRISP Study are documented in the CRISP Manual of Operations, section 3b (Eligibility Criteria).

10.6.2 Enrollment Procedures

Written informed consent, contained within the consent for the entire CRISP Study, will be obtained for participation in this repository. Each collaborating clinical center will obtain one EDTA (5mL) and two heparinized (2 x 8mL) Vacutainer tubes from each donor. The samples from Emory University, the Mayo Clinic, and UAB will be sent to their respective GCRC Core Laboratories. In the case of KUMC, the samples will be sent in insulated Styrofoam shipping containers, provided by the Mayo Clinic, to the Mayo GCRC Core Laboratory by overnight mail. All tubes will be labeled by the local collaborating center with the unique patient code provided by the DCIAC. Only the collaborating clinical center will have access to the patient name. All subsequent work with patient-derived specimens at Emory University, the Mayo Clinic, UAB, and KUMC will utilize only coded materials. Ethnicity is self-declared; declaration of ethnicity for both parents and for all four grandparents will be requested.

10.6.3 Transformation Procedures

Upon receipt of specimens at the GCRC Core Laboratories, Ficoll purified mononuclear cells, isolated from whole blood, are suspended in one well of a 12-well plate with 2mL of RPMI media containing 20% FBS, 0.5ug/ml cyclosporin A and 500ul of an EBV containing culture supernatant derived from culture of B95-8 cells. In addition, plasma will be taken from the EDTA tube for storage, DNA will be extracted from 2x 300ul aliquots (anticipated

yield of 20ug gDNA) and a buffy coat will be prepared from the remaining blood for storage for future DNA needs if the EBV transformation does not work. In the event of a failed EBV transformation on a patient, we will attempt to obtain two additional heparinized tubes for another attempt. Standard biosafety level 2 precautions will be observed for the handling of all specimens and cell cultures. Once sustained lymphoblastoid cell growth has been attained, cells are expanded into larger culture flasks and, when appropriate, frozen and stored in a cryogenic freezer (LN2). We anticipate coding and freezing ….X… vials per donor.

10.6.4 Storage Procedures

Each GCRC will provide two independent LN2 storage freezers (CryoMed CryoPlus freezers) that are located in separate buildings. Both of these freezers are monitored 24 hours a day, seven days a week by the police departments at the respective institutions for malfunctions. A call list is in place to handle any emergency situation. In the event of a major freezer malfunction, LN2 dewer flasks will be available to accept vials. LN2 service is available Monday through Friday. Next day LN2 delivery is available and same day delivery can be accommodated if a request is received before 8 a.m. Experience has shown that proper cryogenic temperatures (<-140°C) can be maintained in the freezer for up to 48 hours after a malfunction.

Storage for DNAs and buffy coats will be in a Forma PowerPlus -80 degC freezer located in the GCRC laboratory. This freezer is also monitored 24 hours a day, seven days a week by the police departments at the respective institutions for malfunctions. A call list is in place to handle any emergency situation. In the event of a major freezer malfunction, there are -20°C walk-in freezer rooms or up-right freezers available to the Pis at each site.

All freezers in the GCRCs are visually checked every weekday and temperature logs are maintained.

10.6.5 Utilization of CRISP Study Genetic Repository

The CRISP Study will generate two categories of genetic materials: 1) material in finite supply, e.g. DNA and buffy coats, and 2) material of unlimited supply, e.g. immortalized cell lines and DNA from immortalized cell lines. In addition, EBV lines will provide a potentially unlimited source of mRNA.

The CRISP Ancillary Studies Committee will review and approve written requests from CRISP investigators for genomic DNA and/or mRNA. The GCRC Core Laboratories at the participating PCCs will provide genomic DNA and mRNA to CRISP investigators at reagent cost.

Within two years of the conclusion of the CRISP study, material in finite supply, e.g. DNA and buffy coats, stored at the participating PCCs will be treated as follows:

1. If a given individual has requested return of samples, that request will be honored.
2. Of the remaining material, half will be returned to the contributing PCC, and half will be archived for the NIDDK (mechanism to be determined).
3. The ownership of these samples will reside with the possessor (e.g. the NIDDK and the individual PCCs respectively).

Within two years of the conclusion of the CRISP study, material of unlimited supply, e.g. immortalized cell lines and DNA from immortalized cell lines will be treated as follows:

1. If a given individual has requested return of the samples, that request will be honored.
2. A viable aliquot of each immortalized cell line will be provided to the contributing PCC.
3. A viable aliquot each immortalized cell line will be archived for the NIDDK (mechanism to be determined).
4. Ownership of the samples will reside with the possessors (e.g. the NIDDK and the individual PCCs respectively).

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11 Urine Handling Methods

Voided urine samples will be collected in chemically clean plastic containers. Freshly voided urine samples are to be collected at a time when the urine is concentrated, but not maximally so.

These samples must **not** have toluene added. 24 hour urine collection containers will contain boric acid for preservation. Aliquot samples of urine will be capped with screw-top caps adequate to prevent evaporation during transportation and storage. Aliquots of urine between 10 and 20 mls will be suitable for any of the projected analysis. The specific types of plastic storage tubes/containers will be left to the discretion of the individual institutions. Each tube/container will be labeled with the participant's study ID number, date of collection and site of collection.

Each institution may collect the required lab tests by standard laboratory tubes and containers of the individual institution. All urine collections are done aseptically by institutional "clean catch" methods. Urinary catheters are prohibited in this study.

Urine samples collected during the iothalamate clearance test will be placed in the containers supplied in the GFR kit, labeled per GFR test instructions and transported in the refrigerated container provided. GFR Test supply kits are provided by Mayo Medical Laboratories. The completed GFR test kit will be sent to Mayo Medical Laboratories, Rochester, MN for test resulting and reporting. See the GFR section (cf. Section 16.10) of this manual.

11.1 Initial screening visit

Collect four 5 ml aliquots of freshly voided urine, BEFORE water loading prep for other tests, for archive. These urine samples will be frozen at -20 C for "surrogate" markers to be explored in pilot studies in certain laboratories. Temporary storage at -80 C can be arranged for additional aliquots upon request. These samples will be sent to the laboratories where the assay will be performed. Each collection container must be labeled with the participant's study ID number, collection date and site of storage. list list

Upon specific request, collect from freshly voided urine, BEFORE water loading prep for other tests, the following tests:

- Collect four 5 ml aliquots of freshly voided urine, BEFORE water loading prep for other tests, for archive. These urine samples will be frozen at -20 C for "surrogate" markers to be explored in pilot studies in certain laboratories. Temporary storage at -80 C can be arranged for additional aliquots upon request. These samples will be sent to the laboratories where the assay will be performed. Each collection container must be labeled with the participant's study ID number, collection date and site of storage.

Upon specific request, collect from freshly voided urine, BEFORE water loading prep for other tests, the following tests:

- urine MCP-1 (10 ml)
- urine osteopontin (10 ml) urine IL-8 (10 ml)
- urine cyst activating factor (CAF) (10 ml) urine TGFb (10 ml, add 0.1 ml acetic acid then freeze at -80C)

- urine metalloproteinase (MMP, TIMP) (10 ml)

Each container must be labeled with the participant's study ID number, date of collection and site of storage. These samples will be collected and stored for studies of genetic linkage.

Collect an additional 10 ml freshly voided urine for the following tests:

- urinalysis dipstick for hemoglobin and protein, including exam for sediment and polarization of lipid bodies, performed by the nephrologist.
- urine pregnancy test. This test must be done within 10 days of date of scans
- iothalamate clearance test. (Test may be done during Baseline visit if completed within the 10 day time limit, 1 ml urine is needed)

Total freshly voided urine needed for storage: 80 ml
Total freshly voided urine needed for testing : 11 ml

Important Note: These tests listed above, CANNOT be taken from the 24 hour urine collection andMUST be freshly voided urine samples BEFORE water loading for other tests.

From the 24 hour urine collection do the following tests:

- measure total volume collected calculate creatinine clearance (24 hour) with hydration during collection

Aliquot 10 ml urine from the 24 hour collection into a chemically clean container for the following tests:

- urine creatinine
- urine protein (24 hour), albumin and microalbumin

Total urine needed for testing: 20 ml

11.2 Baseline visit

From the 24 hour urine collection do the following tests:

- measure total volume collected
- calculate creatinine clearance (24 hour) with hydration during collection

Aliquot 10 ml urine from the 24 hour collection into a chemically clean container for the following tests:

- urine creatinine
- urine protein 24 hour), albumin and microalbumin
- urine electrolytes: Na, K, Cl, Ca, PO4, uric acid, urea, and citrate
- urine pregnancy test, if not completed during initial visit. This test must be done within 10 days of date of scans and iothalamate clearance test. Additional 1 ml urine is needed.

Iothalamate clearance test with hydration. Urine collection and handling as described in the GFR Procedures Section. Additional 10 ml urine is collected during this test.

Total urine needed for testing: 21 ml

11.3 Subsequent Visits

Collect four 5 ml aliquots of freshly voided urine, BEFORE water loading prep for other tests, for archive. These urine samples will be frozen at -20 C for "surrogate" markers to be explored in pilot studies in certain laboratories. Temporary storage at -80 C can be arranged for additional aliquots upon request. These samples will be sent to the laboratories where the assay will be performed.

From 24 hour urine collection do the following tests:

- measure total volume
- calculate creatinine clearance (24 hour) with hydration during collection)

Aliquot 10 ml urine from 24 hour collection into a chemically clean container for the following tests:

- urine creatinine
- urine protein (24 hour), albumin, microalbumin
- urine pregnancy test. This test must be completed within 10 days of date of scans and iothalamate clearance test. Additional 1 ml of urine is needed.

Iothalamate clearance test with hydration, at least once a year. Urine collection and handling as described in the GFR Procedures Section (cf. Section 16.10). Additional 10 ml of urine is collected during this test.

Total urine needed for testing at each visit: 21 ml (x4 years = 84 ml urine)
Total urine needed for storage at each visit: 20 ml (x4 years = 80 ml urine)

11.4 Specialized Urine Collection Done on Demand

These urine tests for study of genetic linkage have been incorporated into the Initial screening visit, to obtain during a more normal state of hydration, BEFOREwater loading for other tests. However, these tests may be obtained during another visit, but must be under the required condition of hydration.

11.5 Local Urine Labs

Each institution may collect the required lab tests by standard laboratory tubes and containers of the individual institution. All urine collections are done aseptically by institutional "clean catch" methods. Urinary catheters are prohibited in this study.

Freshly voided urine collection for testing

- urinalysis dipstick for hemoglobin and protein, including exam for sediment and polarization of lipid bodies, performed by the nephrologist.
- urine pregnancy test. This test must be done within 10 days of date of scans and iothalamate clearance test. (Test may be done during Baseline visit if completed within the 10 day time limit, 1 ml urine is needed)

24 hour urine collection testing

- measure total volume collected

- calculate creatinine clearance (24 hour) with hydration during collection
- urine creatinine (note of toluene was added, or not, to the 24 hour collection)
- urine protein (24 hour), albumin, microalbumin
- urine electrolytes

12 The Web Data Entry System

Data entry for the CRISP study will be done using the Web Data Entry System (WDES). This system allows the data entry personnel at the PCC's to directly enter data into the data management system, which is housed at the DCIAC. The data entry system allows users to fully control their own data, while screening data from other PCC's from them. Thus, the data are entered at the PCC, where maximum information is available about values, and the original values are available to resolve problems.

Generally, the WDES works just like any other data entry system. It allows the data entry person to enter new data, edit old data and delete data (although this should not be necessary often). In most cases, all data are editable.

12.1 Form Access

Forms will be available on the web site. Forms for individual participants in CRISP will be furnished in several ways. First, they will be set up with bar-codes imprinted on the forms. This will be done either upon demand by the PCC's, or by the DCIAC, on a scheduled basis. When data entry personnel access the site, they will be able to set up these forms by selecting the appropriate choice of visits (baseline, year 1, etc.). This form packet will enable the correct data to be gathered by the PCC's. The packets will also be generated automatically when the DCIAC determines that the correct forms packet has not been obtained in a timely fashion by the PCC. These packets will be e-mailed to the PCC. The forms packets should then be printed using the CRISP printer; this printer has been chosen to have the correct version of PostScript for adequate representation of the bar-code and other such information.

After forms are printed, they will be used to gather data from participants. Paper forms are more convenient, transportable and easily stored than are computerized forms. Thus, the primary method for data entry of the CRISP study is the paper form. Once data are entered on the paper form, they will be entered into the CRISP study database using the WDES. It is important that this be done on a timely basis. Timely data entry increases the likelihood of correcting errors and decreases the likelihood of omission of forms. Timeliness of data entry will be part of the study performance feedback.

When forms are accessed on the WDES, data entry personnel will have the choice of data addition, data editing, data deletion and the listing of data for the data form. Each of these will be available for choice from the basic web site.

12.2 Data Entry

Once paper forms are completed, data must be entered into the WDES. The WDES entry point will be found on the CRISP web site, in a location specific to each PCC. Each PCC will be restricted to entering data for its participants, and will be allowed to review and revise data from those persons. Data from all participants in CRISP will be available in summary form for the study. Data from all participants will be furnished to CRISP staff in several ways.

When data entry is done, forms will be chosen from the list of forms available. When the form comes up in the browser, values for the various form items can be entered directly into the blanks for the items. The full range of item types will be used for data entry, including

radio buttons, checkboxes, text areas and the other methods. JavaScript code will be used to check code when relevant, to ensure that checks for the values are done when the data is directly in front of the data entry person.

12.3 Data Editing

Data editing will be done using the overall WDES system. When the basic form is accessed, the editing option will be one of the choices available. When editing is to be done, the basic form will include selection lists which include all current data elements. In some cases, the selection list will have a one-to-one relationship with the data in the system dataset; for instance, the ID data can be uniquely selected by the choice of the CRISP patient ID number. In other cases, the CRISP ID number must be selected first, followed by the selection of a more specific piece of information to select the data values for editing; for instance, data from one CRISP participant may be collected yearly, and thus to select a data element for editing requires the selection of an ID number, followed by the selection of the date for the editing operation to be performed.

12.4 Data Deletion

In some cases, data elements need to be deleted. For instance, if it is determined that the data values entered previously were associated with an incorrect CRISP ID number, those values must be removed. This is done using the Delete option off the basic web version of the form, in the same manner as the editing option. The Delete option should not be used often.

13 Certification Methods

This Section outlines the Certification of CRISP Study Personnel and equipment which needs to occur prior to performing procedures for CRISP.

13.1 Clinical Record Taking

All coordinators, physician assistants and nurse practitioners and other individuals involved in clinical record taking where the records will be transmitted to the DCIAC or are a part of the record keeping at the PCC are required to undergo a certification procedure prior to working on the CRISP study. Any new individual employed by a PCC to participate in this role in the study will require certification prior to any clinical record taking.

The primary clinical coordinators from each of the PCCs will attend a training session prior to the initiation of the study and will develop standards for others as part of that training session.

13.2 MR Equipment

It is the responsibility of each PCC, under direct supervision of the study radiologist, to identify the MR scanner to be used for MR data collection for the CRISP study. This will usually be the most up to date scanner, preferably 1.5 Tesla. This will be identified and validated through the series of kidney phantom tests, such that the capability of the scanner for performing the required imaging sequences for the study protocol and the accuracy for volume determination will be documented. This scanner will be tested for inter-institutional reproducibility through the Pilot Feasibility Study. The same study scanner shall then be used for collection of MR data on human study subjects for the full study.

It is an option for an institution with multiple similar scanners to validate more than one for study use. The preferred approach would be to have a single designated scanner which has been validated with phantoms. The protocol imaging sequences should be saved as a clearly identified CRISP Protocol so that each patient will be scanned with the proper set of sequences.

13.3 MR Technologist

For best image quality, the MR exams should be performed by experienced MR technologists who are ARRT registered Radiologic Technologists preferably with MR Registry. At the discretion of the PCC site Radiologist, a specific technologist may be designated as study technologist; if done a backup study technologist should also be designated. Depending on the local operations, the Radiologist may choose to designate a pool of technologists who may perform the MR scans on CRISP study subjects. It is the responsibility of the Radiologist to train the technologist/s in the proper exam performance and make certain they understand the objectives and proper imaging protocol to use.

13.4 US Equipment

The site PCC Radiologist shall select the most appropriate instrument to utilize for performance of ultrasound procedures on the CRISP study participants. He/she may designate one or more of equivalent quality, but should clearly indicate to the technologist devices

that should NOT be used because of inferior quality. The designated study instrument(s) shall be validated by use during the Standardization Study.

13.5 US Technnologist

To assure high quality, the ultrasound examinations should be performed by a technologist who is an ARRT registered technologist who has received ARDMS certification; for vascular studies if done, the technologist should also have RVT certification. One or more study technologists may be designated by the site PCC Radiologist; it is his/her responsibility to educate the technologist/s in the objectives and procedures of the study.

13.6 GFR Sample Collection

See GFR Testing Manual

13.7 Image Preparation and Transfer

The PCC Workstation should be installed and setup at remote sites to receive MR and Ultrasound studies from scanners on the local network using the DICOM protocol. The installation and setup steps are one-time steps and require no training or certification of personnel.

Personnel who operate the PCC workstation should be able to receive and review studies on the PCC workstation, replace demographic and identifying information with CRISP identifiers and transmit studies to the DCIAC. These test steps should be coordinated with the DCIAC.

1. Transfer two test studies from the MR scanner used during the study to the PCC workstation. These need not be from CRISP patients and may be phantom or quality control scans.
2. Use the procedures documented in the *Clinical Studies Workstation Guide* to register a test patient and to schedule a test MR study.
3. Merge the images from one test study with the scheduled study. This should be done with a study level merge.
4. Place the merged images in the transfer queue and contact the DCIAC to observe and evaluate the images received.
5. Using the same scheduled study, merge the scheduled information with the second test study. This merge should be accomplished at the series level. Merge two different series. You do not need to merge all series.
6. Place the merge series in the transfer queue and contact the DCIAC to observer and evaluate the images received.

13.8 Data Entry and Editing

During the lead-in period for the CRISP study, data entry personnel will be asked to sit through a very brief web-based training session about the WDES. This training session will introduce the system, demonstrate the data entry, data editing and data deletion operations. Following the completion of this brief training session, the data entry person will be issued a data entry certification, which will include the issuance of a data entry number.

13.9 Local Image Archival

The PCC workstation is equipped with a CD-ROM device with read and write capability which will be used to archive the DICOM-based image data at the PCC site. This archive will only be needed for disaster recovery. The assigned personnel should experience writing an image study to a blank disk and verify that the data can be read by the PCC workstation.

The procedure for writing CDs is documented in the Clinical Studies Workstation Guide. Use the two test MR studies that were transferred in the steps above and write those to a CD. Use the Clinical Studies Workstation (CSW) application to open and read the CD. Patient demographics and study information should match what was originally sent by the MR scanner.

13.10 Image Receipt and Registration at DCIAC

The image data coordinator at the DCIAC will evaluate the two test studies sent by the remote site. The image data coordinator will examine the received images and generate a text report that lists the following:

- Participant ID
- Accession Number
- Participant Name (should be blank)
- Protocol Name

The image data coordinator will compare these values with what should have been sent as part of the test process. If any errors are found, we will repeat the process.

13.11 Image Analysis at DCIAC

Individuals who are selected to perform image analysis during the course of the CRISP study, will have to be trained in order to process and measure the image data. A detailed set of training procedures will be created and utilized in order to instruct the individual(s) how to process the images using Analyze software, and how to measure the images once processed. After the training period is complete, a set of test images will be utilized in order to test the individual's ability to process the data and/or measure the data. The results obtained from the test images will be compared to standardized results. If the individual's results are not within an acceptable range as determined by the DCIAC principal investigator, then the individual will need additional training.

13.11.1 Image Analysis Training Procedures

The intent of the training procedures it to equip an individual who does not have any experience with the human kidney anatomy, viewing MR/US images of the kidney for anatomical purposes, utilizing Analyze software for processing and measuring the human kidney, and learning how to measure the renal volume using stereology methods. The training procedure will consist of a hand-on instruction and review of the following materials: (1) a detailed pictorial and written description of the kidney and ADPKD anatomy, (2) sets of T2 and pre-/post-gadolinium enhanced T1 images of the kidney obtained using the CRISP study protocol, (3) sets of US images of the kidney obtained using the CRISP study

protocol, and (4) a detailed (containing all the step-by-step instructions) description of how to use the Analyze software to segment images which include the selection of optimal threshold to image display and boundary determination.

14 Data Coordinating and Imaging Analysis Center: Image Analysis Section

14.1 Function of the IAS

The functions of the Image Analysis Section (IAS) are

1. Propose the development of the initial study protocols for the imaging studies
2. Establish standardization of the imaging data
3. Support the PCC's with imaging data acquisition, secure transmission, central processing and analysis
4. Collect, store, and analyze the imaging data generated by the PCC's
5. Implement a database for image data management and provide image measurements to the BDCS for statistical analysis
6. Oversee implementation and adherence to the study protocol including data auditing and quality control procedures

14.2 Image Transfer Methods

The DICOM protocol is used to transfer images from the acquiring modality to the CRISP Workstation located at the PCC site via the local area network. The workstation provides a facility to remove patient demographics (referred to as "header scrubbing") from the DICOM image study sets, substituting an accession number assigned by the DCIAC. This operation allows patient confidential information to remain at the PCC site.

Following "header scrubbing", the coordinator, or designated representative, enables a software client which creates a Virtual Private Network connection between the PCC Workstation and the firewall device at the DCIAC. Point-to-point Tunneling Protocol (PPTP), Layer 2 Tunneling Protocol (L2TP), and IPSec are used to establish the secure channel over the Internet. Encryption (Data Encryption Standard - 128 bits) is then applied to the image data sent over the VPN.

Images are decrypted by the firewall device at the DCIAC and forwarded over a private local area network to a DICOM storage application on the UNIX computer system dedicated to the CRISP project.

14.3 Image Conversion for Analysis

Software conversion routines have been written to convert the DICOM data into a format compatible with the ANALYZE Image Processing software. (Mayo Foundation, Biomedical Imaging Resource, Rochester, MN.) The individual image data (cross-sectional slices) from the MR scans will be converted to the Analyze volume file format. The ultrasound data is converted to the Analyze individual slice file format.

14.4 Image Analysis Methods

Several image analysis methods have been developed and tested on DCIAC ADPKD volunteers and the standardization participants: stereology, region growing by seed placement, multi-spectral analysis, region-based thresholding, manual border-tracking, and b-spline border tracking techniques. The latter two methods, manual and b-spline border-tracking

techniques, were applied to segment the total kidney region but not considered further because they were tedious and labor intensive. The stereology, region-growing, and multi-spectral techniques are utilized to measure the whole kidney volume including cysts. The multi-spectral and region-based thresholding techniques are used to measure the cyst volume.

14.4.1 Stereology

The stereology technique involves a simple, fast method of visually segmenting an object by counting the number of intersections of a randomly oriented and positioned grid over the object to be measured. This technique has been widely used in cytopathology and medical imaging analysis. The advantage of the stereology technique is it allows the operator to utilize the complex interaction of the human eye and shape recognition to segment complex images, but its weakness is that it is heavily operator-dependent and somewhat subject to display window settings. Thus, accurate and reliable measurement requires training an operator and consistent initial adjustment of display window settings.

To measure the whole kidney volume using Analyze stereology software, a single post-gadolinium T1 series (T1 MR scan containing many individual adjacent slices to form a volume) with no fat saturation is needed that contains both the left and the right kidneys. After the T1 series which contains multiple adjacent images is loaded, the operator will view a image (slice) located in the approximate middle of the kidney(s) and set the maximum threshold to a value that does not saturate the kidney or cysts, but yet enhances the contrast between the kidney and surrounding tissue. Setting the threshold is necessary to improve the visual recognition of the kidney parenchyma and cysts. Grid points over the renal paranchyma and cysts will be mouse-clicked and marked over one kidney at each slice throughout the series. The cross-sectional renal area will be calculated by counting the number of marked grid points and using a conversion factor determined in the DICOM image header, while the volume will be computed from the cumulative number of marked grid points for each kidney.

14.4.2 Region-Growing by Seed Placement

The region-growing by seed placement is rapid thresholding method for measuring the perimeter of the whole kidney image-by-image using a single T2 series with fat saturation. After the T2 series which contains multiple adjacent images is loaded, the operator will view an image located in the approximate middle of the kidney(s) and set the maximum threshold to a value that does not saturate the kidney or cysts, but yet enhances the contrast between the kidney and surrounding tissue. The advantage of this technique allows the operator to place a seed within the kidney and adjust the upper and lower threshold of the seed until the perimeter of the kidney is visually delineated by the operator on an image-by-image basis. After the kidney perimeter is determined, the exterior region is set to a value not found in the kidney (normally set to zero). Therefore, the result is a segmented kidney after all the images have been segmented in this manner. The disadvantages of this method are (1) the subjectivity of determining the initial window setting to improve kidney and surrounding tissue contrast, (2) the subjectivity of determining the best threshold for each individual slice to delineate the perimeter of the whole kidney, and (3) the subjectivity of drawing limits when the region-growing includes the kidney or spleen in the perimeter. The

operator is required to manually draw a limit along the edge of the kidney perimeter in order to exclude the unwanted tissue(s). After a kidney has been segmented, it is saved and the volume measured using Analyze Region-of-Interest (ROI) software. The voxels are automatically counted in ROI by choosing a threshold set above the base value that eliminates the background surrounding the kidney and only includes the perimeter and interior of the kidney. Since the ROI software only counts voxels, the voxel count has to be converted to a volume using a conversion factor (number of voxels times the volume of a voxel) determined by knowing the voxel dimensions as found in the DICOM image header.

14.4.3 Multi-Spectral Analysis

Multi-spectral analysis is a more complex and time intensive method of measuring the whole kidney volume and the cyst volume simultaneously. Analyze multi-spectral analysis software utilizes two series (one post-gadolinium T1 series and one T2 series with fat saturation) of the same subject that are in perfect physical registration to classify/differentiate the different components of the images (kidney, cysts, liver, spleen, fat, muscle, etc.) The major advantage of this technique is its ability to classify in a more objective manner the various tissue types in the images including the cysts. Also, multi-spectral analysis has the ability to classify the areas round the perimeter of the cysts and kidney that are not absolutely known to be either parenchyma or cyst. The major disadvantages are (1) the increased time to measure the kidney, (2) the subjective nature of identifying cysts to be used in the registration process, (3) registration error, and (4) the subjective nature of sampling the tissues in the image to assist in the classification process.

The multi-spectral analysis process initially requires two series to be loaded as described above. Only one kidney at a time can be processed from a single series. Therefore, the left and the right kidneys from each of the two series must be separated into their own series or volumes. In other words, a single T1 series containing both the left and the right kidneys will be separated into two series where each contains a single kidney. The T2 series is separated in the same manner. In order to register the kidneys, some of the cysts from each left kidney (T1 and T2 series containing only the left kidney) must be identified visually and segmented using thresholding techniques. The objective is to identify similar cysts in both left kidney series. Once the cysts have been segmented, they will be used to co-register T1 and T2 series. After registration, the whole left kidney from both series are superimposed/merged into a single volume in order to visualize the any misregistration. If the registration appears to be adequate, the kidneys are now classified in the multi-spectral analysis module. The two registered left kidney series are loaded into the multi-spectral module and sampling of the various tissues begin from an image that is approximately centrally located in the kidney. After sampling the cysts, parenchyma, liver (or spleen for the right kidney), and other tissues that lie outside the kidney, the operator is required to draw separate regions containing points for each sampled tissue type in the classified image as a first approximation for each tissue classification. The multi-spectral module will then create an objective classification. The classified images are visually inspected to determine if the classification process was successful. If so, the volume of each classified component (tissue type or sub-type) in the image is calculated. The above process can be repeated for the right kidney.

14.4.4 Region Based Thresholding

The region-based thresholding method is utilized to measure the volume of cysts from heavy T2 weighted series. Since the heavy T2 weighted series essentially eliminates all tissue types except for water filled cysts, the cysts appear as bright objects (water has a long T2 value compared to other tissue or fat). From a single T2 image, the cyst volume from either the left or the right kidney can be determined. The major advantage of this method is that the cysts can be easily separated from the renal parenchyma with a high tissue contrast. However, some complex cysts may have other component besides water and thus may lose the bright signal intensity. This region-based thresholding method requires four steps: (1) The regular and heavy T2 weighted series are displayed simultaneously slice-by-slice; (2) cysts that are bright in the regular T2 series but not obvious in the heavy T2 series are manually edited to contain bright pixel values using Analyze image edit software; (3) The right and left kidneys in the heavy T2 images are separated. Any other bright objects (spinal fluid) that appear in the left or right series must be removed; (4) A histogram is generated from the pixel values within the left kidney series; (5) A threshold value, which provides a maximum separation of the cysts from the surrounding noise in the series, is determined in the histogram; and (6) The threshold is used to calculate the number of voxels in the cysts. The voxels is converted to a volume knowing the voxel dimensions. The region-based thresholding method is reproducible and less operator-dependent, but choosing the correct threshold value may be subjective. If the regions (cysts and background noise) to be separated in the series have well-segregated pixel values in the histogram, a consistent threshold value is more likely attainable. The above process can be repeated for the right kidney.

14.4.5 US Measurement Methods

When there are more than 3 cases (Ultrasound (US) CRISP Forms) found in the "before QC box" on the wall of Ty's room, you should pick up all of them and go into "CT/MR Visualization Lab (Room# 3337)". Now, it's time to pull up all of the image files on the computer called DCIAC.

Type your USER NAME (Now, you can use mine "suh".) on the screen of the computer, and press the ENTER key. Type your PASSWORD (Now, 0312ucsf) on the screen, and ENTER key.

Right mouse click → Tools → Terminal
In the Terminal window, type "Analyze &" at the command prompt, then → Enter key
Click on "Done" (Not necessary if "Tip of the Day" is not open)
Click on "File" → "Load as" → "Auto Exit After Load" → "File"
Go to the Directory of "dciace" (Year 1 data can be found in "dciacb")
Double click on "dciace" → "pkd" → "pat" → "fv01" (Year 1 data can be found in /dciacb/pkd/pat/bv01)
If the first digit of the accession # found on the US CRISP Form is "5", double click on "5x".
Double click on the directory containing the accession #.
Double click on the first file that contains the "accession #.1.avw" or "accession #.1A.avw→ click "Load"
(If more than one "accession #.?.avw" file exists in the directory, Click "File" → Double click on the second file → click "Load". REPEAT this until all *.avw files are loaded into the "Analyze 4.0" window) * *Each US case has one or two image files; however, sometimes it has 3 files by mistake.*
Click "Cancel".

Now you are ready to measure, but you need to pull up the database, located in the computer in your right side also.

Click "start" → " program" → "Microsoft Access".
Double click "C:\PKD-MS~\crisp".
Click "Forms".
Double click "dbo_us_stereo1".
Type your login ID/ password (Now, "suh"/"mirsuh").
Go to the end of the database.
Fill out all the blanks in the database by using "CRISP NEW US Session Form".
*"*us_review_date" should be same with "start_datetime"; however, it could be different if Ty review the case (Ty is supposed to review cases which have bad image qualities or which do not follow the protocol properly. Actually, you should ask Ty to review the cases.)*
"length" in the database = "L/CC" (If "L/CC" has two instead of one, sum up the two and fill it out.)
"width" = "L/AP"
"width_2" = "T/AP"
"depth" ="T/ML"

In order to fill out "number_of_slices", "kidney", and " shadow" and double-check the agreement between forms and files, now you go to the DCIAC computer.

Regarding Scanning Plane,
*If you see only "transverse" in the form, just type "**Y**" in "kidney_vol_cal_r(l)" blank. However, If you see other than "transverse" (oblique or intercostal), type "**N**" in "kidney_vol_cal_r(l)" blank.*

Within the Analyze 4.0 window, click "Measure" → "Stereology"
Start double-checking.
*"Comments***" in the Forms mean "Areas" in the images.*
If you see Yes *in the "AE**" in the Form, it means the image has shadow area. If shadow areas are more than one, you should sum them up and fill it out to the blank in the "shadow".*
Once you finish double-checking the forms, you should fill out the *"kidney"* and *"shadow"* columns in the database while measuring the data.

Now you are ready to measure cysts in the image file.
Make a grid within the Stereology window by clicking "Generate" → "Grid…" In the Grid Parameters window click "Generate Grid" and make sure the X Spacing and Y Spacing are both 10. Then click "Done"
**You should adjust the intensity to improve measurement by clicking "view → intensity" and reduce the maximum intensity.*
In addition to the image file with grids, you should open another stereology window by clicking "Measure → Stereology" with the same image in it without the grid. Place the two stereology windows side by side as a reference because the US image with the grid on it does not show the cysts clearly.

Click the large + sign next to the stop and go light to move to the next image in the Stereology window. Continue clicking the + sign until you find a slice with "Area" and "Circum" measurements located in the lower right hand corner. Start clicking on the red grid points (or plus signs), located inside of cysts. After you click on a + grid point, it will turn a green color. Be aware that we only want to use images showing area measurements. Do not click on shadow areas!!!

- *You can choose "cursor Size and Shape" interactively by clicking the right mouse button.*
- *If you click on a grid point that should not be included in the cyst measurement and you want to erase the chosen grid point, click the point again while pressing down the SHIFT key.*

Repeat measuring cysts in each image found in the loaded *.avw file as described in the above paragraph. When you finish clicking the + signs in all of the images containing cysts, it is time to save all you have done.

1. Click "File "→ "Save Grid" and Type "accession#_1_your initials with the number 1.grid" (For example: **123456_1_jds1.grid**) → click "Save".
2. Click "stats" → "Log Stats" → Click Right mouse button → "Save Log As" → Type "accession#_1_your initials with the number 1.stats" → Click "Save" → "Done" → "Done"
3. "Control key + S key" → right mouse button → "Save Log As" → Type "accession#_1_sl_your initials with the number 1.stats" → "Save"
   Before clicking "Done", you should fill out the subform called "dbo_us_stereo_slice1" found in the form "dbo_us_stereo1" in the CRISP database with all of the cyst grid counts for each slice as found in each image. Within the "Slice Stat Log" window, you will find two columns of numbers titled Slice and Count. The first slice numbers are typically from the right kidney and the larger slice numbers are typically from the left kidney. If the first slice number is 4 as found in the "Slice Stat Log" window, you will need to place the count number found next to it into the database column "kidney_r" with the number 1 placed in the first row in the "image_no" column. The count found next to slice number 5 in the "Slice Stat Log" window needs to be placed next to the number 2 in the "image_no" column in the database in column "kidney_r". Repeat the placement of count numbers into the "kidney_r" column for all right kidney images. Repeat this method for the count numbers found in the "Slice Stat Log" for the larger "Slice" numbers and place the count numbers into the "kidney_l" column. Once again, the first count number for the left kidney should be place first row in the "kidney_l" column with "image_no" equal to 1.
   Click "Done".

Now you have one last step.
Go to the first images for the right kidney first then the left kidney (1 right + 1 left) for making an area measurement of the whole kidney, and click all the grids found inside the outline of the kidney.
"Control key + S key" → Find the above two "Slice Count" → Fill out "kidney_ster_area_r" & "kidney_ster_area_l" boxes in the database form "dbo_us_stereo1".

If there is something unusual, you can write down the problems in the "us_stereo_comment" box.

One extra-step:
Click "Form" in the database.
Click "Study_from_US_Query"
Go to the accession# by clicking the bottom arrow.
Fill out "qc_date" with today's date, "image quality" & "protocol" with your own judgement.

Put the Form into the "after QC" box on the wall of Ty's room.

If you have done more than 15 cases, pull up those grid files in the JAWS computer for review and ask Ty to review those.

After Ty's review, you have to put Ty's slice count into the "cyst_r(l)" in the data base.

14.4.6 Specific Details About MR Measurement Methods

Before Ty Bae's quality control (QC) of the MR images

Ty needs to perform QC on all of the MR series received from a PCC site for two reasons: (1) to determine if the MR series were performed correctly, and (2) to determine which MR series for a given accession number need to be measured. Ty records his QC comments in the CRISP database. All of the series for each accession number need to be opened so Ty can perform the QC.

Each of the T1 and T2 series received for a particular accession number will be reviewed by Ty Bae for quality control, completeness and for making a decision as to which series within an accession number are to be measured. For the 3-5 mm T2 series, Ty has to decide which slices are to utilized in each series that contains only a portion of the kidney. Since the slice thickness is so small, and the acquisition time for T2 series is so slow, multiple series acquisitions are required to cover the entire kidneys.

When you see more than 3 cases (3 MR CRISP Forms) in the "before QC box" on the wall of Ty's room, you should pick up all of them and go into "CT/MR Visualization Lab (Electronic Radiology Laboratory Room # 3337)". Now, it's time to open up all of the series files on the computer called: JAWS.

Type Ty's USER NAME (tbae) on the computer called: JAWS.
Type Ty's PASSWORD (aloevera).

Right mouse click → Tools → Terminal
(**NOTE:** throughout the remainder of this document the symbol → will represent either (1) click with the mouse button while the cursor is placed over the following word or (2) press the following key on the keyboard.
In the Terminal window, type "Analyze &" at the command prompt, then → Enter key
Click on "Done" (Not necessary if "Tip of the Day" is not open)
Click on "File" → "Load as" → "Auto Exit After Load" → "File"
Go to the Directory of "dciace" (Year 1 data can be found in "dciacb")
Double click on "dciace" → "pkd" → "pat" → "fv01" (Year 1 data can be found in /dciacb/pkd/pat/bv01)
If the first digit of the accession # found on the MR CRISP Form is "4", double click on "4x".
Double click on the directory containing the accession #.
Double click on the first file that contains the "accession #.series #.avw" → click "Load"
(More than one "accession #.?.avw" file should exist in the directory, click "File" → Double click on the second file → click "Load". REPEAT this until all "accession #.series #.avw" files are loaded into the "Analyze 4.0" window)
Go to the directory that has the next accession number as found on the MR CRISP Forms. Repeat the loading of the files found in these directories.
Click "Cancel".
Let Ty know that there are the QC cases for in the JAWS computer.

After Ty Bae performs MR QC

After Ty performs the MR QC, you need to open several of the MR series for an accession number so that the different types of MR series can be measured. Each series that needs to be measured for each accession number will be noted in the database by Ty Bae.

Measurement Method	MR Sequence	Kidney Volume	Cyst Volume	Paren. Volume	Blood Cyst Volume	Hrs/Patient
Stereology	Post-Gad T1 Pre-Gad T1	*			 *	1-2 Hrs 0.5-1 Hr
Autotracing	T2	*				1-2 Hrs
Region-Based	T2		*			1-2 Hrs

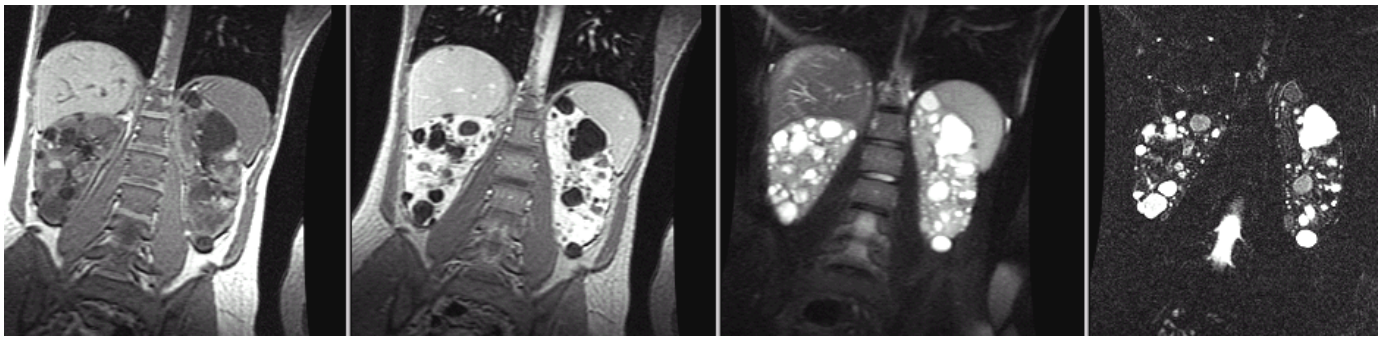
Table Image Analysis Summary
* Stands for the type of volume measurement to be performed.

MR protocol (T1 image)
1. 3mm pre-gad T1 (3D VIBE/FMPSPGR) without FS
2. Gad injection, MR angiography.
3. 3mm post-gad T1 without FS. Two series required one at 2 and one at 3 min after start of injection.
4. Breath-hold, phase-contrast technique of renal blood flow measurement

MR protocol (T2 image)
1. 9mm regular T2 (SSFSE/HASTE) with FS achievable in a single breath-hold (BH)
2. 3mm regular T2 with FS one breath hold for small kidney but may need 3 breath holds with neighboring series overlapped by one 3mm slice
3. Adjusted (3-9mm) regular T2 with FS best attainable with one breath hold
4. Adjusted as above heavy T2 with FS with 1 to 3 breath holds

MR protocol

MR Sequence	**Cyst**	**Parenchyma**
T1	Dark	Gray
Post-Gad T1	Dark	Bright
T2	Bright	Gray
Heavy T2	Bright	Dark



T1 **Post-Gad T1** **T2** **Heavy T2**

In the CRISP database, you can find Ty's QC comments in the form called: "dbo_Study_from_MR_Query4".

You can easily go to the correct accession # in the database by typing the accession # into the box called "Find Accession #" located in the upper left-hand corner of the Query4.

Now it's time to open up all series files, where Ty recently performed QC for the accession numbers, on the computer called: DCIAC.

Type your USER NAME (Now, you can use mine "suh".) on the DCIAC computer screen, and ENTER key.
Type your PASSWORD (Now, 0312ucsf) on the screen, and ENTER key.

Right mouse click → Tools → Terminal
Type "Analyze &" → Enter key
Click on "File" → "Load as" → "Auto Exit After Load" → "File"
Go to the Directory called: "dciace"
Double click on "dciace" → "pkd" → "pat" → "fv01"
If the first digit of the accession # found on the MR CRISP Form is "1", double click on "1x".
Double click on the directory with the correct accession #.

STEP 1. Create New Files for Measurement (Autotrace, Hemorrhagic cysts, Stereology, Liver cysts)

1. **Autotrace of the Whole Kidney**

In the CRISP database QC form called: "dbo_Study_from_MR_Query4", you will see columns and rows as shown below for a given accession number.

series _no	wdes_series_ descrip	thickness	no_of_ slices	fov	measure_ needed	slices_to_ measure	orientation
4	T2 FatSat	3	17	350x35	y	1-14	pos
5	T2 FatSat	3	17	350x35	y	1-15	mid
6	T2 FatSat	3	17	350x35	y	4-16	ant

Sometimes a single T2 series is obtained with a single breath-hold if the kidney is small; however, most of time the T2 series for the kidneys are obtained with 2 or 3 breath-holds. (NOTE: Please ignore the Heavy T2 series images that are collected for an accession number. Barry Brunsden is currently using a specially designed measurement method to measure the cysts in Heavy T2 images.) In this case, *there were 3 breath-holds (anterior-mid-posterior)*. Therefore, you have to append these 3 files to create one new file for measurement. You need slice numbers *4-16* from the anterior portion (*#6* series), slice numbers *1-15* from the mid-portion *(#5* series), and slice numbers *1-14* from the posterior portion (*#4* series).

Note on **Append command in Analyze**: The files you want to append must be in a left to right order. The file on the left will have the file on the right appended to it and so on.

The following series must be loaded from anterior to posterior, that is, from series 6 to series 4.

Double click "xxxxxx.6.avw".
Click "Subregion" tab in the "Load As 4.0" window.
Type *4* and *16* in the "Low" and "High" sections of the "Z" row.
"Load".

Click on the "File" button in the "Load As 4.0" window.
Double click "xxxxxx.5.avw".
Click "Subregion".
Type *1* and *15* in the "Low" and "High" sections of the "Z" row.
"Load".

Click on the "File" button in the "Load As 4.0" window.
Double click "xxxxxx.4.avw".
Click "Subregion".
Type *1* and *14* in the "Low" and "High" sections of the "Z" row.
"Load".

Now you have opened three new files.
Shift key + Click on "xxxxxx_6" file, then on "xxxxxx.5.avw", then on "xxxxxx.4.avw". All while holding down the shift key. All three files should be high-lighted in the Analyze 4.0 window with a red border around them.
Right mouse click → "Append" → "Don't Unload"
Click on "File" → "Save As" → Type "xxxxxx_6_5_4Ap.avw" → Save.

Click on "File" in the "Load As 4.0" window.
Double click on "xxxxxx_6_5_4Ap.avw".
Click on "Interactive(XY)" found under the SubRegion tab.
Cut all unnecessary volume from the exterior of both kidneys by using the "green lines". Make sure you have cut as much off from the left side of the right kidney and right side of the left kidney as possible.
Click "Done" → Load

Now click on "File" in the "Analyze 4.0" window then "Save As". In the "Save As" window, click no the "File" button then select the file named "xxxxxx_6_5_4Ap.avw"→ "Write Over the Existing File"
Click "Process" → "Filter" → "Spatial" → "Generate" → "Filters" → "Inhom. Correct." → "Filter" → "Change a Copy of the Loaded Volume".
Now click on "File" in the "Analyze 4.0" window then "Save As". In the "Save As" window, click no the "File" button then save the file with the following name:
"xxxxxx_6_5_4Apicatk.avw".

Click on "File" in the "Load As 4.0" window.
Double click on "xxxxxx_6_5_4Apicatk.avw".
Click on "Interactive(XY)".
Cut all unnecessary volume from the exterior of the right kidney by using the "green lines". Make sure you have cut as much off from the left side and right side of the right kidney as possible. Jongdae says you need to make the width of the image volume as small as possible so when you perform the region based and hemorrhagic cyst measurements with three separate Analyze measurement windows open, you need the size of the image to be as narrow as possible.
Click "Done" → Load

Now click on "File" in the "Analyze 4.0" window then "Save As". In the "Save As" window, click no the "File" button then save the file with the following name:
"xxxxxx_6_5_4Apicatkr.avw".

Click on "File" in the "Load As 4.0" window.
Double click on "xxxxxx_6_5_4Apicatk.avw".
Click on "Interactive(XY)".
Cut all unnecessary volume from the exterior of the left kidney by using the "green lines". Make sure you have cut as much off from the left side and right side of the left kidney as possible.
Click "Done" → Load

Now click on "File" in the "Analyze 4.0" window then "Save As". In the "Save As" window, click no the "File" button then save the file with the following name:
"xxxxxx_6_5_4Apicatkl.avw".

Get rid of all files in the "Analyze 4.0" box .
Shift key + click on "xxxxxx_6" → Right mouse button → "All".

Load the two new files.
"xxxxxx_6_5_4Apicatkr.avw" & "xxxxxx_6_5_4Apicatkl.avw"

2. Hemorrhagic cysts

From now on, the file creation explanation will be simplify because you can just use the methods described above to load and save the processed series. For the hemorrhagic cysts, only one PreGad T1 series is obtained, so no appending is necessary. The names of the files will change a described below.

In the CRISP database QC form called: "dbo_Study_from_MR_Query4", you will see columns and a single row as shown below for the same accession number as above.

series _no	wdes_series_ descrip	Thick ness	no_of_ slices	fov	measure_ needed	slices_to_ measure
14	Pre T1	3	52	350x35	y	

Click on "File" in the "Analyze 4.0" window and then "Load As".
Double click "xxxxxx.14.avw".
Click "Subregion" → "Interactive (XY)".
Cut all unnecessary volume except for both kidneys by the "green lines" → "Load".
Save as "xxxxxx_14_pshc.avw".

Make 2 new files for the right and for the left kidneys by the same procedure described above in Autotrace. Make sure you have cut as much off from the left side and right side of the kidneys as possible. Then save as "xxxxxx_14_pshcr.avw" and "xxxxxx_14_pshcl.avw".

3. Stereology of the Whole Kidney

In the CRISP database QC form called: "dbo_Study_from_MR_Query4", you will see columns and a single row as shown below for the same accession number as above.

series no	wdes_series_ descrip	Thick ness	no_of_ slices	fov	measure_ needed	slices_to_ measure

16	Post Gad T1	3	52	350x35	y	

Click on "File" in the "Analyze 4.0" window and then "Load As".
Double click "xxxxxx.16.avw".
Click "Subregion" → "Interactive (XY)".
Cut all unnecessary volume except for both kidneys by the "green lines" → "Load".
Save as "xxxxxx_16_psk.avw".

Make 2 new files for the right and for the left kidneys by the same procedure described above in Autotrace. Make sure you have cut as much off from the left side and right side of the kidneys as possible. Then save as "xxxxxx_16_pskr.avw" and "xxxxxx_16_pskl.avw".

From the above Image Analysis Summary Table, the Post-Gad T1 series needs to be measured using Analyze's Stereology module. In order to improve the speed of measuring the images with stereology, the Post-Gad T1 series (e.g. file name /dciacd/pkd/pat/2001.01/046337/046337.12001-3.avw) needs to be loaded using the Load As option in Analyze. Use interactive (XY) located in the SubRegion Tab to reduce the area around the kidneys to include only the 2 kidneys and not the entire body. If the volume is loaded using these smaller x,y,z values, the Analyze volume file is smaller and therefore, Analyze Stereology module increments through the slices more rapidly.

After the SubRegion has been loaded, this new volume needs to be saved to the same directory it was loaded with the following new name: 046337.12001-3_psk.avw First, the Analyze volume file name (046337.12001-3.avw) which was used to create the SubRegion, will have the additional characters "_psk" appended to the end of the name. The additional letters represent the file was processed "p", stereology measurements are to be made on the file "s", and the kidneys in the file are to be measured "k". For example, the file name 046337.12001-3 had the following characters "_psk" appended 046337.12001-3_psk.avw to represent the file was processed for measuring the kidney with stereology.

After saving the file with the name: 046337.12001-3_psk.avw, this file now needs to be loaded. Once loaded, use the Save As module to save the right kidney and the left kidney as individual volume files. Within the Save As module, use the interactive (XY) feature in the SubRegion Tab to save just the right kidney. The file name given to the right kidney should be: 046337.12001-3_pskr.avw Thr right kidney is actually located on the left side of the volume as you look at it because the patient is facing you in the volume. Now save the left kidney (located on the right side of the volume) with the name: 046337.12001-3_pskl.avw

E-mail Paul Commean at commeanp@mir.wustl.edu to let him know the accession numbers for the stereology files you just created are ready to be measured.

4. Liver Cysts

In the CRISP database QC form called: "dbo_Study_from_MR_Query4", you will see columns and a single row as shown below for the same accession number as above.

series_no	wdes_series_descrip	Thickness	no_of_slices	fov	measure_needed	slices_to_measure
9	T2 FatSat	6	52		y	

Click on "File" in the "Analyze 4.0" window and then "Load As".

Double click "xxxxxx.9.avw".
Click "Subregion" → "Interactive (XY)".
Cut all unnecessary volume except for both kidneys by the "green lines" → "Load".
Save as "xxxxxx_9_8_7APL.avw" or "xxxxxx_9PL.avw".

Make the new file for the liver by the same procedure described above in Autotrace. Make sure you have cut areas outside of the liver that are not necessary for measurement.

STEP 2. Database Preparation for Autotrace, Region Based, Hemorrhagic Cyst, and Stereology.

After unloading all unnecessary images on the screen, Load the two new images "xxxxxx_14_pshcr.avw" and "xxxxxx_14_pshcl.avw". Now a total of four images named as follows should appear in the "Analyze 4.0" window: "xxxxxx_14_pshcr.avw", "xxxxxx_14_pshcl.avw", "xxxxxx_6_5_4Apicatkr.avw", and "xxxxxx_6_5_4Apicatkl.avw".

You have to fill out the database before making measurements. Open the CRISP database.
Go to "Tables" and open both tables "dbo_mri_param" & "dbo_mri_proc".
In "dbo_mri_param" table, you should see column headings as shown below.

accession_no	series_no	no_of_slices	slices_to_measure	Orientation	measure_needed	mri_param_comment
363330	6	17	4-16	Ant	y	

thickness	wdes_series_descrip	image_header_series_descrip	vol_file
3	T2 FatSat	WET-KID-PK-	/dciace/pkd/pat/fv01/3x/363330/3

Copy the directory path from the "vol_file" column and paste it into the last blank of the "vol_file" column in the "dbo_mri_proc" table. Then fill out the whole row. Concerning "depth_z; height_y; width_x", you can find it in the series file by first clicking on the image in the "Analyze 4.0" window, then "right mouse click"→ "Info" (look in the end part of the Info file). After copying the four separate "vol_file" directory paths from the "dbo_mri_proc" table to the "dbo_mri_proc" table and filled out all of the rows as shown below, you are ready for measuring the series.

vol_file	proc_method	Staff_name	proc_file	proc_date	proc_ descrip	proc_ formula
/dciace/pkd/pat/fv01/3x/363330/363330.6.avw	Region Based 2	Jongdae Suh	363330_6_5_4 Apicatk.avw	1/28/02	Both Kidneys	
/dciace/pkd/pat/fv01/3x/363330/363330.6.avw	Autotrace 1	Jongdae Suh	363330_6_5_4 Apicatk.avw	1/28/02	Both Kidneys	
/dciace/pkd/pat/fv01/3x/363330/363330.14.avw	Stereology 3	Jongdae Suh	363330_14_pshc.avw	1/28/02	Both Kidneys	
/dciace/pkd/pat/fv01/3x/363330/363330.16.avw	Stereology 1	Jongdae Suh	363330_16_psk.avw	1/28/02	Both Kidneys	

proc_formula	depth_z	height_y	width_x
	3	1.367188	1.367188
	3	1.367188	1.367188
	3	1.367188	1.367188
	3	1.367188	1.367188

If you go to "dbo_mri_proc_Autotrace_1_Query" & "dbo_mri_proc_Region_Based_1_Query" tables, you will see that all of the newly entered text information for your accession numbers in the "dbo_mri_proc" table will appear in the top portion of the forms (portion of the form where the "dbo_mri_proc" information is displayed when you do a search on an accession number by using the "Find proc_file" feature. The "proc_file" must be used to find the information or you can just use the date to sort the data from "Z to A". Then all of the newest files you just entered into the "dbo_mri_proc" table will appear.)

You have to modify "dbo_mri_stereo_hcyst" table because a form doesn't presently exist for hymorraghic data entry. Copy the **proc_file name** "363330_14_pshc.avw", from the "dbo_mri_proc" table and paste it into the "dbo_mri_stereo_hcyst" table in the column called "proc_file_sh" as shown below. Fill in the other columns as necessary.

proc_file_sh	measure_no	proc_ method	staff_ name	cyst_review_date
363330_14_pshc.	1	Stereology	Jongdae	1/28/02

cyst_ space_x	cyst_ space_y	low_ threshold_ cyst_r	high_ threshold_ cyst_r	proc_ cyst_ file_l	start_ datetime_ cyst_l	end_ datetime _cyst_l	vox_cnt _cyst_l

high_thresh old_cyst_r	proc_cyst _file_r	start_datetim e_cyst_r	end_datetime_ cyst_r	vox_cnt_ cyst_r	cyst_stats_file_r

cyst_slice_stats_ file_r	cyst_grid _file_r	low_threshold_ cyst_l	high_ threshold_ cyst_l

Now you have blanks in the forms and tables waiting for your measurement results.

STEP 3. Kidney and Cyst Measurement Methods

1. **Autotrace Kidney Segmentation Method (**xxxxxx_6_5_4**Apicatkr(l).avw or** xxxxxx_6_5_4**picatkr(l).avw files) (Autotrace 1)**

   Determining the threshold for segmenting the kidney using Autotrace methods is not easy. It's somewhat of a subjective process. Run Region Of Interest (ROI) by selecting Measure then Region of Interest in the Analyze 4.0 window on an example file (xxxxxx_6_5_4Apicatkr.avw) in order to find the maximum intensity value using the Historgram option. Turn on Histogram and open Sample Options (NOTE: more details for each click and options will be given below). Turn Summing On, and change Sample to All Slices. Click on the image to start the histogram. Look at the histogram and you will most likely see one large hump near the zero portion of the axis, and trailing off as you move right (positively) along the x-axis. As the number of intensity occurrences trail off on the x-axis, pick an x value that is approximately 80 to 90% of the maximum intensity value seen. Don't be concerned if you are seeing the exact maximum value or finding exactly the 80 or 90% value point. The objective is to just find an approximate intensity value for thresholding the images. You can see the X: value below the word Intensity in the "Histogram – Region Of Interest" window when you use the mouse cursor to point at the histogram. Keep this threshold number in mind for starting the Autotrace segmentation.

   These two files ("xxxxxx_6_5_4Apicatkr.avw", and "xxxxxx_6_5_4Apicatkl.avw") should already be loaded now, if not load them, and segmented using Image Edit autotrace feature. Use the threshold found above as the maximum intensity value to brighten the image. Scroll through the images to make sure this threshold intensity value allows you to easily see the perimeter of the parenchyma, even though the parenchyma may still very dark in comparison to the cysts. If you find it difficult to delineate a border of the kidney against the darker background, then decrease the maximum intensity value until you can more easily see the perimeter of the kidney parenchyma. Using the Image Edit autotrace feature to segment the kidney is rather easy to do. Just place a seed in the kidney area and adjust the intensity sliders so the parameter of the kidney is captured. Determining where the perimeter of the kidney lies may not be an easy matter sometimes. In many cases, you will need to use the "Add Limit" feature in "Image Edit" to cut off any areas included in the kidney by autotrace that are not part of the kidney. Trying to trace the border of the kidney with the "Add Limit" feature is very subjective sometimes. If you find it difficult to determine the perimeter/border of the kidney, you may need to load the Post Gad T1 image with ROI to help in determining the exact border. You can find a similar slice in the T1 image as found in the T2 image to help with border segmentation. You will also need to cut out all kidney hylum that is directly connected to the region outside of the kidney. You will almost always need to use the "Add Limit" feature to drawn the hylum area for exclusion. After cutting off all parts outside of the kidney, select the Off Edge feature and pick the "Flood Fill" button containing the spilled bucket and clock in it. Click now inside of the image but outside of the autotrace area. A small red down pointing arrow with the word Fill above it should appear in the image. When you select "Change Image" now, the areas outside of the kidney will be deleted and all of the exterior values

from around the kidney should be given a value of zero. After completing the editing process for all slices in the series, save the right kidney file as: xxxxxx_6_5_4Apicatkre.avw.

First, determine intensity range by histogram for Autotrace editing.
Click on an image file in the "Analyze 4.0" window then → "Measure" → "Region of Interest". In the "Region of Interest" window, select "Generate" → "Sample Options". In the "Sample Options" window, turn "Summing" **On** , then turn "Sample" **All Slices** on by clicking the button next to it → Done. In the "Region of Interest" window, select "Generate" → "Histograms". In the "Histogram" window, turn "Histogram Display" **On** → Done. Now click on the T-1 image in the "Region of Interest" window.

Fill out the database column called "low_threshold_r" with the "Minimum number" which is normally always found to be zero as shown in the ROI Stats window. Then select Done in the ROI Stats window to close the window. From the Histogram window, choose a threshold as described above by looking at the Histogram.

Click on "xxxxxx_6_5_4Apicatkr.avw" file → "Process" → "Segment" → "Image Edit" → "View" → "Triple" → "View" → "Intensity" → Type "the above maximum #" → Done

Fill out the database column called "high_threshold_r" with the "Maximum number" you find.

Start segmenting the kidney image by image as described above.

During segmentation, you should remember the lowest intensity value use used for editing the kidney so you fill out the "edit_low" column in the database. The highest intensity should always be the same for the same series, place the maximum intensity value into the "edit_high" column in the database.

After finishing segmentation, click "File" → "Save Volume" → Type "xxxxxx_6_5_4Apicatkre.avw" → Save
Click on "ROI" → "Samp Opts" → Type "7" in the "Minimum" box → "Summing" **On** and "Sample" **All Slices** on → Done → Click on T1 image.

Fill out the "voxel_cnt_kidney_r" column in the database with the # on """>= 7 & <= ??? = #".
Click "Log Stats" → Right mouse click → Save Log As → Type "-----Apicatkre**_jds** (yours instead of mine)1.stats" → Save

Use the same Autotrace procedure for the left kidney.

2. Region Based and Hemorragic Cyst Segmentation Method

Region Based Measurements of the Kidney Cysts Using the Autotraced Regular T2 series created above (Region Based 1)

You need two Analyze AVW files for segmenting the cysts. First, a Pre-T1 series file will be necessary to measure the hemorraghic cysts using stereology. The hemorraghic cysts will appear bright in the Pre-T1 series images. Secondly, a Regular T2 series file that has been edited to contain only the kidney with cysts using Autotrace methods will be used to measure the cyst volume in the kidney slice by slice using Region Based Measurement methods. Two Analyze windows are necessary to perform the Region Based measurements. The Autotraced series file

needs to be opened in the Image Edit window and opened in the ROI window. The Autotraced series file in the Image Edit window is used to compare the thresholded cyst volume in the ROI window.

Setting Up the Stereology Window for Measuring Hemorraghic Cysts

Perform a Histogram using an ROI window for the "xxxxxx.pshcr.avw" file to determine the intensity threshold in order to segment the hemorraghic cyst volume. The Histogram curve may only have one very large peak and a relatively small flat area on the right side of the curve that trails off to zero. For hemorraghic cysts, Jongdae picks approximate 90% maximum intensity value from the Histogram curve initially, then changes the threshold in the Stereology window so that the contrast between the bright cysts and the parenchyma is good.

Fill in the threshold column(s) in the CRISP database

Select the "xxxxxx.pshcr.avw" file in the "Analyze 4.0" window. Now select "Measure" → "Stereology". After adjusting intensities to the threshold found in the above Histogram, and changing the size to quadruple in the Stereology window, make a grid (4x4) on the image file. Put the Stereology window on the left side of the screen.

Setting Up the Image Edit Window for Measuring Non-Hemorraghic Cysts

The Autotrace Image Edit window should still be open with the intensity set as described above in the Autotrace segmentation method. If the Autotraced Kidney in the Image Edit window is not open, then use the following method to open it. You will need to set the intensity value in the Image Edit window to that used during Autotrace.

In the Analyze 4.0 window, click on "-----Apicatkr0" → "Process" → "Segment" → "Image Edit" → "View" → "Size" → "Triple" → Put the Image Edit window image file in the middle of the computer screen. The "-----Apicatkr0" file was saved as the "-----Apicatkre.avw" file. Open the "-----Apicatkre.avw" file if you need to load it and then open it in Image Edit to see the Autotrace results.

Setting Up the Region of Interest (ROI) Window for Measuring Non-Hemorraghic Cysts

The Region Based measurements are made using the Region of Interest module in Analyze.

In the Analyze 4.0 window, click on "-----Apicatkr0" → ROI → Triple the size → "View" → "Intensity" → "Loaded Volume" → "Window" → "Threshold" → Put this image file on the right side of the screen.

Measuring Hemorraghic Cyst Volume with Stereology

Jongdae does not always pick all of the smallest hemorraghic cysts. Now Jongdae moves through the Pre-T1 images one slice at a time comparing the Pre-T1 slices in the Stereology window to the Regular T2 slices in the Image Edit window trying to find the same slice in each window that contains the same parenchyma and cyst morphology. Once he finds slices with similar morphology, he then goes back to the first slice where the kidney/cysts exist in both windows at the same time. Then he moves through the slices one at a time looking for hemorraghic cysts in the Stereology window and performs a thresholding in the ROI window at the same time trying to make the cyst area in the ROI window appear to be the same size as the cysts seen in the Image Edit window. If a hemorraghic cyst is seen in the Stereology window but does not exist in the Image Edit window, Jongdae will select the stereology crosses that lie in the hemorraghic cyst. If the hemorraghic cyst is darker gray, he will not choose all of the crosses in the hemorraghic cyst because of partial volume averaging. If the hemorraghic cyst is included in the Image Edit window, then he does not include the area in the Stereology window. The objective is to only include a cyst area once in both the Stereology and Image Edit window. Total cyst volume is calculated from adding the cyst volume from the Image Edit window and the Stereology window.

After finishing with stereology hemorraghic cysts measuring, don't forget to save the following:
xxxxxx_x_pshcr_jds(instead, your initials)1.grid
xxxxxx_x_pshcr_jds1.stats
xxxxxx_x_pshcrsl_jds1.stats

Measuring Regular T2 Cyst Volume with Region Based ROI Methods
Starting with the first slice that contains either a portion of kidney or cyst in the Image Edit and Region of Interest windows, adjust the minimum slider to change the threshold in the "Intensity Loaded Volume – Region of Interest" window so the cyst area as seen in the ROI window is approximately the same as seen in the Image Edit window. Jongdae says he does not always care about the smallest cysts. If the smallest cysts do not appear or are not the same size in both windows that is all right because the largest cysts affect the cyst volume more than the small cysts. By increasing or decreasing the threshold by a small amount, the area surrounding the large cysts can greatly decrease or increase which can easily offset the lost volume or increased volume of the small cysts. Jongdae tries to balance the cyst area in the ROI window so that the total cyst area is equivalent subjectively with that seen in the Image Edit window, but he mostly looks at the large cyst areas. He also looks at the connectivity of the cysts in the ROI window. He compares how connected the cysts appear to be, meaning how large is the connection or how close are the cysts to each other, in the Image Edit window and tries to match that in the ROI window changing the threshold. He says it's easier and less subjective to look at the connectivity of the cysts, instead of looking at the cyst size. Jongdae says it more difficult to subjectively determine that all cyst areas are the same size in both windows, but it is less subjective to determine the connectivity. Jongdae also likes to look at several slices using the threshold found for a particular slice to make sure the next slices appear to be good also. Normally, the inhomgeniety between slices doesn't vary much so this method should hold. He then records the threshold for the first slice in the database column called "low_threshold_r" next to the correct "slice_no". He then move to the next slice in both the Image Edit and ROI windows and compares the cyst areas. Since most of the time, the area will still be all right, he moves to the next slice. He keeps comparing the cyst area until he see a difference. At that point, he adjusts the threshold again, and move forward a few again to make sure this threshold will be good for a few more slices. Then he records this new threshold value in the database column "low_threshold_r" next to the correct "slice_no" as shown in the database. He keeps repeating this until he reaches the end of the kidney. For the most part, a threshold intensity value pattern has been seen in almost all of the cyst measurements. Usually, the intensity threshold will start as a larger number in the front portion of the kidney, then decrease as you move into the middle of the kidney and then increase as you move toward the back of the kidney. After Jongdae has found all of the intensity values for the different slices, then he goes back to the ROI window, starts with the first slice and starts with the first threshold. He then has the ROI program automatically calculate the cyst volume slice by slice and records each in the database column called "voxel_cnt_cyst_r". He adjusts the threshold as he determine previously for each slice encountered in the series. He says doing the measures this way by first determining all of the thresholds first, and doing the ROI measurements second is a much faster way of measuring.

3. Stereology Measurements of the Whole Kidney (Stereology 1)

The MR Post-Gad T1 series needs to be measured using Analyze's Stereology module. Before starting the stereology measurements, a repeatable method needs to be utilized to determine the best intensity threshold for viewing the individual slices. First, load the file Accession#.Series#_pskr.avw. Create a Histogram using the ROI module for all the slices in the right kidney (Accession#.Series#_pskr.avw). Look at the histogram to find the maximum value

plotted. Use approximately 90% of the maximum value as the high window threshold limit and leave the low threshold alone. Repeat these steps to find the high window threshold limit for the left kidney using the file Accession#.Series#_pskl.avw

To measure the whole right kidney volume using stereology, open the Stereology module using the filename Accession#.Series#_pskr.avw. Using the above threshold, set the high window threshold. Use Generate Grid to change the grid size from the default of 10 x 10 to 7 x 7. Use the mouse cursor to highlight the red crosses found within the kidney. The right mouse button can be utilized to change the "Cursor Shape" from a "crosshair" to a "box". The size of the box "Cursor Size" can be changed with the right mouse button. The sizes vary from 2 to 32. After the crosses have been highlighted (turned green) within the kidney for a slice, repeat highlighting the crosses in the remaining slices. After all of the slices has been highlighted, save the following three files: (1) the slice file (Display the slice file by pressing the "control key" and the letter "s" at the same time. To save the file, right mouse click within the "Slice Stat Log – Stereology" window, then use "Save Log As".), (2) the statistics file (Generate Statistics), and (3) the grid file (File Save Grid) for the right kidney using the naming convention detailed below. Use the exact same name as the "avw" file loaded into the "Stereology" module, but either change ".avw" to "sl.stats" for slice file, or ".stats" for the statistics file, or ".grid" for the grid file. Measured the left kidney using the left kidney high window threshold and save the same files.

For stereology measurements of the whole kidney, the following are examples of file names:
Accession#.Series#_pskr_jds1.grid – Save the stereology grid for the right kidney.
Accession#.Series#_pskr_jds1.stats – Save the statistics for the right kidney stereology measurement.
Accession#.Series#_pskrsl_jds1.stats – Save the slice values for the right kidney stereology measurement.

The CRISP Sybase database located on DCIAC should be opened and each table should be completed as the data is processed and measured. To access the CRISP database on DCIAC, a Microsoft Access front end has been created to input the data. The tables of importance for processing are: dbo_mri_vol and dbo_mri_proc. Within the dbo_mri_proc table, use the name "Stereology 1" for the column labeled "proc_method". After processing, use the dbo_mri_stereo table to store the results of the stereology measurements.

Measuring the Kidney Cysts with Stereology (Stereology 1)

The above methods will be slightly extended in order to measure the cysts in the Post-Gad T1 series images. The 046337.12001-3_pskr.avw and 046337.12001-3_pskl.avw files should already be loaded from the above Stereology processing and measurement of the whole kidney. Save the right kidney file 046337.12001-3_pskr.avw as 046337.12001-3_pscr.avw As can be seen, only the "k" has been replaced by a "c" which stands for cyst in the file name. Repeat this saving process for the left kidney. Now load both the 046337.12001-3_pscr.avw and the 046337.12001-3_pscl.avw files.

To measure the cysts found in the right kidney using stereology, open the Stereology module using the filename 046337.12001-3_pscr.avw. Use Generate Grid to change the grid size from the default of 10 x 10 to 4 x 4. Use the same threshold as found above for the right kidney. Now only highlight crosses located in the dark cysts found within or on the surface of the kidney. After highlighting the cysts in each slice, save the same three files as described above for the whole kidney with the letter "k" changed to "c".

For stereology measurements of the cysts found in the right kidney, use the following file names:
046337.12001-3_pscrsl.stats – Saved the slice values for the right kidney stereology measurement.
046337.12001-3_pscr.stats – Saved the statistics for the right kidney stereology measurement.
046337.12001-3_pscr.grid – Save the stereology grid for the right kidney.

The following list of letters are given to aid in understanding all of the different processing and measurements that need to be performed:

p = processed
s = stereology measurement method
at = autotrace method
rb = region based method
k = kidney volume measurement
c = cyst volume measurement
r = right kidney
l = left kidney
sl = slice or individual image
A = appended files with preceding numbers representing the appended file names such as 10_9 means that volume files 10 and 9 were appended to form the current file.
e = edited
hT2 = Heavy T2 image
ic = Inhomogeneity Correction (IC)
hc = hemorrhagic cysts

046337_10_9Ap.avw – Appended volume files 10 and 9 together to form on file.

14.5 Image Processing Methods for Phantoms

14.5.1 Whole Kidney Phantom Measurement

T1 Images Measured

1. Load : phan111s03.avw (64 slices)
2. Display Multiplanar sections : Look through the images and select slices (e.g. 18 - 48).
3. Load as Subregion : Type 18 at low Z and 48 at high Z
4. Process Filter Spatial Inhomogenity Correction : Adjust thresholds from 20 to maximum and window size to 45.
5. ROI : Draw regions and measure region values. Pick a maximum value (e.g. 235).
6. Save as : phan111s03IC
7. Measure Stereology Intensity : Adjust thresholds from minimum to maximum (e.g. 235). Size : triple Grid : Type 10 at x spacing and y spacing. Mouse right button : size (resizable) Mouse left button : Pick points. Stats : See the resulting volume and save.

14.5.2 Cyst (Balloon) Measurements

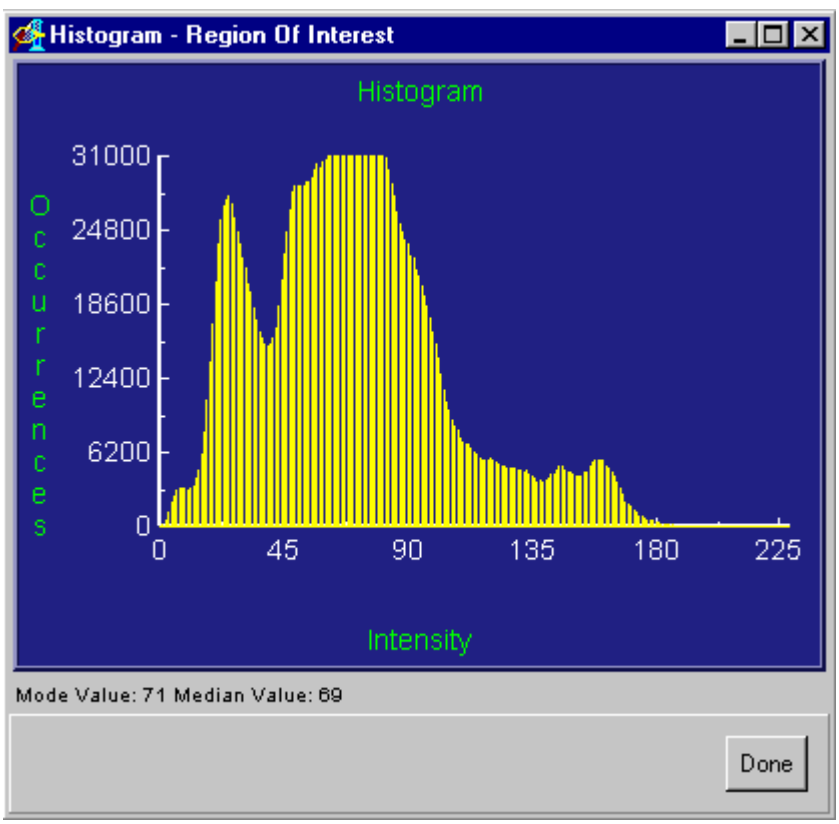
T2 Images Measured

1. Load : phan121s03.avw
2. Process Filter Spatial Inhomogenity Correction : Adjust thresholds from 20 to maximum and window size to 45.
3. Process Segment Image Edit : Select some slices to be deleted and fill with rectangles (e.g. #17, #18, #1, #2). Edit intensity with the defined value (e. g. -10). Click 'Chang images'. Fill out rectangles over the images without cutting the whole phantoms. Click 'Chang images'.
4. ROI Histogram Sample Options : Click 'Selected region', 'Summing' and ' All slices'. See the histogram and select minimum and maximum intensities (e.g 800-3000).
5. Save as Subregion : Type 16 at low Z and 3 at high Z. Interactive XY : Crop the images. Save as phan121s03ICedit.
6. Measure Stereology Intensity : Adjust thresholds from minimum to maximum ((e.g 800-3000).). Size : triple Grid : Type 4 at x spacing and y spacing. Mouse right button : size (resizable) Mouse left button : Pick points. Stats : See the resulting volume and save.

14.5.3 Stereology Measurement Method for Balloon Phantom Whole Volume (1/2002)

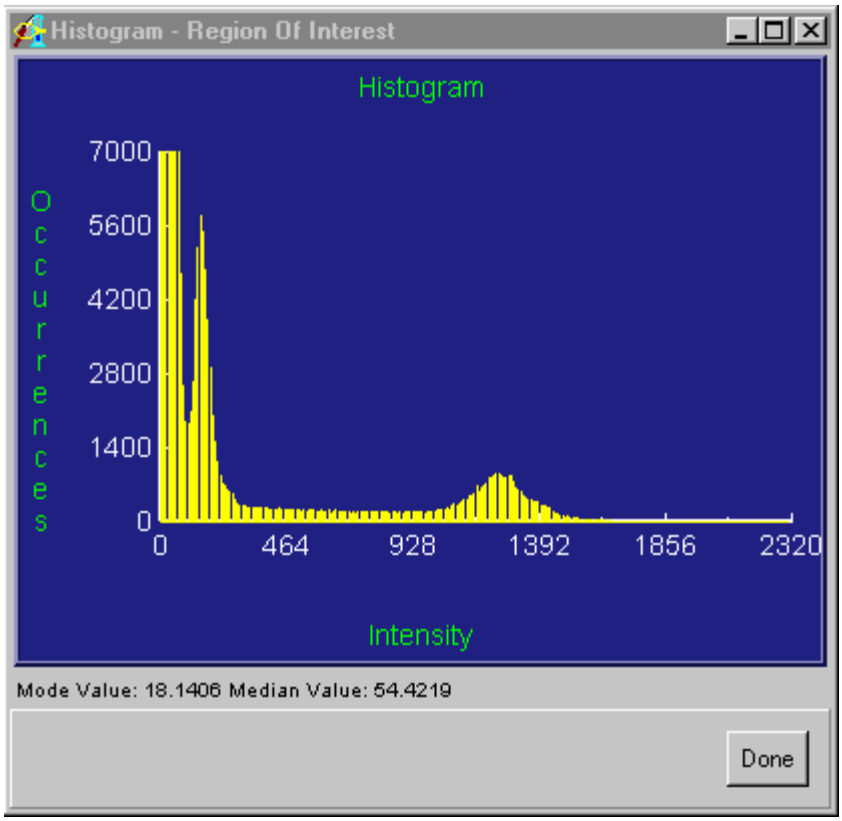
1. The spreadsheet containing the measurements is located on the ERL G drive. G:\PKD\Standardization2\Phantoms\1st Balloon Phantom Information\Stereology-whole1stballoon-T1-Jan2002-pkc1.xls
2. The measured balloon phantom data is found on the unix computer called dciac in the following directory: /dciacb/pkd/stardard2/1st_balloon_phantom2
3. T1 MR scans were used to measure the whole phantom volume.
4. An ROI was used to determine the threshold for setting the intensity for all images in an MRI scan (see Figure below). We typically plot a histogram from the ROI measurement module in Analyze and pick an intensity value that is approximately 95 to 98% of the maximum intensity found in the images (all slices for the scan). The 98% maximum intensity value from the figure below would be approximate 175.
5. A 7x7 grid was used to measure the whole balloon phantom volume.
6. All crosshairs inside the perimeter of the phantom are chosen (change the crosshairs to green color).
7. Determining the boundary points to include in the phantom are the difficult points to choose. If a black line region exits between the bright phantom parenchyma portion of the phantom and the oil, we will select all the crosshairs that have their center located from the middle of the black line region to the bright phantom parenchyma. Crosshairs where their centers lie exactly in the middle of the black line region will also be chosen 100% of the time. Crosshairs where their centers lie outside of the middle of the black line region and toward the oil will not be chosen. If a black line does not exist at the phantom perimeter, but a gray scale region exits, we are to treat this gray scale region like it was a black line. Try to determine the inside and outside boundary of the gray scale region and then chose the crosshairs within this region just like you would for the black line region above.

Histogram of uab_pklarge1_s04.avw file.



14.5.4 Autotrace Measurement Method for Balloon Phantom Whole Volume (2/2002)

1. The spreadsheet containing the measurements is located on the ERL G drive. G:\PKD\Standardization2\Phantoms\1st Balloon Phantom Information\Autotrace-whole1stballoon-T1-Jan2002-pkc1a.xls
2. The measured balloon phantom data is found on the unix computer called dciac in the following directory: /dciacb/pkd/stardard2/1st_balloon_phantom2
3. T2 MR scans were used to measure the whole phantom volume.
4. An ROI can be used to determine the threshold for setting the intensity for all images in an MRI scan, but was not used because using an ROI on a kidney won't give you the same type of histogram as the kidney with pure oil surrounding it. Because the oil is pure and totally surrounds the kidney phantom, the histogram plots a graph showing the intensity of the balloons being very different from the agarose/oil surrounding the balloons (See Figure below). We typically plot a histogram from the ROI measurement and pick an intensity value that is approximately 95 to 98% of the maximum intensity found in the images (all slices for the scan). If we chose the 95% point on this plot we would select a threshold of approximately 1450. With a threshold of 1450, the intensity of the oil and agarose, is much two dark and the boundary between the agarose and the oil can not be visibly seen. Therefore, by adjusting the threshold of a phantom slice with the balloons easily seen within the Image Edit module until you can now see the oil appear, the boundary of the agarose will be clearly seen. A threshold of approximately 300 was necessary in most all cases. With a threshold of 300, the balloons are all saturated (much too bright) but the boundary of the kidney is the important aspect in the image since are trying to measure the volume of the whole kidney.
5. Now a seed point can be placed in the kidney and autotrace will automatically draw the boundary of the phantom/kidney based on the threshold used for the seed. Once the threshold has been adjusted for the seed to include all of the phantom/kidney, the outside of the phantom/kidney can be set to zero using the delayed fill option.
6. Sometimes a single seed point can be used to segment the entire phantom/kidney. Other times you must adjust the threshold of the seed between slices.
7. After the phantom/kidney has been segmented from its surroundings, save the segmented emory_pklarge2_s02.avw file as emory_pklarge2_s02_pate.avw. Load this file: emory_pklarge2_s02_pate.avw and perform an ROI measurement on it using a threshold value of 7-Maximum intensity value. Save the "Stats Log" in the directory /dciacb/pkd/stardard2/1st_balloon_phantom2 and record the measured value in the spreadsheet listed above.



Histogram of emory_pklarge2_s02.avw file.

14.6 Image Archiving

The image studies (MR and Ultrasound) collected from the PCC sites are stored on-line using a computer system dedicated to the CRISP study. The computer system, a SUN Ultra-10 currently supports over 54 GB of on-line storage. The on-line data consists of the original DICOM image sets, image sets transformed to "Analyze" format, and derived image data sets used in the analysis.

For the CRISP study, a Sybase relational database was designed and is being used to track all relevant information pertaining to the image analysis. The derived data is incrementally transferred to the Division of Biostatistics once per week. Each PCC site must archive the original image data set to CDROM using the CRISP workstation at that site. The DCIAC system utilizes a system backup policy of full disk backup initiated once per week, and is done by the system manager during periods of low system activity. The image data and Sybase database are transferred to tape using a Quantum DLT4000 tape unit. The tapes are labeled and stored in an environmentally controlled facility. The Sun system - dciac.wustl.edu is located behind a Nortel Networks firewall and is backed up using a Quantum DLT4000 tape unit that is locally attached over the SCSI bus. A simple shell script was written to backup the system and user disk partitions using the standard Unix - ufsdump command.

14.7 Transfer of Information from IAS to BDCS

The IAS will create a database containing information about the MR/US data transfer to Washington University in DICOM format, image processing, and measurements. The database will be stored on a Unix workstation located in the IAS lab behind a virtual network (Nortel Switch) for data security. The database will be based on a Relational Model using Sybase (SQL) to store the information, and Microsoft Access will be utilized for data input. The DBCS will periodically query the IAS database to obtain the needed information for quality control inspection and statistical analysis.

15 Data Coordinating and Image Analysis Center: Biostatistics and Data Coordinating Section

15.1 Data Management Activities

The Biostatistics and Data Coordinating Section (BDCS) is a component of the DCIAC. The CRISP study will include the acquisition, storage and analysis of data from a variety of different sources. First, the PCC's will enter a variety of types of data directly into the Web Data Entry System (WDES). The WDES will include all features of a data management system, including data editing, data entry and data deletion. Second, the image data will be transmitted to the imaging section at the DCIAC. After data analysis is done by the imaging group, the relevant data will be transferred to the data management system. Third, a variety of data will be analyzed by either the central laboratory at Mayo Clinic, or by each of the PCC's. These data will also be entered into the WDES.

15.2 Data Archiving

Data will be backed up on a regular basis in the standard backup procedures of the Division of Biostatistics. Backups are done daily, on a rotating schedule which ensures that all backups are saved for at least 7 days. In addition, weekly backup are maintained to augment the daily backups. Finally, monthly backups will be supplement the other values. During the SAS data management process, individual values entered using the WDES are maintained both in the master system datatable, and as transactions in a parallel transaction datatable. The processing of the transaction datatable will recapitulate all operations to the master system datatable. These alternative versions of the master datatable will both be stored separately.

At the conclusion of the study, a public use dataset will be created according to policies developed by the Steering Committee.

15.3 Forms Development

Forms development will be done during the initial phase of the CRISP study. Forms are originally written in Word. The Forms Committee closely supervises this process, using email and other electronic communications tools, and indicates final approval of all forms. Forms are then distributed in several ways to the PCC's.

All forms are available on the web site in a generic and unlabeled manner, and can be examined by CRISP personnel at any time. Using the web site, the forms may be assembled into a packet which has a barcode and identifying number stamped on each form at the top; these forms are stored in .pdf format.

These forms packets can be handled in several ways. First, they may be saved at the PCC by right-clicking on the appropriate place when prepared and returned using the browser. Secondly, they can be viewed with the browser; the browser will then use the Acrobat plug-in to view the form, or will endeavor to obtain the plug-in if it is not available. Finally, once the forms packet has been saved locally, the forms may be viewed with the Acrobat Reader. These packets of forms can be either printed directly from either the browser or Adobe Acrobat.

15.4 QC/QA Methods and Procedures

A variety of QC and QA methods will be used for CRISP. These will have several levels:

- JavaScript will be used to check for impossible values during the data entry process itself.
- Values for logical evaluation will be included in the form from other datatables stored at the DCIAC.
- Logical checks will be used after the data are sent to the DCIAC to ensure that timely information is received, and that the data are not being submitted at an inappropriate time. In particular, since no names or other identifying information is being kept about participants, it will be important to verify that certain tests and images are made at the time scheduled, so that the ID numbers can be verified.

15.5 Audit Methods for Forms and Information at the PCCs

During the CRISP study, data from the PCC's will be audited at the DCIAC. On a periodic basis, the PCC's will be asked to fax certain copies of the forms to the DCIAC. These will be compared on a value-by-value basis with the internal information stored in the files. Approximately 10% of the forms will be faxed. This process will begin relatively early, so that problems of the data entry and data management system can be determined as soon as possible.

15.6 Data Entry Using the WWW and the SAS System

Data entry methods have been discussed elsewhere (cf. Section 12.2). Essentially, the Web Data Entry System is a method of directly editing SAS datatables from remote locations. The system presents forms from a location on the CRISP web site. After determining which form is to be entered, and displaying the form on the browser, the person doing the data entry is given the choice of adding new observations, editing existing ones, deleting old observations, listing observations or returning to the calling page. The methods make considerable use of selection lists for subject selection and use JavaScript code to ensure that data are as complete as possible, while ensuring that data entry is flexible and user-friendly.

15.7 Statistical Methods

Statistical methods will specifically answer study questions. At the beginning of the study, the main interest lies in the consistency and reproducibility of the imaging methods. During the Standardization Study, the measures from the images of the different traveling participants will be compared for the equivalence of the results. During the full study, methods will concentrate on the estimation and description of measures of kidney function and structure, considered longitudinally.

15.8 Web Site

The CRISP website (http://www.pkd.wustl.edu/crisp) is used for access to forms, for communication with participating clinical centers, for data access and for retention of records

of the CRISP project. It is maintained by the Data Center. The site is divided into several main areas including a section for each committee, the DCIAC, Study Coordinators, Study directory, the MOP, forms development, and data entry/reporting. The sections for the committees, DCIAC, and Study coordinators each have an associated mailing list. All emails posted to these email lists are automatically posted to the web site in a searchable format, allowing a permanent record for all emails (considered to be official communications) to be maintained automatically. Additionally, in the Steering Committee section, all presentations and minutes for Steering Committee/EAC meetings are archived. The forms development section contains copies of all versions of study forms in PDF format.

Each clinic associated with CRISP has its own section on the site. Access to a web-based data entry system (WDES) and some study reports has been provided in these sections. A periodically-updated clinic-specific unified data set is located in the reports section for each clinic. Each clinic is able to access its own section, but is not able to access other clinics' sections, so that the data for the clinic may be maintained in confidence. In addition, other datasets are posted to the clinic sites. Some of these datasets are updated on an as-needed basis, initiated by the clinics (i.e., the GFR evaluation dataset).

The CRISP website is password protected. A valid user id and password is needed to access the site. Passwords can be changed at any time via a link on the main page. Some additional restrictions have been added to the clinic (and DCIAC) areas so that data and reports associated with a particular clinic are limited to users from the specific clinic.

15.9 Study Performance Feedback

During the study, feedback will be provided to ensure that all study participants are aware of performance of each PCC. Feedback will provide information about the following categories of data:

- Recruitment targets
- Timeliness of appointments
- Timeliness of communication with DCIAC
- Errors in data entry following audit of faxed forms
- Frequency of dropouts and other loss-to-followup cases
- Quality of images and other problems in image system

15.10 SYBASE Database Description

The PKD Grant database was created by Paul Koppel and Paul K. Commean using Sybase and Microsoft Access 97 in 2000. Sybase was utilized for security reasons and its general ability to handle a large amount of data. Since we don't have any software that allows for easy data input into the Sybase database, Paul Koppel decided to create an Access user interface. Data is entered using the Access tables and forms. The Sybase database is located on the Unix computer called: DCIAC The Sybase database is stored on the hard disk called: dciaca The Access user interface is stored on the hard disk called: dciacb The name of the Access user interface file is called: pkd.mdb for the initial reliability testing Phase I portion of the PKD Grant and it is stored in the pkd-ms_access directory. The current PKD Grant Access database name is called: crisp.mdb and is also stored in the /dciacb/pkd-ms_access directory.

Each table, the fields, and the keys for each table in the Sybase database will be described below. The name of each table is underlined. The primary keys in the tables are bold face type. The foreign keys in the table are noted in italics. Any non-key fields are shown as normal type.

<u>Table name</u>
Table variables
variable_a – Primary key.
variable_b – Foreign key.
variable_c – Any non-key field in the table.

<u>dbo_site</u> – Contains the names of the PKD Grant Study locations
1. **site_id** – Unique number given to each PKD site.
2. site_name – Name of the site where the PKD study is being conducted.

<u>dbo_manufac</u>
1. **manufacturer** – Name of the company who manufactures the MR scanner(s) located at each site.

<u>dbo_scanner</u> – Contains the MR and US scanner manufacturer information used in the Study.
1. *site_id* – Unique number given to each PKD site.
2. **scanner_id –** Unique number given to each scanner located at each PKD site.
3. machine_name – Name of the scanner as given by the PKD site.
4. device_type – Type of scanner system utilized such as MR, US, CT, etc.
5. manufacturer – Name of the manufacturer of the scanner.
6. product_name – Name of the scanner as given by the manufacturer.
7. ip – Internet address of the scanner.
8. ae_title – Unknown.
9. net_connect – Unknown.

<u>dbo_study</u>
1. *site_id* – Unique number given to each PKD site.
2. *scanner_id* – Unique number given to each scanner located at each PKD site.
3. **accession_no** – Unique number given to each study. See definition of study below*.

4. participant_id – Unique number given to each participant who enrolls in the PKD project. Each patient identification number starts with the same integer value as the site_id number.
5. study_date – Date the study occurred.
6. study_type – The type of scanner used to perform the study. (MR or US)
7. study_descrip – A description of the study to enable phantoms or participants (Patient) to be noted.
8. image_rec_date – Date the study was received by WUERL.
9. dicom_dir – Directory location where the received DICOM data is stored.
10. conv_script – Directory path and name of the script used to process the DICOM files.
11. *vol_dir* – The directory where the script created ANALYZE volume file is stored.
12. qc_date – Date when a doctor reviews the MR or US series for quality control and measurement file determination.
13. study_comment – General study comments. Before we added the fields, image_quality and protocol, Ty Bae was using this comment field to contain the information for these fields. Ty used IQ=? for image_quality, and Protocol=? for protocol.
14. image_quality – A numerical value ranging from 1-5 (1 poor and 5 great) describing the overall quality of all the images in the single MR Study. Normally, Ty Bae will include a comment explaining the reason for the grade.
15. protocol – A numerical value ranging from 1-5 (1 poor and 5 great) describing how well they followed the MR protocol as defined in the Manual of Procedures. Normally, Ty Bae will include a comment explaining the reason for the grade.
16. status – Will contain the status of the study in regards to ERL data received, quality control performed by Ty Bae, MR images processed, and MR/US images measured. If the study is Open, then all three have not been completed. If the study is Closed, all three are complete. For the measurements, all four MR measurement methods must be complete, and the stereology measurements must be reviewed.
17. visit_no – the number given to each subject's visit. A visit number was added because you can not count on a particular year to guarantee whether a subject's visit is baseline (BV01), or follow-up visit (FV01), or FV02, etc. Originally, all baseline visits occurred in 2001, and all first year follow-up visits occurred in 2002, but by the end of 2002, the steering committee decided to add more baseline visits, and a second year follow-up visit occurred 2002. Also, not all FV01 subjects were scanned in 2002.

    *Study – Is defined to be a single visit (on a given day and time) by a participant to a scanner (MR or US) to have a series of individual scans performed while the subject is at the scanner.

<u>dbo_scannerhist</u>

1. ***scanner_id*** – Unique number given to each scanner located at each PKD site.
2. software_version – Version of software utilized by the scanner.
3. hardware_version – The scanner hardware version.
4. **scannerhist_ref_date** – Date when a new hardware or software update occurred.
5. scannerhist_comment – Comments about the scanner.

<u>dbo_wdes_series_descrip</u>

1. **wdes_series_descrip** – A brief description of the MRI scanner parameters the PCC sites utilized for each series obtained from the Web Data Entry System (WDES).

<u>dbo_mri_param</u>

1. *accession_no* – Unique number given to each study. See definition of study.

2. series_no – Unique number given to each scan of a participant. Multiple scans are acquired during each study. Each scan consists of multiple contiguous images/slices in order to obtain a 3D volume of the kidney(s).
3. no_of_slices – Number of slices acquired during a given series number.
4. slices_to_measure – Ty will determine which slice numbers within a series should be measured.
5. orientation – Ty will give an orientation description to a particular series such as posterior, anterior, middle, entire, etc
6. measure_needed – Ty will note with a "y" for yes which series should be measured and if the series is only ½ or 1/3 or ¼ of a kidney. An "n" for no or if there field is blank, then so measurements are to be obtained from that particular series.
7. mri_param_comment – Comments will be included while reviewing the series for QC.
8. thickness – The thickness of a slice/image normally given in millimeters.
9. *wdes_series_descrip* – A brief description of the MRI scanner parameters utilized for each series.
10. image_header_series_descrip – Comments Steve Moore obtains from the MR DICOM image header that are typed into the MR console by the MR tech.
11. **vol_file** – File name of the Analyze formatted file that Steve Moore generates from the DICOM series images. Initially, the directory path was not part of the file name, but it became readily apparent, that we needed to know the directory location where the files are located.
12. tr – Relaxation time constant for a given series number.
13. te – Excitation time constant for a given series number.
14. flip_angle – Angle for a given series number.
15. scan_duration – The time normally given in seconds the series or scan lasted.
16. fov – The size of the field of view (fov) given in pixels in the x and y plane.
17. repeat_scan – This variable is used to indicate whether a participant's MR scans in a study need to be repeated. Sometimes, only the T1 or T2 images from a study will need to be repeated. A"Y" is used to indicate a repeat in necessary. A "Maybe" used to indicate the should be repeated if possible.

<u>dbo_proc_method</u>

1. **proc_method** – Method of measurement utilized to measure the series.
2. proc_method_ref_date – the date the method was initially used for making measurements
3. proc_method_comment – a description of the measurement method and whether that method is obsolete or not.

<u>dbo_staff</u>

1. **staff_name** – Name of the person who processed and/or measured the images.

<u>dbo_mri_proc</u>

1. *vol_file* – File name of the Analyze formatted file that Steve Moore generates from the DICOM series images along with its directory path.
2. ***proc_method*** – Method of measurement utilized to measure the series.

3. ***staff_name*** – Name of the person who processed the images.
4. ***proc_file*** – Name of the processed file created from the vol_file. These files are normally contained within the same directory as found in field vol_file. We add letters to the end of the series numbers and before the ".avw" extension to give an indication as to the type of processing and measurements that were performed on the file. The letters have the following meaning: p = processed, s = stereology, k = kidney, h = hemorrhagic, c = cysts, A = appended files, ic = inhomogeneity correction, at = autotrace, r = right, l = left, P = processed, L = liver, e = edited,
5. proc_date – Date the proc_file was created.
6. proc_description – A description determining which kidneys or both are located in the proc_file.
7. proc_formula – A description of the formula used to process the vol_file. Currently, this variable is not used.
8. depth_z – The slice or image thickness given in millimeters (depth of kidney).
9. height_y – The y axis lies along the long axis of the kidney given in millimeters.
10. width_x – The x axis lies along the width of the kidney given in millimeters.

<u>dbo_mri_stereo</u>

1. **proc_file_s char** – Name of the processed stereology file created from the vol_file.
2. **measure_no int** – indicates the number of times a measurement person had measured the images.
3. **proc_method** – the method utilized to measure the series.
4. **staff_name char** – Name of the person who processed the images.
5. kidney_review_date – the date the kidney was reviewed by Ty Bae for quality assurance. Most of the time Ty would make changes to the initial file created by a measurement person.
6. kidney_space_x int – the x axis spacing determines the number of voxels chosen in the along the x-axis when a cursor point is chosen in stereology. For the kidney measurements, we have always chosen 7 x 7 (49) voxels to be chosen with every cursor point identified.
7. kidney_space_y int – the y axis spacing determines the number of voxels chosen in the along the y-axis when a cursor point is chosen in stereology.
8. vox_size real – currently not used but could be calculated from depth_z times height_y times width_x.
9. low_threshold_kidney_r int – the threshold was given a zero in most all cases since most of the data values start with zero and go to 2000 or 3000 in value.
10. high_threshold_kidney_r int – the high intensity threshold was determined by using Analyze software region of interest module. Each kidney was given its own intensity threshold. The histogram option was turned on with summing turned on for all slices. Then the measurement person would chose a point on the histogram graph that was approximately 90% of the maximum visible intensity value on the graph. This maximum value was use to set the threshold for making the stereology measurements in order to standardize the measurement process and allow the measurement person to see the cysts more clearly.
11. proc_kidney_file_r – the name of the file containing the right kidney.
12. start_datetime_r – the date when the right kidney was measured. Initially, we were going to include times, but we decided not to include them.
13. end_datetime_r – the date when the right kidney was measured.
14. vox_cnt_kidney_r int – the number of voxels chosen for all slices in the right kidney.

15. kidney_stats_file_r – the name of the Analyze file containing the voxel count for the right kidney.
16. kidney_slice_stats_file_r – the name of the Analyze file containing the voxel count for each slice in the right kidney.
17. kidney_grid_file_r – the name of the Analyze file containing all of the stereology right kidney grid information.
18. low_threshold_kidney_l int – the threshold was given a zero in most all cases since most of the data values start with zero and go to 2000 or 3000 in value.
19. high_threshold_kidney_l int – the high intensity threshold was determined by using Analyze software region of interest module. Each kidney was given its own intensity threshold. The histogram option was turned on with summing turned on for all slices. Then the measurement person would chose a point on the histogram graph that was approximately 90% of the maximum visible intensity value on the graph. This maximum value was use to set the threshold for making the stereology measurements in order to standardize the measurement process and allow the measurement person to see the cysts more clearly.
20. proc_kidney_file_l – the name of the file containing the left kidney.
21. start_datetime_l – the date when the left kidney was measured.
22. end_datetime_l – the date when the left kidney was measured.
23. vox_cnt_kidney_l int – the number of voxels chosen for all slices in the left kidney.
24. kidney_stats_file_l – the name of the Analyze file containing the voxel count for the left kidney.
25. kidney_slice_stats_file_l – the name of the Analyze file containing the voxel count for each slice in the right kidney.
26. kidney_grid_file_l – the name of the Analyze file containing all of the stereology left kidney grid information.
27. cyst_space_x int – initially, cysts were measured using stereology, but it because readily apparent that we could not measure the cyst volume efficiently with stereology. So these cyst attributes are not used anymore.
28. cyst_space_y int
29. proc_cyst_file_r
30. start_datetime_cyst_r
31. end_datetime_cyst_r
32. vox_cnt_cyst_r int
33. cyst_stats_file_r
34. cyst_slice_stats_file_r
35. cyst_grid_file_r
36. start_datetime_cyst_l
37. end_datetime_cyst_l
38. vox_cnt_cyst_l int
39. cyst_stats_file_l
40. cyst_slice_stats_file_l
41. cyst_grid_file_l
42. mri_stats_comments
43. mri_stereo_comment – stereology training cases are noted in this column.
44. primary_value – is assigned a 1 if the voxel count fields are to be utilized by the Biostatistics department for performing their statistical analysis. Otherwise, a zero is assigned to this column.

dbo_mri_stereo_view

This table was created as a view of the dbo_mri_stereo table to assist the Department of Biostatistics in determining which stereology kidney files had been measured and what voxel count should be used. This table only contains the rows from the dbo_mri_stereo table where primary_value = 1. All of the fields in this table are described in the dbo_mri_stereo table above.

dbo_mri_autotrace_kidney

1. **proc_file_ak char** – Name of the processed file created from the vol_file.
2. **measure_no** int – indicates the number of times a measurement person had measured the images.
3. **proc_method** – the method utilized to measure the series.
4. **staff_name** char – Name of the person who processed the images.
5. proc_kidney_file_r – the name of the file containing the right kidney.
6. start_datetime_r – the date when the right kidney was measured.
7. end_datetime_r – the date when the right kidney was measured.
8. low_threshold_r int – was determine to be the lowest intensity value found in the series.
9. high_threshold_r int – the high intensity threshold was determined by using Analyze software region of interest module. Each kidney was given its own intensity threshold. The histogram option was turned on with summing turned on for all slices. Then the measurement person would chose a point on the histogram graph that was approximately 90% of the maximum visible intensity value on the graph. This maximum value was use to set the threshold for making the autotrace measurements in order to standardize the measurement process and allow the measurement person to see the cysts more clearly.
10. edit_low_thres_r int
11. edit_high_thres_r int
12. voxel_cnt_kidney_r int – the number of voxels chosen for all slices in the right kidney.
13. kidney_vol_r int – not used now.
14. edited_file_r – after the autotrace file has been edited, the file is saved with a new name ending in e = edited.
15. stats_file_r – the name of the Analyze file containing the voxel count for each slice in the right kidney.
16. proc_kidney_file_l – the name of the file containing the left kidney.
17. start_datetime_l – the date when the left kidney was measured.
18. end_datetime_l – the date when the left kidney was measured.
19. low_threshold_l int – was determine to be the lowest intensity value found in the series.
20. high_threshold_l int – the high intensity threshold was determined by using Analyze software region of interest module.
21. edit_low_thres_l int
22. edit_high_thres_l int
23. voxel_cnt_kidney_l int – the number of voxels chosen for all slices in the left kidney.
24. kidney_vol_l int – not used now.
25. edited_file_l – after the autotrace file has been edited, the file is saved with a new name ending in e = edited.
26. stats_file_l – the name of the Analyze file containing the voxel count for each slice in the left kidney.
27. mri_autotrace_comments

dbo_mri_stereo_hcyst

1. **proc_file_sh char** – Name of the processed stereology hemorrhagic file created from the vol_file.
2. **measure_no int** – indicates the number of times a measurement person had measured the images.
3. **proc_method** – the method utilized to measure the series.
4. **staff_name char** – Name of the person who processed the images.
5. cyst_review_date –
6. cyst_space_x int – the x axis spacing determines the number of voxels chosen in the along the x-axis when a cursor point is chosen in stereology. For the cyst measurements, we have always chosen 4 x 4 (16) voxels to be chosen with every cursor point identified.
7. cyst_space_y int – the y axis spacing determines the number of voxels chosen in the along the y-axis when a cursor point is chosen in stereology.
8. low_threshold_cyst_r int – the threshold was given a zero in most all cases since most of the data values start with zero and go to 2000 or 3000 in value.
9. high_threshold_cyst_r int – the high intensity threshold was determined by using Analyze software region of interest module. Each kidney was given its own intensity threshold. The histogram option was turned on with summing turned on for all slices. Then the measurement person would chose a point on the histogram graph that was approximately 90% of the maximum visible intensity value on the graph. This maximum value was use to set the threshold for making the stereology measurements in order to standardize the measurement process and allow the measurement person to see the cysts more clearly.
10. proc_cyst_file_r – the name of the file containing the right kidney.
11. start_datetime_cyst_r – the date when the right kidney was measured. Initially, we were going to include times, but we decided not to include them.
12. end_datetime_cyst_r – the date when the right kidney was measured.
13. vox_cnt_cyst_r int – the number of voxels chosen for all slices in the right kidney.
14. cyst_stats_file_r – the name of the Analyze file containing the voxel count for the right kidney.
15. cyst_slice_stats_file_r – the name of the Analyze file containing the voxel count for each slice in the right kidney.
16. cyst_grid_file_r – the name of the Analyze file containing all of the stereology right kidney grid information.
17. low_threshold_cyst_l int – the threshold was given a zero in most all cases since most of the data values start with zero and go to 2000 or 3000 in value.
18. high_threshold_cyst_l int – the high intensity threshold was determined by using Analyze software region of interest module. Each kidney was given its own intensity threshold. The histogram option was turned on with summing turned on for all slices. Then the measurement person would chose a point on the histogram graph that was approximately 90% of the maximum visible intensity value on the graph. This maximum value was use to set the threshold for making the stereology measurements in order to standardize the measurement process and allow the measurement person to see the cysts more clearly.
19. proc_cyst_file_l – the name of the file containing the left kidney.
20. start_datetime_cyst_l – the date when the left kidney was measured.
21. end_datetime_cyst_l – the date when the left kidney was measured.
22. vox_cnt_cyst_l int – the number of voxels chosen for all slices in the left kidney.
23. cyst_stats_file_l – the name of the Analyze file containing the voxel count for the left kidney.
24. cyst_slice_stats_file_l – the name of the Analyze file containing the voxel count for each slice in the right kidney.

25. cyst_grid_file_l – the name of the Analyze file containing all of the stereology left kidney grid information.
26. mri_stats_comments
27. mri_stereo_comment

dbo_mri_stereo_hcyst_view

This table was created as a view of the dbo_mri_stereo_hcyst table to assist the Department of Biostatistics in determining which stereology hcyst files had been measured and what voxel count should be used. This table only contains the rows from the dbo_mri_stereo_hcyst table where measure_no = 1. All of the fields in this table are described in the dbo_mri_stereo_hcyst table above.

dbo_mri_region_cyst

1. **proc_file_rc char** – Name of the processed file created from the vol_file.
2. **measure_no int** – indicates the number of times a measurement person had measured the images.
3. **proc_method** – the method utilized to measure the series.
4. **staff_name char** – Name of the person who processed the images.
5. start_datetime – the date when the right kidney was measured.
6. proc_kidney_file_r – the name of the file containing the right kidney.
7. **slice_no** – the slice number within the series.
8. low_threshold_r int
9. voxel_cnt_cysts_r int – the number of voxels chosen for all slices in the right kidney.
10. cysts_vol_r int – not used.
11. proc_kidney_file_l – the name of the file containing the left kidney.
12. low_threshold_l int
13. voxel_cnt_cysts_l int – the number of voxels chosen for all slices in the left kidney.
14. cysts_vol_l int – not used.
15. mri_region_cyst_comment

dbo_mri_rg_lv_cyst

1. **proc_file_lv char** – Name of the processed file created from the vol_file.
2. **measure_no int** – indicates the number of times a measurement person had measured the images.
3. **proc_method** – the method utilized to measure the series.
4. **staff_name char** – Name of the person who processed the images.
5. start_datetime – the date when the right kidney was measured.
6. **slice_no** – the slice number within the series.
7. low_threshold_r int
8. voxel_cnt_cysts int – the number of voxels chosen for all slices in the right kidney.
9. cysts_vol int – not used.
10. mri_region_cyst_comment

dbo_us_stereo

1. *accession_no* – Unique number given to each study. See definition of study above.
2. **us_filename** – File name of the Analyze formatted file that Steve Moore generates from the DICOM series images. No directory location is listed, but the directory can be found in the dbo_study table under the vol_dir field.

3. start_datetime – the date when the kidneys were measured.
4. end_datetime – the date when the kidneys were measured.
5. us_review_date – the date when the doctor reviews the quality of the ultrasound images.
6. distance_factor -
7. length_r – the length of the kidney on Sag/Cor images measured by ultrosonographer
8. width_r – the width of the kidney on Sag/Cor images measured by ultrasonographer
9. depth_r– the depth of the kidney as measured by ultrasonographer from the transverse images
10. number_of_slices_r – the number of slices that were required to measure the entire length of the kidney. The slice thickness is assumed to be 10mm.
11. grid_file_r – the name of the Analyze file containing all of the stereology right kidney grid information.
12. stats_file_r – the name of the Analyze file containing the voxel count for the right kidney.
13. slice_file_r – the name of the Analyze file containing the voxel count for each slice in the right kidney.
14. length_l – the length of the kidney on Sag/Cor images measured by ultrosonographer
15. width_l – the width of the kidney on Sag/Cor images measured by ultrasonographer
16. depth_l– the depth of the kidney as measured by ultrasonographer from the transverse images
17. number_of_slices_l – the number of slices that were required to measure the entire length of the kidney. The slice thickness is assumed to be 10mm.
18. grid_file_l – the name of the Analyze file containing all of the stereology right kidney grid information.
19. stats_file_l – the name of the Analyze file containing the voxel count for the right kidney.
20. slice_file_l – the name of the Analyze file containing the voxel count for each slice in the right kidney.
21. kidney_ster_area_r – stereology measurement of the first slice only in order to determine the conversion factor between the area given by the US equipment and the stereology grid. The conversion factor is computed by dividing the area of the slice by the number of voxels in the slice. The conversion factor is used to compute the area of cyst when making the stereology measurements.
22. kidney_ster_area_l – stereology measurement of the first slice only in order to determine the conversion factor between the area given by the US equipment and the stereology grid.
23. us_stereo_comment – a comment added by the doctor.
24. width_r2 – The second width measurement as found in the transverse image.
25. width_l2 – The second width measurement as found in the transverse image.
26. kidney_vol_cal_r – A "Y" for yes or "N" for no is placed into this column to help determine whether the volume needs to be calculated or not. An "N" is used to indicate the scanning plane was not uniquely from transverse images.
27. kidney_vol_cal_l – A "Y" for yes or "N" for no is placed into this column to help determine whether the volume needs to be calculated or not. An "N" is used to indicate the scanning plane was not uniquely from transverse images.
28. length_meas_r – number of length measurements that the ultrasonographer was required to make in order to measure the entire length of the kidney.
29. length_meas_l – number of length measurements that the ultrasonographer was required to make in order to measure the entire length of the kidney.
30. measure_needed – After reviewing the image quality, the doctor determines whether the images should be measured or not. "y" means yes measure the images.

dbo_us_stereo_slice

1. **us_filename** – File name of the Analyze formatted file that Steve Moore generates from the DICOM series images. No directory location is listed, but the directory can be found in the dbo_study table under the vol_dir field.
2. image_no – the image number within the ultrasound series.
3. kidney_r – area of the kidney including cysts within a given image number as measured by the ultrasonographer. The area is printed on the image and placed into the database.
4. kidney_ster_area_r – stereology measurement of the slices when the kidney_r value is not present in the image. But this is not always true
5. cyst_r – stereology grid points chosen when measuring the cyst area in a given image number.
6. kidney_l – area of the kidney including cysts within a given image number.
7. kidney_ster_area_l – stereology measurement of the first slice only in order to determine the conversion factor between the area given by the US equipment and the stereology grid.
8. cyst_l – stereology grid points chosen when measuring the cyst area in a given image number.
9. us_stereo_slice_comment
10. shadow_r – the area in the US shadow was measured by the ultrasonographer and is shown on the US image. The value is entered into the database in order help with computing the cyst volume more accurately since no cysts can be seen in the shadow.
11. shadow_l – the area in the US shadow was measured by the ultrasonographer and is shown on the US image.

dbo_mri_autotrace_Hcysts (This table is not being used anymore. Very little data (10 rows) is contained in this table. Stereology measurements of hemorrhagic cysts are now being conducted.)

1.proc_file_ac char
2. staff_name char
3.measure_no int
4. proc_kidney_file_r
5. start_datetime_r
6. end_datetime_r
7. low_threshold_r int
8. high_threshold_r int
9. edit_low_thres_r int
10. edit_high_thres_r int
11. voxel_cnt_kidney_r int
12. kidney_vol_r int
13. edited_file_r
14. stats_file_r
15. proc_kidney_file_l
16. start_datetime_l
17. end_datetime_l
18. low_threshold_l int
19. high_threshold_l int
20. edit_low_thres_l int
21. edit_high_thres_l int
22. voxel_cnt_kidney_l int
23. kidney_vol_l int

24.edited_file_l
25.stats_file_l
26.mri_autotrace_comments

dbo_mri_region (Originally, we intended to measure cyst volume from the heavy T2 images, but we found this was not possible. Very little data (23 rows) is contained in this table. So the table is not used.)

1.proc_file_rb char
2.staff_name char
3.measure_no int
4.edit_start_datetime
5.edit_end_datetime
6.edited_file
7.proc_cysts_file_r
8.start_datetime_r
9.end_datetime_r
10.low_threshold_r int
11.high_threshold_r int
12.edit_low_thres_r int
13.edit_high_thres_r int
14.voxel_cnt_cysts_r int
15.cysts_vol_r int
16.stats_file_r
17.proc_cysts_file_l
18.start_datetime_l
19.end_datetime_l
20.low_threshold_l int
21.high_threshold_l int
22.edit_low_thres_l int
23.edit_high_thres_l int
24.voxel_cnt_cysts_l int
25.cysts_vol_l int
26.stats_file_l
27.mri_region_based_comments

16 PCC Procedures

16.1 Schedule and Overview of Patient Visits

Each participant enrolled in the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study is seen in the CRISP clinical center for a set of baseline tests and for follow-up visits at twelve months after entry in the study and at twelve month intervals thereafter for three years. These visits are the primary time points at which clinical data are collected for study purposes. At three-month intervals between clinic visits a telephone interview will be conducted by the clinic coordinator.

If necessary for patient care, an appointment may be made for any participant to be seen one or more times between scheduled study visits at the discretion of the physician. All information relevant to these extra visits should be recorded on the appropriate forms.

Because of the importance of obtaining uniform and complete information on every participant, each follow-up visit should be completed according to the schedule specified for the Study. At the time each participant is entered into the Study, the DCIAC generates an appointment schedule for the participant that is sent to the clinical center. This appointment schedule specifies the target date of each follow-up visit and scheduled telephone interview and the permissible interval (time window) during which the visit may be completed. It will also provide a place for the clinic coordinator to record the date the visit was completed.

The time limits acceptable for completion for each follow-up visit are shown in the Study Calendar (cf. Section 3.2).

16.1.1 Initial Visit

Although the required baseline tests may take place over a period of a few days (or weeks), the purpose of the visit is to determine the participant's eligibility and to record pertinent baseline information for use in later analyses.

Participant Identifiers including MR accession and US accession numbers - see ID Numbers (cf. Section 4.3).

The forms to be completed are shown in the Study Calendar (cf. Section 3.2).

At this visit an appointment should be made for the patient to return for the first follow-up visit in one year. At the conclusion of the visit a notation should be made in the clinic coordinator's calendar:

- To call the participant in three months - a visit/telephone reminder is sent from the DCIAC each month to remind the clinic coordinator about the calls and visits to be scheduled;
- To send a written reminder approximately one month before the scheduled date of the visit;
- To contact the participant by telephone about 24 hours in advance of the visit and again remind them of the appointment.

This time schedule is also available on the CRISP website[12].

[12] See URL `http://www.pkd.wustl.edu`

16.1.2 Follow-up Visits

All participants enrolled in the CRISP study should be scheduled for the first follow-up visit twelve months after the date of entry into the Study. In making this and all subsequent appointments, the clinic coordinator should refer to the participant's appointment schedule and make the appointment as close as possible to the target date specified. Special effort should be made by the clinic personnel to assure that each participant completes every scheduled clinic visit.

The forms to be completed are shown in the Study Calendar (cf. Section 3.2).

The information on the Identification Form (#1) should be reviewed with the patient and updated. If a patient misses an annual visit a Missed Visit Form (#19) should be completed.

If the patient is pregnant at their Annual Clinic Visit they should be rescheduled for a time three months post partum and two weeks post nursing.

16.1.3 Telephone Interview

In order to maintain contact with the participant and to learn about changes in the patient's health and medical status, telephone interviews are conducted by the clinic coordinator at three month intervals (refer to section Study Calendar (cf. Section 3.2) for schedule). The participant, or, if the participant is unable to respond, a family or household member is interviewed. Any physician who has examined/treated the participant since the last visit or telephone interview is contacted to obtain information about the participant's health. The Follow-up Study form is completed (#13) after this interview. If a telephone interview cannot be conducted within the time window a Missed Visit Form (#19) is completed.

16.1.4 Time Limits for Completing Study Visits

The time limits for completing each CRISP study visit or telephone interview are shown in the Study Calendar (cf. Section 3.2). Time is measured from the date of the Baseline Visit. All study visits should be scheduled at the beginning of the time window to insure the completion of the visit within the window. If not completed with the specified limits, the clinic visit or contact is considered a protocol violation and should be made up at the earliest possible time.

16.1.5 Missed Examinations

In some cases, a participant may visit the clinical center within the required time interval but only part of the required examinations may be completed. The other portions should be completed as soon as possible. If they are not made up within the time window, then it will be considered a protocol violation.

16.1.6 Non-Study Visits to Study Physician

In certain cases, the CRISP physician may decide that it is in the participant's best interest to return for additional visits beyond the follow-up visits required by the CRISP protocol for data collection purposes. Participants who experience difficulties also may call and

request such a visit. The information obtained at non-study visits should be recorded on the appropriate forms and the information sent to the DCIAC.

16.1.7 Maintaining Contact with Participants

Maintaining contact with the patient between visits to the clinical center has been demonstrated to be important in maintaining continued patient interest and satisfaction and achieving complete follow-up of all patients. Other than the telephone interviews every three months, birthday cards, holiday cards and other expressions of personal interest encourage patients to stay in contact with the clinic staff and return for visits.

16.1.8 Transfer Participants

If any participant expects to move from the area served by the CRISP clinical center in which he or she is enrolled, the physician and the participant should determine whether it is feasible for the patient to transfer to a closer CRISP clinic for follow-up. The participant should be given the name, address, and phone number of the physician and clinic coordinator at the new clinical center and the clinic coordinator should schedule an appointment for the participant at the new clinical center. When contact with the new clinical center has been made and an appointment scheduled, the original clinical center should forward copies of all the participant's records, including the signed consent form, to the new clinic. After the patient has been seen once in the new clinical center and appropriate forms completed including the Transfer Form (#18), the DCIAC transfers that patient officially to the new clinic. The participant retains the original ID number.

16.1.9 Death of Participant

If a participant dies in a hospital, a copy of the hospital summary should be obtained. If the participant dies elsewhere, a summary of the recent medical history should be obtained from the physician(s) caring for the patient. A Death Notification Form (# 15) should be completed.

16.2 PCC MR Procedures

In order to facilitate orderly performance, study subjects should be prescheduled for the MR examination, preferably at least one week ahead. At some institutions, longer preschedule period may be needed if the clinical MR schedule is very heavy. This will be at the direction of the PCC site Radiologist and Principle Investigator. When scheduled, the patient shall be clearly identified as a participant in the CRISP PKD study. Arranging an appropriate study code at the site will be helpful to ensure this and to ensure charging costs to the correct study.

Consent form shall be signed either at the time of the MR examination, or preferably, previously at the time of screening, such that the patient may be excluded due to MR contraindications. The study coordinator thus must be trained in MR contraindications, including the size and weight restrictions of the designated study scanner (it may be useful to produce a "hula hoop" in the size of the scanner diameter, or to merely use a tape measure), aneurysm clips, cardiac pacemakers and other implanted electronic devices, metallic foreign

objects in the eye or other sensitive locations, cochlear implants, etc. Patients that suffer from claustrophobia such that premedication would be required will be excluded. Known reactivity to gadolinium contrast shall be considered an exclusionary criterion on initial screening.

The study will then be performed on the designated study scanner by the appropriate technologist. It is expected that the PCC site Radiologist will directly monitor the examination. He/she should monitor and make modifications as needed. Field of view may be increased from initial study parameters to allow complete coverage of the kidneys and to avoid aliasing artifact. If in an individual the kidneys are too large to cover in a single breath hold with standard study parameters, the Radiologist may: increase slice thickness on T1 weighted images to 3 or 4 millimeters maximum, and on T2 weighted images to 6 or 7 millimeters maximum. If this is not sufficient, 2 acquisitions may be made (not interleaved). HASTE sequences may be used for full coverage in shorter time. If a patient cannot complete the entire examination for some reason, they shall be rescheduled to return for completion as soon as possible.

If it is not possible in certain circumstances for the PCC site Radiologist to monitor directly, he/she may designate for this purpose another Radiologist who has been familiarized with the objectives and procedures of the study. Following the MR, at the direction of the Radiologist, the images will be sent to the PCC PC and processed for transmission to the DCIAC.

The PCC Radiologist shall examine the images from each procedure to assure quality. He/she also will identify presence or absence of any significant findings in addition to cystic disease. A local report should be generated at no charge to the patient or third party payer to document performance of the examination and presence or absence of any significant findings for the medical record. If there are significant findings, they shall be transmitted to the Principle Investigator and the patient's primary care physician, or other physician designated by the patient. If the patient has no primary care physician, they may be referred to the PCC Primary Care Clinic. It is at the discretion of the PCC whether to create hard copy films for archival, or to utilize electronic means but images should be archived on site for potential future clinical needs.

If there are significant imaging related findings, those should be sent to the DCIAC (using the patient's study code only). If further evaluation is needed, that can be recommended to the patient's physician, but costs of that workup will not be borne by the CRISP study. Serious illnesses that would have significant likelihood of preventing the patient from completing participation in the full course of the study, such as incidental malignancy, may be considered as an indication to drop the patient from the study.

It is the responsibility of the technologist and Radiologist at each PCC to monitor the patient for adverse events during the MR procedure. Each PCC shall have established procedures for such monitoring, which may be delegated by the study Radiologist to another appropriate physician if necessary. If necessary, an adverse event should be treated appropriately, and reported by the PCC site Radiologist to the local Study Coordinator, the PCC Principle Investigator, the local Institutional Review Board and to the DCIAC. If of a serious enough nature to warrant it, the adverse event should be reported to the IRB's at the other PCC sites. Serious reaction to gadolinium contrast may be considered as reason to drop the patient from the study, although continued inclusion using non-gadolinium sequences may be considered.

16.3 PCC US Procedures

It is the responsibility of the site PCC Radiologist to monitor performance of the study, to direct transmission of the image data to the DCIAC, to document the performance of the procedure and presence or absence of any significant imaging related findings in a similar fashion as for MR.

16.4 Usage of PCC Workstation

A standardized computer has been purchased by each PCC. This system is to be used for both the transfer of images to the DCIAC, for the printing of forms and labels, and for data entry.

16.4.1 Image Acquisition

At system boot, a process is activated which provides DICOM Storage Service on the PCC Workstation. The imaging modality, MR or US, initiates the transfer of the image study to the PCC Workstation. Individual files are uniquely identified by DICOM attributes which are embedded in the image header. The data is written to a local disk file.

16.4.2 Image Registration, Editing and Transmission Preparation

Once the patient has been registered in the DCIAC database, a unique patient identifier is assigned. An image study identifier (accession number (cf. Section 4.3)) is made available for the current imaging study). These identifiers are printed on the patient forms at the local PCC site. The PCC workstation provides software which allows the operator to select the assigned accession number from a list of available accession numbers. The software then removes the patient confidential information from the image headers and inserts the DCIAC assigned patient study identifier and accession numbers. The image study is then enqueued ready for transmission to the DCIAC. Initiation of the security client, software by NORTEL, enables the establishment of a secure virtual private network channel over the Internet. The digitally encrypted transfer is initiated by the operator at the PCC site.

(*Details of this procedure can be found in the section PCC Workstation (cf. Section 16.4).*)

16.4.3 Image Archiving at the PCC

A CD-ROM unit is attached to the PCC workstation. The DICOM image files should be written to the disk and stored as a local archive at each site prior to purging from the local disk.

(*Details of this procedure can be found in the section PCC Workstation (cf. Section 16.4).*)

16.4.4 Image Header Processing on PCC Workstation

The Clinical Studies Workstation application provides several different views of the data sent by the instruments and stored by the DICOM Storage Service. The goal of this step is to replace identifying information that might be important for your institution with data

needed for the CRISP study. The editing step will also remove or replace attributes in the header which could be used to determine the actual identity of the patient.

After the instrument has sent the entire study to the PCC Workstation, start the Nortel Extranet client and enter the assigned password. This step connects you to the Virtual Private Network used by the DCIAC storage system and allows you to send data to that storage system. This step also removes you from your campus network until the Nortel software is disconnected. Therefore, it is important that this step take place after the MR or Ultrasound scanner has completed its transmission.

Using the Clinical Studies Workstation, select the *Modality Worklist* view. This will provide dual scrolling lists with data received from the scanners and data in a worklist (created in the Study Registration steps). Select the MR or US study just completed and the corresponding study worklist item in the rightmost scrolling list.

For each scan or series in the study protocol, select the series which was produced by the scanner and the corresponding series in the worklist. Push the merge button which is located between the dual scrolling lists. This instructs the application to replace image attributes (patient identifier, accession number, protocol description) with values from the worklist. Even if the worklist has a real patient name, this step will replace the patient name with an empty string. After the attributes have been merged, push the enqueue button. This writes a text file in the queue area and instructs the DICOM Export Service to send the images to the DCIAC. Repeat the steps above for each scan or series in the study protocol.

You can use the Clinical Studies Workstation application to view the queue entries for images to be transferred to the DCIAC storage system. When the queue is empty, you are free to disconnect the Nortel Extranet client software so that your workstation can be seen on your campus network.

16.4.5 Data Processing on PCC Workstation

Several types of data processing are done on the PCC workstation. These involve the calculation of quantities needed for form completion. In particular, the estimation of the GFR using the Cockcroft-Gault approximation is performed using a JavaScript-enabled calculator, installed on the CRISP web site. To use the calculator, the Data Coordinator enters the age, weight (kg), height (cm) and sex of the participant. After pushing an on-screen button, the GFR estimate and BSA is returned, and then can be used for determination of eligibility.

16.5 Forms Archiving at the PCC

The following forms will be archived at every PCC:

Demographic and Contact Information: Form 1A

Consent forms: Original consent form and any other consent forms signed by each subject

Medical History Information:

- A copy of a medical record stating a date and diagnosis of ADPKD in all patients as well as a date and diagnosis of hypertension patients identified as hypertensive.

- A copy of a medical record stating diagnosis of ADPKD in utero or in the first year of life in appropriate individuals for risk profiling
- A copy of a medical record stating the occurrence and the date of the occurrence of gross hematuria in male ADPKD subjects for the purposes of risk profiling.

Physical Examination: A copy of the physical examination performed at the time of enrollment and for each annual visit.

Laboratory Data Screening Data: Copies of laboratory reports obtained from medical records or clinical laboratories where tests are run are required for the serum creatinine concentration that determines entry into the study.

- Copies of the 24 hour urine collection laboratory results that determine creatinine clearance and urinary protein excretion for classification of high vs low risk.
- Copies of the CBC, Chemistry panel that prove entrance eligibility.

Laboratory Data: Post-Enrollment Data:

- Copies of GFR iothalamate reports from the MAYO clinic laboratory
- Copies of the 24 hour urine collection results
- Copies of serum chemistry and CBC results
- Copies of lipid panel results

Interim Visits: A copy of the date and time of each interim visit as well as forms associated with those visits.

Adverse Events: Medical records of hospitalizations, doctors visits and ER visits should be obtained whenever possible. The adverse event form should be kept on site.

CRISP data forms: All completed forms should be kept with all forms for a participant being kept together. Source documents may be kept in a clinical chart separately from the CRISP forms.

16.5.1 Duration of Retention

All forms and associated source documents must be kept for at least 7 years after the completion of the CRISP study.

16.6 Forms Audits

Forms are audited in the CRISP study in one primary ways. Forms are selected for comparison in a small percentage of cases to determine the frequency of errors. This is primarily done to determine if there are structural errors or changes which can be corrected in the forms themselves. In the CRISP Study, this has resulted in a change in the entry of laboratory units. Rather than entering laboratory units for each separate form, laboratory units are now entered into a "standardization form" and then used for each individual form. If there is a change in the units for a certain test for one form, the PCC data entry personnel are responsible for making the change on the form. This event does not occur frequently, however.

Additionally, a data query system has been defined in the CRISP study. The data query system is an integrated tool within the Web Data Entry System. Using the data

query system, a query is defined. Queries may involve single variables (i.e., values outside of an allowable range, values above an allowable limit, values below an allowable minimum, values missing) or pairs of variables (i.e., values of Variable A above Variable B value). These queries are defined by the Data Center. The queries are then used to determine variable values which need to be checked. Values which are flagged as questionable are then evaluated by the Data Coordinator at the Participating Clinical Centers. A response for each flagged value is needed. Values flagged may be corrected, or may be annotated with several types of messages. These messages include "Value checked and correct", "Value omitted" and "Patient refused procedure". This approach to data evaluation allows data with extreme values to be entered and evaluated later. The Data Query tool is integrated into several of the procedures which provide laboratory values, so that the values can be checked and responses made at the time of data entry. This approach is favored by data coordinators, as it saves considerable labor.

16.7 Scanner Breakdown

It is likely that at some point in the course of the study, the study MR scanner will undergo technical failure such that the imaging protocol cannot be performed or completed as scheduled.

In those sites with more than one scanner, a backup scanner may be designated. If an identical scanner is available it should be validated as the backup scanner. If a scanner is available but not identical, if it can perform the study sequences it may be validated as backup. This validation may be done using the kidney phantom or human subject. The study protocol should then be saved in the memory of the designated backup scanner.

In sites with no available backup scanner, or if the backup scanner is also unavailable for use, the patient should be rescheduled for the earliest available date for rescanning, preferably within 2 weeks. This may be done as an outpatient visit if only MR imaging must be performed.

16.8 Scanner Replacement

At present we expect that the MR sequences developed and finalized in the standardization study will be used for the duration of the full study. There may be some modification in MR sequences and scanning techniques, but no dramatic change requiring a new hardware. Over the course of the study, however, upgrade or replacement of the designated MR scanner(s) may occur. This change should be notified to the DCIAC, and it is the responsibility of the site PCC Radiologist to validate a new scanner. If only a software upgrade is performed, as long as the study protocol can be followed, there is no concern. If a new device is installed, this should be validated for equivalent magnetic field strength and homogeneity and its ability to perform the study sequences (or equivalents) preferable by use of a kidney phantom. Alternatively, comparison of a scan on a study subject with previous MR may be used.

If new technologists are added to a site, they should be trained in the objectives and procedures for the study at the direction of the site PCC Radiologist with the assistance of the study technologist(s).

16.9 Scanner Periodic Quality Control

It is the responsibility of the site PCC Radiologist to assure continued image quality. It is expected that there will be a regular Quality Control Program of the MR facility (as is routine for clinical purposes). The Radiologist shall monitor the study procedures as they are performed, and document proper performance or reasons for any variation from standard protocol or for variation in quality. Overall Quality should be reviewed on weekly or monthly basis (depending on volume) over the course of the study. Periodic review with the technologist to address any decline in quality shall be done as needed.

CRISP Study

CONSORTIUM FOR

INNOVATIVE IMAGING

TO ASSESS PROGRESSION OF

POLYCYSTIC KIDNEY DISEASE

GFR Testing Manual

Participating Clinical Center:

Study Coordinator:

Office Phone:

Pager:

E-MAIL:

MML Account #:

MAYO
MEDICAL LABORATORIES

MAY 23, 2003

17.10 GFR PROCEDURES

This section is extracted from the GFR Manual provided by the Mayo Clinic Laboratory and adapted specifically for the CRISP Study.

17.10.1 GFR TESTING Using the Cold Iothalamate Clearance Method

1. Title

Short Renal Clearance
Iothalamate Clearance
Cold Iothalamate Clearance

2. Principle

- The short non-radiolabeled Iothalamate Clearance Test is a simple test that is done to obtain an estimate of a patient's glomerular filtration rate (GFR) without subjecting the patient to the more-expensive and time-consuming Standard Renal Clearance.
- **A dose of 300 mg of Iothalamate Meglumine** (Conray® 60%), for patients >40 kg, **is given subcutaneously** (See 5. A). Iothalamate, (like Inulin), is filtered by glomeruli but is not secreted nor reabsorbed by the renal tubules, therefore, can be used to estimate GFR.
- **A 'blank' urine sample (U_0) is collected** prior to the injection of Iothalamate. A 15-ml aliquot is saved for analysis. The purpose of this sample is to rule out the presence of any substance interfering with the measurement of Iothalamate.
- **Iothalamate is injected** (See 5. A). It is absorbed from the injection site into the blood stream where it is carried to the kidneys for filtration. A 60-minute (± 5 min) Equilibration Period is necessary to allow blood levels to peak and become stable.
- After the 60-minute, (± 5 min), Equilibration Period, a urine sample **(U_E)** is collected. **Urine flow rate must be equal to or greater than 3 ml per minute**. If the flow rate is **not** equal to or greater than 3 ml per minute, the **test must be rescheduled**. Record the Time Void Ended and Urine **(U_E)** volume. Bladder emptying is monitored. † This urine sample **(U_E)** is discarded.
- **P_1 - Within 5 minutes after collecting U_E, a blood sample is collected and centrifuged to separate the Plasma from the cells. The Plasma (P_1)** aliquot is saved for analysis.
- **U_1** – After U_E, **All urine voided is collected and saved for at least 45 minutes.** NOTE: If the patient is unable to void at 45 minutes, the time may be extended, but should be no greater than 90 minutes. **Urine flow rate for U_1 must be equal to or greater than 3 ml per minute.** The time void ended and urine (U_1) volume are recorded. Bladder emptying is monitored. † A fifteen (15)-ml aliquot is saved for analysis.
- **P_2 - Within 5 minutes after collecting U_1, a blood sample is collected and centrifuged to separate the Plasma from the cells. The Plasma (P_2) aliquot** is saved for analysis.
- The concentration of Iothalamate is determined for U_0, U_1, P_1 and P_2 by capillary electrophoresis.
- **NOTE: Adequate patient preparation [hydration, satisfactory urine flow rate (≥ 3ml per minute), consistency in fasting and time of the day the test is performed] is critical to consistent results. (See Appendix C – GFR CHECKLIST).**
  - The GFR test will always be performed as close as possible to 0800 (morning).

3. Patient Preparation and Instruction

- **NOTE: (SEE APPENDIX C, THE GFR CHECKLIST). If the answer to ANY of the GFR CHECKLIST statements is "NO", the GFR TEST MUST BE RESCHEDULED.**

A. In the EVENING BEFORE GFR Testing:
- Patient is to drink three 8-oz glasses of water between 9:00 PM and 10:00 PM.
- Patient is to eat nothing after midnight, but may continue to drink water.

B. On the DAY OF GFR Testing:
- Instruct the patient to drink six 8-oz glasses of water between 6:00 AM and 8:00 AM. (May include 1 cup of black, decaffeinated coffee).
- Patient not to urinate during the 45 minutes before GFR Testing (U_0), if possible.

4. Set-up

A. Assemble all supplies (See 5. Equipment, below) and open the GFR Collection Kit.

B. Fill out the Request Form using a BLACK ballpoint pen. Press firmly to ensure all copies of the forms are legible. **Enter the following information**:
- **Patient Initials** (first, middle, last); put in a dash (-) if the middle initial is not available. ***This information should be entered on the first line of the form in the space that is marked "Patient Last Name"
- **Patient Gender**. ***Should be entered on the first line of the form(M/F)
- **Patient Date-of-Birth**. ***Should be entered on the first line of the form
- **Patient Identification Number** (6 digit). ***Should be entered on the second line of the form in space that is marked "Patient Number"
- **Collection Date.** ***Should be entered on the third line of the form
- **Patient Weight** in kilograms
- **Patient Height** in centimeters

- **Note:** To convert Weight in Pounds to Kilograms: **Weight in pounds x 2.2 = Weight in kilograms**
  To convert Inches to Centimeters: **Number of inches ÷ 2.54 = Height in centimeters**

- **NOTE: It is important that the above information be provided**. (See C, D & E below).
- **Mayo Medical Laboratories will contact you** to obtain missing information or to verify information that is inconsistent.

C. You must indicate on each specimen collection tube which specimen it is: **(i.e. U_0, P_1, U_1 or P_2).**

D. You must write the patient's initials, identification number, and date of collection on each specimen collection tube label. (If a label is not on the specimen container, please apply a plain white self-adhesive label to the container and label appropriately).

E. One (either one) of the URINE specimen containers and one (either one) of the BLOOD specimen tubes must have a small green-bordered **Control Number label** applied to it. [These green-bordered control-numbered labels are found at the top right-hand corner of the Short Renal

Clearance Request Form provided in GFR Kits by Mayo (MML)].

5. Equipment, Reagents, Special Supplies

A. The following SUPPLIES ARE provided by Mayo in GFR TESTING KIT:

- Iothalamate Meglumine injection Conray®, U.S.P. 60% - *Mallinkrodt Medical*.
  - Each ml contains **600 mg** Iothalamate Meglumine.
  - Each Vial is to be a SINGLE USE VIAL
- Sterile Bacteriostatic water.
- Sample aliquot tubes:
  (2) Clear 60-ml containers for urine
  (2) Clear 6-ml tubes for plasma
- Short Renal Clearance Request Form

B. The following SUPPLIES ARE NOT provided by Mayo:

- 70% Isopropyl alcohol (Alcohol pads).
- Tourniquet
- Syringes *Terumo* Corporation ® 1 ml Tuberculin and 6 ml.
- Neolus™ Needle 22 Ga x 1" needles.
- Winged Infusion (Butterfly) Set – 22 ga. x ¾" needle (*Terumo* Corporation)®.
- Heparin Lock Flush Solution [Available in TUBEX Cartridges **(30 units/3ml),** Interlink ™ System by Abbott®**].**
- 5 ml green-topped Vacutainer® (Sodium Heparin).
- Vacutainer® sleeve
- Gauze sponges - 3 x 3 12-ply Bandage – Kling®.
- Conforming Gauze - 2 inch.
- Cups – 12-oz Dixie ®.
- Kleenex ®.
- Large rigid Biohazard disposable container for sharps.
- Exam gloves.
- Disinfectant, *Virex* TB®.
- Bladder Scan - (Pads, gel, Ultrasound)
  Bladder Volume Instrument
  Model No. 2500 or 3000
  Diagnostic Ultrasound
  18109 NE 76th Street
  Redmond, WA 98052

❖ C. Iothalamate Dose Preparation:

- **A dose of 300 mg (0.5 ml) of Iothalamate Meglumine (Conray® 60%), for patients >40 kg, is given subcutaneously.**
- **Each vial of Iothalamate should be used as a SINGLE DOSE VIAL.**
  - With a one (1)-ml Tuberculin Syringe, draw up **0.5 ml of Iothalamate.**
  - **Add 0.5 ml of sterile Bacteriostatic Water.**
  - **This mixture will be injected subcutaneously into the opposite arm that is used**

for blood draws.

- **USE BEST ARM for blood draws**

6. Instructions for Blood Collection - PLEASE READ CAREFULLY! (See 7. Procedure)

A. Put on gloves. It is recommended that gloves be worn when collecting blood specimens.

B. Prior to Iothalamate Injection, determine which arm has the best venous access and select the site for the blood draw in that arm.

C. For $\mathbf{P_1}$ and $\mathbf{P_2}$, collect 3-ml blood for each specimen (2-ml minimum for all patients). This blood is then centrifuged and the plasma separated.

D. **NOTE:** If the patient has POOR veins or has a history of difficult blood draws, USE THE BUTTERFLY INFUSION SET without attempting Antecubital venipuncture. When a Butterfly Infusion Set is used, distal branches of the cephalic vein, closer to the hand are preferred.

E. Venous access with the Butterfly should be established before the patient voids specimen $\mathbf{U_E}$. (This may be done any time after U_0 and up to U_E).

F. As the Butterfly Infusion Set needle is very small, it should be kept patent with Heparin flush. **Use Heparin Lock Flush Solution (30 units/3ml).** This is available in 3-ml TUBEX cartridges (Interlink ™ System by Abbott®).**

****NOTE:** When using the Heparin Flush Solution, make certain that an equal amount of waste is removed prior to the blood draw. (i.e. If 1 ml of Heparin Flush Solution is used, **WITHDRAW** and **DISCARD 1 ml "waste"** prior to obtaining desired specimen for P_1 or P_2.

G. If the patient has GOOD venous access with no history of difficult blood draws, choose a venipuncture site in the Antecubital Fossa. NOTE: The method preferred (Butterfly Infusion Set Vs Antecubital Venipuncture) can be decided at each Site.

- If the Antecubital Fossa is chosen, preferred veins located there are the Median Cubital, Cephalic and Basilic. If a tourniquet must be used, **DO NOT** apply for more than ONE minute. Hemoconcentration may cause erroneous test values.
- Avoid excessive hand pumping.
- Cleanse the site using 70% Isopropyl Alcohol (Alcohol pads).
- Allow the site to dry. **Note**: Performing the venipuncture before the site dries may result in a burning sensation when the puncture is performed and may cause hemolysis of the specimen.
- To prevent contamination, do not touch the site after cleansing.

7. Procedure

A. **REVIEW GFR CHECKLIST** with patient – **(See APPENDIX C).**

- **NOTE: The GFR test must be rescheduled if the answer to any of the statements in the Checklist is "NO". If all criteria are met**, **continue** with the Iothalamate Clearance test

B. Explain the duration (approximately 2 hours), the nature and the course of the GFR Test to the patient.

C. Confirm fasting, hydration, patient's weight (kg). and height (cm).

D. Question Iodine sensitivity

- NOTE: If the patient has had a severe reaction to contrast in the past, immediately notify your Principal Investigator in regard to canceling the test.
- If the patient has had a mild or moderate reaction to contrast, make a notation to that effect, proceed with the test and carefully observe the patient.

7. Procedure (continued)

E. U_0 = Urine collected before Iothalamate injection (Baseline Urine)

- Have the patient void a pre-test, pre-injection, "blank" urine sample (U_0).
- Aliquot 15 ml of urine for U_0 sample into the clear 60-ml urine container.
- Label the container U_0 along with the patient's initials, 6-digit ID number and date of collection.
- Record the Time Void Ended on the Short Renal Clearance Request Form.
- Discard the remainder of the urine sample.

F. Iothalamate Preparation and Injection

❖ **Prepare the dose of Iothalamate:**

- **A dose of 300 mg (0.5 ml) of Iothalamate Meglumine (Conray® 60%), for patients >40 kg, is given subcutaneously.**
- With a one-(1) ml Tuberculin Syringe, **draw up 0.5 ml of Iothalamate**. **Add 0.5 ml of sterile Bacteriostatic water**. This mixture will be injected subcutaneously into the arm OPPOSITE the arm that is selected for blood drawing. USE BEST ARM FOR BLOOD DRAWS.

❖ **After U_0 is obtained, inject the Iothalamate subcutaneously** into the POSTERIOR aspect of the upper arm**.**

- **Venous access, if using the Butterfly Infusion set, should be established before the patient voids specimen U_E. Butterfly may be inserted any time after U_0 and up to U_E.**
- Instruct the patient to wait for a 60-minute (±5 min) Equilibration Period and to drink 8-16 oz of water to maintain output.
- After the Equilibration Period, another urine collection (U_E) and the first plasma specimen (P_1) will be drawn. The Butterfly must be kept patent with a Heparin flush. **Use Heparin Lock Flush Solution (30 units/3ml) [**See 5. Equipment].

G. U_E = Urine collected 60 minutes after Iothalamate injection.

- After the Equilibration Period, 60-minute (± 5 min), a urine sample **(U_E)** is collected. Ask the patient to completely empty the bladder (U_E).
- **Urine flow rate must be equal to or greater than 3 ml per minute**. If the flow rate is not **equal to or greater than 3 ml per minute**, the test must be rescheduled. (See Appendix C)
- Bladder emptying is monitored. † Scan the empty bladder with bladder scanner 3-5 times, within 1 – 2 minutes, average the readings and record the average volume.
  - Be sure the bladder is empty, i.e. bladder volume is < 20 ml OR
  - In some patients with high-urine outputs and large bladders, urine volumes less than 10 % of voided urine and always less than 50 ml would also be acceptable.
  - If the bladder is not empty, have the patient try to void again.
  - If the patient is still unable to empty the bladder, extend the test for 5 minutes and then have him/her try to void again.
- Record the Time Void Ended and Urine (U_E) volume.
- This urine sample (U_E) is discarded.

H. P_1 = Plasma collected immediately after collecting U_E.

- **NOTE:** If the patient has POOR venous access or has a history of difficult blood draws, USING THE BUTTERFLY INFUSION SET (without attempting an Antecubital venipuncture is acceptable), draw 3 ml of blood for P_1 specimen in a 5-ml green-topped Vacutainer.
- If the patient has GOOD venous access with no history of difficult blood draws, using the venipuncture site in the Antecubital Fossa, draw 3 ml of blood from for P_1 specimen in a 5-ml green-topped Vacutainer.
- Venous access with the Butterfly should be established before the patient voids specimen U_E. This may be done any time after U_0 and up to U_E. **(PLEASE See #6. Instructions for Blood Collection).**
- This P_1 blood draw must be done within 5 minutes of U_E void ending.
- **NOTE: If a tourniquet is used, it MUST be on the patient's arm for LESS than 1 minute.**
- Centrifuge blood specimen for 10 minutes at 3000 RPM to separate plasma from cells.
- Separate the Plasma (P_1) specimen into the clear (6-ml) tube provided.
- Record the exact P_1 Collection Time on the Short Renal Clearance Request Form.
- Label the tube P_1 with the patient's initials, 6-digit ID number and the date of collection.
- Have the patient drink (1-2) 8 oz Glasses of water and wait 45 minutes.
- Proceed to the collection of U_1 specimen.

I. U_1 = Urine collected for at least 45 minutes after U_E.

- **For forty-five (45) minutes after UE** (and no longer than 90 minutes), collect the urine (U_1) † using the same procedure as for (UE).
- NOTE: † IF MORE THAN ONE VOID, BE SURE TO POOL AND SAVE ALL URINE for an accurate volume total and to obtain a representative urine sample.
- Bladder emptying is monitored. † Do Ultrasound readings of bladder x 3-5 (within 1 minute), average and record. (Ultrasound should be done fairly quickly).
    - **Be sure the patient empties the bladder as completely as possible. i.e. bladder volume is < 20 ml OR**
    - In some patients with high-urine outputs and large bladders, urine volumes **less than 10 % of voided urine (and always less than 50 ml)** would also be acceptable.
    - If the voided urine volume OR the residual bladder volume is not acceptable, have the patient void again.
    - If the patient is still unable to empty the bladder, extend the test for 15 to 30 minutes (always less than 90 minutes total). Have the patient walk during this time, then have the patient void again.
    - **NOTE: The minimum urine flow rate must be equal to or greater than 3 ml per minute**. If the flow rate is not equal to or greater than 3 ml per minute, the **test must be rescheduled**. (See Appendix C)
- Aliquot 15 ml of urine for U_1 (or TOTAL POOLED URINE SAMPLE, if more than one void) into the clear (60 ml) urine container.
- Label the container U_1, with the patient's initials, 6-digit ID number and date of collection.
- Record the Total Volume of urine (U_1) and Time Void Ended on the Short Renal Clearance Request Form.
- The (U_1) urine sample (minus the 15-ml aliquot) is then discarded.
- NOTE: If any urine is discarded from the U_1 collection period, (rather than pooled and saved), **test must be rescheduled**.

J. P_2 = Plasma collected immediately after collecting U_1.

- This P_2 blood draw must be done within 5 minutes of U_1 void ending.
- **Draw 3 ml of blood in a 5-ml green-topped Vacutainer** (using Butterfly or Antecubital vein) for P_2 specimen.
- **NOTE: If a tourniquet is used, it MUST be on the patient's arm for LESS than 1 minute.**
- Centrifuge blood specimen for 10 minutes at 3000 RPM to separate plasma from cells.
- Separate the Plasma (P2) specimen into the clear (6-ml) tube provided.
- Record exact P_2 Collection Time on the Short Renal Clearance Request Form
- Label the tube P_2 with the patient's initials, 6-digit ID number and date of collection.

♦ **NOTE:** The U_1 collection time can be extended to 90 minutes (BUT NO LONGER) to assure an adequate collection volume. The Collection time must NOT exceed 90 minutes.

♦ If the U_1 collection time needs to be extended or if the patient needs to void more than once during the U_1 collection time, combine and save all urine voided and….

♦ Use the LATEST collection time on the Request Form and collect the plasma within 5 minutes of this extended urine-collection time.

❖ There have been no severe reactions noted in over 2000 studies with the small dose of Iodine used in this procedure, but in theory this could occur.
(Refer to Appendix D - Contrast Reactions — Nursing Perspective).

❑ THIS ENDS THE RENAL CLEARANCE TEST.

8. Procedure Notes

A. Criteria for Immediate Notification of Investigator:

- Iothalamate allergic reaction.
- Incomplete bladder emptying.
- Low urine output.
- Headache, nausea, diarrhea.
- other physical complaints (see Appendices D & G).

B. For **U_E and U_1 urine collections, minimum flow rates of 3 ml per minute are required.**

C. Ultrasound bladder readings must be accurate.

D. If the patient has trouble emptying:

- Extend collection periods as below:
  - For UE, may extend time up to 5 minutes longer (i.e. 60 minutes + 5 minutes).
  - For U_1, if the patient is unable to void the required minimum of 3 ml per minute, save all voided urine and extend the collection period for a total of (up to **but no longer than**) 90 minutes after U_E..(i.e. U_1 would be collected for 45 to 90 minutes after UE.) in an attempt to facilitate bladder emptying.
- Instruct the patient on the importance of total emptying and how to accomplish it.
- Ask the patient if he/she would prefer to try emptying in a public restroom.
- Question whether or not the patient has to have a bowel movement.
- If any urine is discarded from the U_1 collection period, **the test must be rescheduled.**

9. Collection, Handling and Labeling of Specimens

A. PLASMA (P_1 and P_2):

- Draw 3 ml of blood (2-ml minimum for all patients) in a 5-ml Sodium Heparin (green-topped) Vacutainer.
- Record exact time specimen obtained.
- Centrifuge for 10 minutes at 3000 RPM, to separate plasma from cells.
- Separate the Plasma 1 specimen (P_1) into the clear (6-ml) tube provided and label.
- Separate the Plasma 2 specimen (P_2) into the second clear (6-ml) tube provided and label.
  - **NOTE**
    - P_1 = Plasma which has been centrifuged from the blood specimen collected immediately (5 minute maximum) after collecting U_E
    - P_2 = Plasma which has been centrifuged from the blood specimen collected immediately (5 minute maximum) after collecting U_1

B. URINE (U_0 and U_E):

- U_0 = Urine collected before injection of Iothalamate. (Aliquot 15 ml into the clear 60-ml Urine container provided).
- Actual Iothalamate Injection Time, immediately after U_0
- U_E = Urine collected 60 minutes (± 5) minutes after injection
  - (Specimen discarded)
- U_1 = Urine collected for at least *45 minutes after U_E.

NOTE: *Times may vary with the patient's ability to void, but it **will not be less than 45 minutes** and **will not exceed 90 minutes**. At least **3-ml flowrate** of urine per minute will be required to consider the test acceptable. A bladder monitor using ultrasound will be used to assure emptying.

C. ADEQUACY OF SPECIMENS

- **URINE:**
  - At least 15 ml urine for U_0 and U_1 aliquots.
  - Urine flow must be **≥ 3 ml per minute** during GFR Testing.
- **BLOOD:**
  - At least 2.0 ml blood (preferably 3 ml), must be collected, centrifuged and then separated for the P_1 and P_2 specimens.
  - P_1 and P_2 must be obtained within **5 minutes** of U_E and U_1.
  - NO blood in P_1 and P_2 specimens.
  - Avoid hemolysis. (See 9 A.)

10. Limitations

- Tests that require laxatives for preparation are contraindicated the same day as GFR test, due to patient dehydration.
- Contrast studies within 12 hours prior to this test may interfere with the Iothalamate Clearance.

11. Procedure Location

- **CRISP Manual Of Operations**

17.10.2 SUPPLIES PROVIDED by Mayo Medical Laboratories

- **GFR Specimen Collection Kits**

- Supplies for collecting specimens are provided in a generic GFR kit. Expiration dates are printed on Iothalamate and Bacteriostatic water bottles. Please check these dates and discard any expired bottles.
- Reorder the necessary kits from Mayo Medical Laboratories (MML) by calling Mayo Laboratory Inquiry at 800-533-1710 (Do not send FAX to request supplies)
- Please be certain to specify your account number and your Site

- **Short Renal Clearance Test Request Form**
  - A test Request Form has been developed for the GFR testing kit. Each form should be filled out completely using a BLACK ballpoint pen.
  - Mayo Medical Laboratories will contact you when a Request Form is received and information is missing.
  - An example of the Short Renal Clearance Request Form is included in Appendix A.
- **Other Supplies**
  - Transport boxes with Styrofoam liners and coolant packs

  - NOTE: Kits are not automatically re-supplied.
    - To order additional supplies, please call Mayo Laboratory Inquiry at 800-533-1710. (Do not send FAX to request supplies)
    - When reordering supplies, please be sure to allow at least one (1) week for shipping and handling and provide the following information.
    - Your Account Number (provided by Mayo)
    - Detail of supplies needed
    - Supplies will be sent to you via appropriate courier service.

17.10.3 Specimen Processing and Packaging

1. GFR Testing Overview

A. Specimen Processing: Urine and plasma samples will be collected in this order during the GFR test:

- **U_0 = Baseline Urine collected before Injection**
  - **i.** Review **GFR CHECKLIST**. If all criteria are met, (see Appendix C), continue with the Iothalamate Clearance test
  - **ii.** Have the patient void a pre-test, pre-injection, urine sample (U_0). Inject the Iothalamate subcutaneously. **Record injection time** on the Short Renal Clearance Request Form.
  - **iii.** Aliquot 15 ml of urine for U_0 sample into the clear 60-ml urine container. It is not necessary to measure the total U_0 volume.
  - **iv.** Label the container, U_0, along with the patient's initials, 6-digit ID number, and date and time of collection.
  - **v.** Record the Time Void Ended (U_0)on the Short Renal Clearance Request Form.
  - **vi.** Discard the remainder of the urine sample.

- **U_E = Urine collected 60 (±5) minutes (after injection).**
  - **i.** Ask the patient to completely empty the bladder (U_E).

ii. Scan the empty bladder with bladder scanner 3-5 times within 1 minute, average the readings and record the average volume.

iii. Urine flow rate must be equal to or greater than 3 ml per minute.

iv. Be sure the bladder is empty, i.e. bladder volume is < 20 ml. In patients with high-urine outputs, urine volumes less than 10% of voided volume (and always less than 50 ml) would also be acceptable.

- If the bladder is not empty, have the patient try to void again.
- If the patient is still unable to empty the bladder, extend the test for 5 minutes and have him/her try to void again.

v. Record the Time Void Ended on the Short Renal Clearance Request Form.

vi. **Discard this (U_E) urine specimen**.

- **P_1 – A Sodium Heparin Plasma Specimen** (3 ml blood drawn in a 5-ml green-top vacutainer, centrifuged and the Plasma separated)

  i. Must be collected within 5 minutes of collecting the **U_E**– Equilibration urine.

  ii. Gently mix the blood and centrifuge the green-top vacutainer for 10 minutes at 3000 rpm in a balanced centrifuge to separate the plasma from the cells.

  iii. Separate the Plasma (**P_1**) into the clear 6 ml tube provided.

  iv. Record the collection time on the Request Form and on the clear 6-ml tube.

  v. Note: Blood is drawn from the arm opposite the injected arm.

- **U_1 – GFR testing urine collection.**

  i. This specimen is collected for at least 45 minutes and no longer than 90 minutes after the U_E (Equilibration) urine specimen is obtained.

  ii. Be sure the bladder is completely empty; **a minimum flow of 3 ml of urine per minute is required.**

  iii. Accurately measure■ and record the Urine (U_1) volume and Urine collection time on the Request Form.

  ■ NOTE: It is preferable to weigh the EMPTY urine-measuring container FIRST, then weigh the container PLUS the urine (One ml = 1 oz). Each Site will determine preferred urine measurement method.

  iv. Aliquot 15 ml of urine into the second clear 60 ml urine container.

  v. Record the collection time on the Request Form.

- **P_2 A Sodium Heparin plasma specimen** (3 ml blood drawn in a 5-ml green-top vacutainer, centrifuged and Plasma separated)

  i. Must be collected within 5 minutes of collecting the **U_1**– GFR testing urine.

  ii. Gently mix the blood specimen and centrifuge the green-top Vacutainer for 10 minutes at 3000 rpm in a balanced centrifuge.

  iii. Separate the plasma (**P_2**) into the second clear 6-ml tube.

  iv. Record the collection time on the Request Form and on the clear 6-ml tube.

- **U_1 Collection Duration** – Record the time difference from the U_E collection time to the

U_1 collection time, in minutes, on the Request Form.

B. Specimen Packaging:

i. **Ensure that each and every specimen container is correctly labeled** as "U_0", "U_1", "P_1" OR "P_2", along with the Patient's initials, 6-digit ID number, the Date and Time of Collection. In addition, one (either one) of the URINE specimen containers and one (either one) of the BLOOD specimen tubes must have a small green-bordered **Control Number label** applied to it. [These green-bordered control-numbered labels are found at the top right-hand corner of the Short Renal Clearance Request Form provided in GFR Kits by Mayo (MML)].

ii. Complete the required areas at the top of the Short Renal Clearance Request Form (i.e. Patient's Initials, Gender, Date of Birth, Patient's 6-digit ID Number and the Collection Date).

iii. Ensure that the bottom portion of the Short Renal Clearance Form is completed. Appropriately complete all blanks (i.e. Patient's Weight in kg and Patient's Height in cm; Time U_0 [Time Void Ended]; exact Iothalamate Injection Time; Time U_E [Time Void Ended - specimen discarded]; Plasma P_1 Collection Time; GFR Testing Urine [U_1 Collection Time Void Ended] and U_1 Volume; Plasma P_2 Collection Time).

iv. Put the LABELED containers of the Plasma and the urine aliquots into the "Refrigerated Specimen" pink transport bag.

v. Place the top two copies (white) of the completed Short Renal Clearance Request Form into the outer pocket of the pink transport bag. Seal the bag.

vi. Place the transport bag into your refrigerator while you make transportation arrangements.

vii. Specimens are to be shipped IMMEDIATELY by FEDERAL EXPRESS to Mayo Medical Laboratories.

viii. Place several layers of paper toweling on top of the solidly frozen cold pack. * Then place all specimens (in pink transport bag) into the Styrofoam container that is inside the cranberry-colored shipping box.

- * Follow directions regarding Coolant on label inside box.

17.10.4 Pre-shipment Checklist: (See B. Packaging, GFR Overview)

- Prior to sending specimens to Mayo Medical Laboratories, you should review each of the following criteria:

1. The proper specimen container has been used.
2. The correct types of specimens have been collected.
3. Plasma has been checked and does not show signs of being grossly hemolyzed.
4. **Specimen containers have been properly labeled** and **writing is legible**.
5. The test Request Form has been properly completed and the two top white copies are enclosed in the side pocket of the "Refrigerated Specimen" pink transport bag.
6. The specimens have been stored in a refrigerator while shipping arrangements have been made. The specimens will be shipped refrigerated.

17.10.5 Shipment by Federal Express

- Federal Express will be your primary courier service.

1. Specimens must be completely packaged in shipping containers prior to Federal Express pickup.
2. REFRIGERATED specimens should be placed into the pink "Refrigerated Specimen" transport bag, and the Short Renal Clearance Request Form placed in the outside pocket of the bag (as noted previously in the packaging instructions).
3. Place a paper towel on top of the solidly frozen cold pack.
4. Place the pink transport bag (with specimens) into the Styrofoam box inside the "Refrigerate Only" cranberry-colored shipping container provided by Mayo Medical Laboratories. Seal the container.
5. NOTE: Freeze and store cold packs in a -10º freezer, **not on dry ice**. Dry ice freezes the cold packs at a temperature that may cause samples to freeze more readily.
6. Complete a Federal Express (airbill NOT included in MML supplies). Call Federal Express at 1-800-238-5355 (U.S.) to obtain airbills.

7. PLEASE be sure to request Priority Overnight service and to indicate date to be delivered (cont'd) (e.g. "Deliver Saturday") on the airbill, if you have to ship on Friday.
8. Write your return address on the shipping container.
9. Call Federal Express at 1-800-238-5355 (U.S.) by noon for same-day service. Provide the following information:
10. Exact location of pick-up site.
11. Number of boxes in shipment.
12. Assist the Federal Express courier in finding the shipping box (es), if requested.
13. **FAX** a copy of a properly-completed "**Shipment Alert" form** to:
    Mayo Medical Laboratories, Transportation Department at 1-507-284-1790.
    - No cover sheet is necessary. (see Appendix E)
14. The following information should be provided:
    - Your name and the location of your Study Site
    - Federal Express(tracking number (top right corner of airbill)
15. Please FAX Mayo Laboratory Inquiry at FAX (507) 284-1769, or you may call 1-800-533-1710 and ask for the Renal Function Lab, if you have questions regarding these arrangements

17.10.6 Shipments to Mayo Medical Laboratories (See Appendix E)

- DO NOT collect any specimen on the day before a national holiday (e.g., December 24 or 31), because transportation services are frequently not available and results may be compromised by late arrival at MML.
- Please note the following national holidays for 2003 through 2004:

- **2003 Holidays:**

January 1st	New Year's Day
January 20th	Martin Luther King Day
February 17th	President's Day
May 26th	Memorial Day
July 4th	Independence Day

September 1st	Labor Day
October 13th	Columbus Day
November 27th	Thanksgiving
December 25th	Christmas

- **2004 Holidays:**

January 1st	New Year's Day
January 19th	Martin Luther King Day
February 16th	President's Day
May 31st	Memorial Day
July 4th	Independence Day
September 6th	Labor Day
October 11th	Columbus Day
November 25th	Thanksgiving
December 23rd	Christmas

17.10.7 Test Cancellation Policy

- Mayo Medical Laboratories is committed to providing laboratory data that clinically correlates with the patient's condition. Therefore, we may cancel tests under the following conditions:
  - The specimen is received beyond the acceptable stability period.
  - Plasma is grossly hemolyzed.
  - The specimen has been damaged during transit.
  - The patient's initials **and 6-digit Study ID number** are not clearly identified.

- Should a test be canceled for any reason, a Mayo Medical Laboratories representative will contact you directly, explain the reason for the cancellation and discuss the appropriate action.

17.10.8 Study Completion

- When the study has been completed, please review your data to ensure that all expected laboratory reports have been received. Contact the Mayo Study Coordinator if you have questions concerning testing.

- Kits and other laboratory or transport supplies provided but not used for this study may be recycled for other use or discarded. PLEASE DO NOT return these materials to Mayo Medical Laboratories.

17.10.9 Result Reporting

- Results will be sent to you via FAX. Patient and Visit information are in the upper right corner, followed by Investigator and Sponsor information. Your Site account number appears above the investigator's name (preceded by "C").
- Should you have questions on results, please use the above information to properly identify the patient's

record. All results have been grouped (where applicable) with the test name followed by the result flag, result, reference range and units.

APPENDIX A

LABORATORY REQUEST FORM

MAYO Short Renal Clearance Request Form

PATIENT REQUISITION FORM

General Collection and Processing Instructions

(for more complete instructions, see the instruction sheet included in the kit)

1 Record the patient's height and weight in the area provided below.

2 **Uo** - Initial pre-injection urine sample. Aliquot 5 mL into one of the urine containers provided. Record the collection time below. Write "Uo" on the urine bottle.

3 **Iothalamate Injection Time**- Record the injection time below.

4 **Ue** - Equilibration urine collection. Collect this specimen 60 minutes after the iothalamate injection time. Be sure the bladder is completely empty. Record the collection time below and discard the urine specimen.

5 **P1** - Collect a sodium heparin plasma within 5 minutes of collecting the Ue. Aliquot the plasma into the tube provided. Record the collection time below. Write "P1" on the vial.

6 **U1** - GFR testing urine collection. Collect specimen 45 minutes after the Ue collection. Be sure the bladder is completely empty; minimum of 100 mLs of urine is optimal. Aliquot 5 mL into the 2nd urine container provided. Quantitatively measure the U1 volume and record both the volume and collection time below. Write "U1" on the urine container.

7 **P2** - collect a sodium heparin plasma within 5 minutes of collecting the U1. Aliquot the plasma into the 2nd tube provided. Record the collection time below. Write "P2" on the vial.

8 U1 Collection Duration - Record the time difference from the Ue collection time to the U1 collection time in minutes in the space provided below.

Packaging Instructions

1 Insure that all specimens are labeled correctly.
2 Put the plasma and urine aliquots into the "Refrigerated Specimen" transport bag.
3 Place the top two copies of the completed requisition form into the outer pocket of the transport bag.
4 Store the specimen in the refrigerator until the specimen is shipped.
5 Ship the specimen at refrigerate temperature.

Test 81476 Short Renal Clearance

THE FOLLOWING INFORMATION MUST BE PROVIDED BEFORE TESTING CAN BE COMPLETED.

Collection Date ___-___-___ Identification Number _____

Patient Initials ____ Patient Gender M__ F__

Patient Weight: _____ . __ kg (in kilograms) Patient Height: _____ . __ cm (in centimeters)

Initial Urine Collection Time (Uo): _____ : _____ am nm Iothalamate Injection Time: _____ : _____ am nm

Equilibration Urine (Ue) Collection Time: (Specimen Discarded) _____ : _____ am nm

Plasma (P1) Collection Time: _____ : _____ am nm (Must be no longer than 5 minutes after Ue Collection)

GFR Testing Urine (U1) Collection Time: _____ : _____ am nm

Plasma (P2) Collection Time: _____ : _____ am nm (Must be no longer than 5 minutes after Ue Collection)

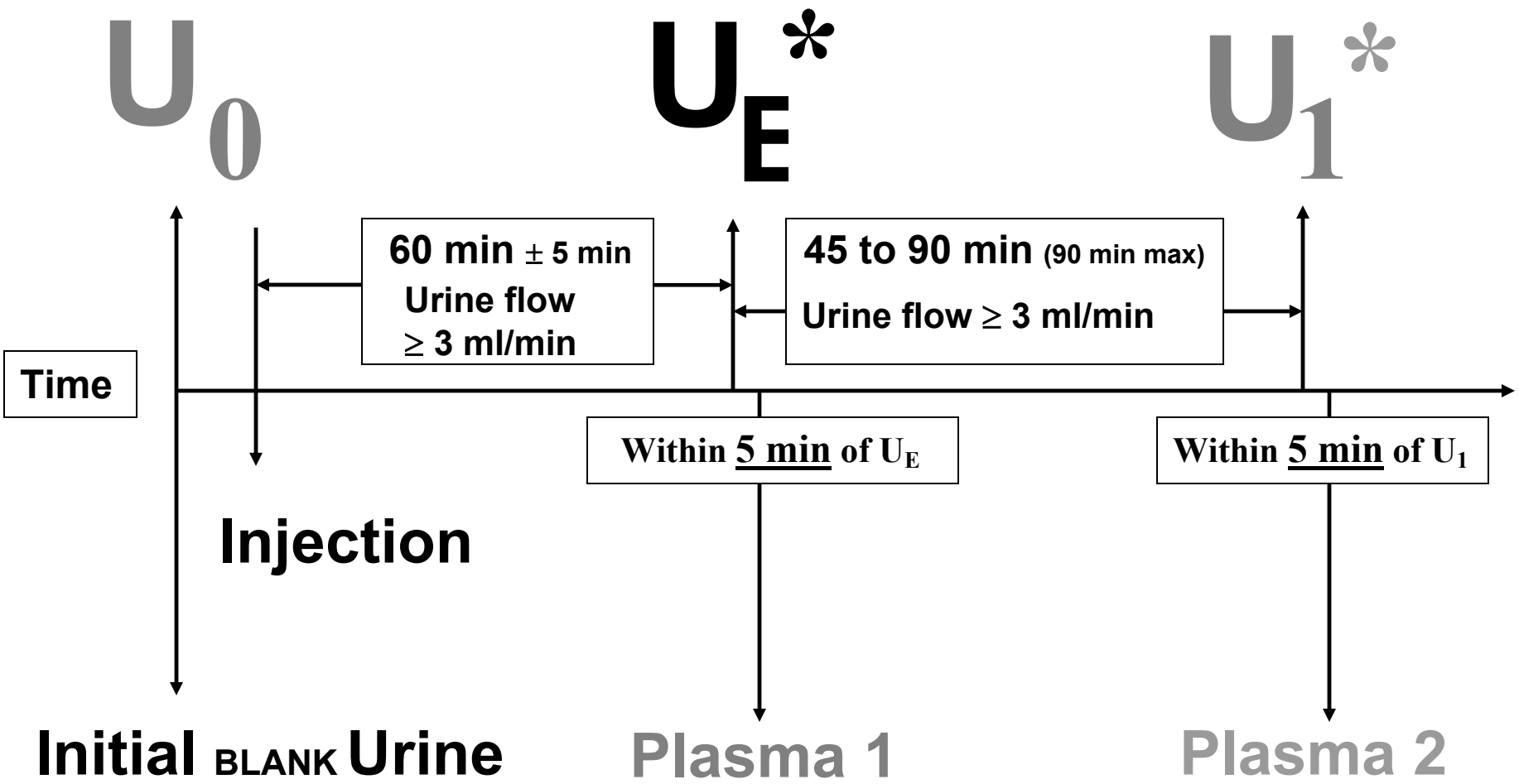
U1 Collection Volume: _____ **mLs**

U1 Collection Duration: _____ minutes
Time Difference from Equilibration Urine (Ue) to GFR testing Urine (

APPENDIX B

GFR Testing Flowchart

GFR Testing Flowchart



***Residual volume <20 ml or 10% of voided volume - always less than 50 ml.**

Items highlighted in grey are samples to be sent to Mayo Medical Labs.

APPENDIX C GFR CHECKLIST

THIS FORM MUST BE COMPLETED at all SITES
AND RETURNED WITH Study SPECIMENS to MML!!
This is necessary to provide a means of tracking and resolving problems.

- **Patient Initials: ___.___.___ MML Control Number: _____**
- **SITE: (Circle One) Alabama Emory Kansas Mayo**
- **Date of Collection:_____/_____/20_____**
  Month Day Year
- **CLINICAL STABILITY: No ☐ Yes ☐**
- **[NOTE: Clinical Stability is defined as the ABSENCE OF symptoms such**
- **as fever, Viral Syndrome, acute pain, diarrhea, etc.]**
- **Compliance with non-allowed medications: No ☐ Yes ☐**
- **Fasting (> 8 hours) No ☐ Yes ☐**
- **Hydration as per Protocol No ☐ Yes ☐**
- **Equilibration time 60 ± 5 minutes No ☐ Yes ☐**
- **Urine Flow rate ≥ 3 ml/minute for UE No ☐ Yes ☐**
- **P1 within 5 minutes of UE No ☐ Yes ☐**
- **Residual bladder volume < 20 ml OR No ☐ Yes ☐**
  - **10% of voided urine (NOT > 50 ml) @ UE**
- **Collection time for U1 is 45 - 90 minutes. No ☐ Yes ☐**
- **P2 is within 5 minutes of U1 No ☐ Yes ☐**
- **Residual bladder volume < 20 ml OR**
- **10% of voided urine (NOT > 50 ml) @ U1 No ☐ Yes ☐**

***All SITES PLEASE NOTE: If the answer is "No" to any of the above statements,**
THE GFR TEST MUST BE RESCHEDULED.!

MML - NOTE: Please send this form to:
Lorna Stevens, R.N.,
Eisenberg S-33 K. Thanks! (4-0944)

If you have any questions regarding this form, PLEASE don't hesitate to call Lorna Stevens, R.N.: Pager (507) 255-3750 or (507) 284-0112 (AUDIX)

APPENDIX D

NURSING PERSPECTIVE – Contrast Reactions:

Acute reactions to iodinated contrast media are classified by their severity and patient outcome. Three commonly-used **Categories of Contrast Reactions** are:

- **MILD**: nausea, vomiting, altered taste, sweats, cough, headache, dizziness, anxiety, chills, pallor, shaking, flushing, warmth (heat), mild urticaria, rash, hives, itching, nasal congestion, swelling – eyes/face.

TREATMENT: Requires close observation and assurance, but usually no medication.

- **MODERATE**: more-pronounced degree (sufficient to be clinically evident) of mild signs/symptoms and/or systemic symptoms including pulse change and/or:

1. Diffuse hives --Patient has several hives on face and torso and often complains of itching and discomfort. Also may be associated with sneezing and watery eyes.
2. Erythema -- Patient is generally red all over, and may or may not be uncomfortable.
3. Hypotension –Hypotension may be transient. If hypotension is a vasovagal response from ureteral compression, pain or anxiety, the patient is usually pale, diaphoretic, lightheaded, and nauseated. Patients with erythema who become hypotensive are usually red and puffy but start to look mottled as fluid is redistributed to the interstitial space. These patients complain of dizziness and state that their "skin feels tight."
4. Hypertension -- Patients present with flushed face, dizziness, and headache.
5. Bronchospasm -- Patients often complain of tightness in the chest, coughing and wheezing along with restlessness and feel the need to sit up.
6. Laryngospasm -- Patients experiencing moderate symptoms of laryngeal edema will frequently complain that their "throat feels full" and that they are having difficulty swallowing. You may notice hoarseness, wheezing, stridor, or cyanosis.
7. Angina -- Patients complain of chest pain or chest tightness and sometimes shortness of breath. They normally appear anxious.

TREATMENT For Moderate Reactions: Requires prompt recognition, close, careful observation and often treatment, but usually not hospitalization.

- **MAJOR** (Severe): potentially life-threatening signs and symptoms, more-pronounced degree of moderate or severe signs and symptoms, e.g. laryngospasm plus seizures, arrhythmias, pulmonary edema, persistent hypotension and cardiac arrest.

1. Pulmonary edema -- Patients will sometimes complain of immediate shortness of breath and will become terribly agitated, diaphoretic and cough pink, frothy sputum or a patient may complain of a vague sense of discomfort and then progress slowly to the state mentioned above.

2. Cardiac arrest -- Patient becomes unresponsive, breathless, and pulseless.

TREATMENT: Requires prompt recognition and treatment; almost always requires hospitalization.

APPENDIX E

MAYO CENTRAL LABORATORY FOR CLINICAL TRIALS

Shipment Alert Form

_____
Company Name

_____
Protocol Number

NOTE: This information will help MCLCT track your shipment. Please make additional copies of this form as Necessary. FAX a completed Shipment Alert Form each time you make a Federal Express® shipment to MCLCT for this protocol. Thank you.

TO: FAX Number - (507) 284-1790

NAME: Transportation Department

***Shipment is from*:**

Investigator's Name:_____

Site Location (City, State):_____

Name of person making shipment:_____

Telephone Number:_____

Federal Express® **Airbill Number(s):**_____

Number of boxes in shipment:_____

Date of shipment:_____

Is shipment known to be infectious? **YES** **NO**
(E.g. Known HIV, Hepatitis or culture material)

Does the shipment contain Dry Ice **YES** **NO**

APPENDIX F

APPENDIX F (FAX SUPPLY REQUISITION)
is NO LONGER NEEDED -

To Order GFR Kits from
Mayo Medical Laboratories

PLEASE CALL: 1-800-533 1710

16.11 Incidental Diseases

In order to document all new diagnoses and clinical events significant enough for the participant to have a physician visit, all physician visits and hospitalizations are documented throughout the followup period. The participant is queried about each such event at the followup telephone calls every 3 months and at the annual followup in clinic visit. Those events meeting the criteria of an adverse event are appropriately documented.

16.12 Clinic Coordinator Responsibilities

The responsibilities of the clinic coordinator include, but are not limited to, the following:

1. To coordinate the Clinical Center activities related to the CRISP study;
2. To have a thorough understanding of the CRISP design and methods;
3. To coordinate activities between the participants, the Clinical Center, the General Clinical Research Center (GCRC), and the Radiology Department;
4. To act as a resource for other Clinical Center personnel concerning details of the protocol;
5. To schedule and coordinate participant visits;
6. To maintain participant interest in the study by contacts during scheduled visits, contact by telephone between scheduled visits, and by expressing concern for the participant's welfare and problems;
7. To maintain study documentation including:
   - Current Manual of Procedures;
   - Copies of current study forms;
   - Current addresses and other information required to locate each participant;
   - Participant Log Book containing study identifiers (ID number and accession numbers), informed consent documentation, and the Identification Form for each participant;
   - Appointment notebook with the CRISP follow-up schedule for each participant;
8. To ensure the Iothalamate Clearance Test is performed according to the GFR Testing Manual;
9. To be present at each radiological examination and assist with the data collection and transfer of images to the DCIAC;
10. To review all forms and materials for accuracy and completeness before sending them to the DCIAC or Mayo Medical Laboratories (MML);
11. To enter data into CRISP study database and assure that copies of all completed forms are retained in the CRISP files at the Clinical Center;
12. To organize regular clinic staff meetings of all CRISP personnel;
13. To respond to queries from the DCIAC and MML.

To maintain a record of participants who are ineligible, fail to enroll, and are withdrawn from the study.

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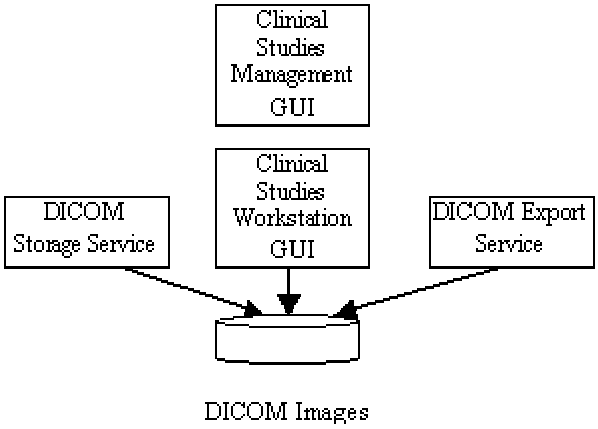
17 PCC Workstation

The DICOM Workstation for PCC sites consists of commercial PC hardware and software and special applications developed at the DCIAC. The purpose of the workstation is to provide a mechanism for collection sites to receive DICOM image data from clinical or research scanners, modify header information and to forward the modified images to the DCIAC.

17.1 Software Architecture and Components

The figure below shows a block diagram of the software components provided by the DCIAC. The Clinical Studies Management GUI is a graphical user interface used to manage patient identifiers and accession numbers. The Management GUI allows the user to register a new patient by associating that patient with a patient identifier and to link patients with accession numbers which identify studies (MR or Ultrasound).



The DICOM Storage Service is a Windows service which acts as a DICOM SCP for the storage of MR, Ultrasound and other images. This service is enabled when the PC is started and is available to accept images from scanners at any time. The DICOM Storage Service writes the images (one image per file) to disk and performs no further processing.

The Clinical Studies Workstation GUI provides a view of the images that have been received and stored by the DICOM Storage Service. The user interface allows the operator to specify changes in attributes in the image headers for one series or the entire study and then to place that series or study in a queue for transmission to the DCIAC.

The DICOM Export Service is a Windows service which is enabled when the PC is started. It reads queue entries produced by the Workstation GUI, applies changes to the attributes of the designate images, and then transmits the images to the DCIAC using DICOM C-Store commands.

Current implementations of the DICOM Standard provide no data encryption. With advice from the Mayo Institute, the DCIAC has chosen to use a hardware/software package from Nortel that will create a Virtual Private Network (VPN) between the PCC workstation

and the DCIAC storage system. When this VPN is enabled, data can be transmitted across the network (internal or Internet) using encryption.

The Nortel software consists of a client application which is loaded on the PCC workstation. In order to send data to the DCIAC storage system, users at the PCC site will have to enable the VPN by starting the client and entering a password. The DCIAC storage system is on a private network at Washington University and can only be accessed through this software.

See the Image Header Editing Section (cf. Section 16.4.4) and DICOM Storage and Transmission Section (cf. Section 16.4.2) for operating instructions.

17.2 DICOM Storage and Transmission

17.2.1 DICOM Storage

The DICOM Storage Service starts at system boot time and is always listening for connections from DICOM instruments. When a device makes a connection and sends images, the Storage Service writes the images to disk files using a directory structure which identifies the sending device, study and series. Individual files are uniquely identified by DICOM attributes which are taken from the image header.

The Storage Service writes the files to disk and does not make any database entries. It is assumed that the number of studies stored on the system will be relatively few and that a database is not required.

17.2.2 DICOM Transmission

The Workstation GUI identifies changes to be made in a study or in a series by writing a text file which describes those changes. For example, the text file would specify that the patient name entered at the original instrument is replaced with a null entry before transmission. The text file also indicates that the study or series should be transferred and the destination.

The DICOM Export Service polls for these text files. When it finds a new text file in its queue, the Export Service applies the designated attribute changes and then transmits all images to the DCIAC. Images are transmitted by opening a DICOM Association with the DCIAC storage system and using DICOM C-Store commands to send the modified images. After the images have been successfully transmitted, the text file is moved to another location as a record of the transaction.

17.3 Remote Administration

There may be instances where support staff at the DCIAC will need to respond to a software bug, or to install software upgrades. With the assistance of the coordinator at the PCC site, the VPN connection to the DCIAC site will be established. Once the connection is established, a system administrator at the DCIAC can logon to the workstation, using Symantec's PcAnywhere software and remotely administrate the workstation.

17.4 PCC Workstation Specification

The PCC workstation is based on a PC running Microsoft Windows NT 4.0 (Service Pack 5). It contains several commercial software packages as well as custom software developed for this project. Following are the specifications for the PC.

Device	Manufacturer	Model	Purchase From	Price
Computer	Dell	See quote	Dell	$2445
Laser Printer	Lexmark	Optra M410	Micro Warehouse	$670
Printer Memory		32 MB SDRAM 4x64 3.3 V66 MHZ 10 ns (MY8087)	Micro Warehouse	$90
LP Cable		DB25M/C3 6M 6Ft	Micro Warehouse	$16
Bar code reader	Zebex	Zebex Intelligent Wedge Wand: 91009	Micro Warehouse	$150
Communication SW	Symantec	pcANYWHERE host only	Micro Warehouse	$90
Microsoft Office	Microsoft	Standard Version. This should include Word, Excel, PowerPoint		

17.5 PKD Clinical Studies Workstation User's Guide

Revision 1.3.0

May 28, 2003

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A: Password Management 170

1 Introduction

The Clinical Studies Workstation (CSW) is a PC compatible computer with custom software developed to assist in image anonymization and collection for clinical trials.

This manual describes how to install, use and maintain this workstation. It includes sections on hardware installation as well as software configuration for participant anonymization.

2 System Overview

Figure 2.1 below shows a diagram of the components found at the screening center. Some components are omitted from the diagram.

Participants are scanned on a MR scanner. Depending on local protocol, these images are probably stored on a Picture Archive and Communications System (PACS) in the radiology department or they may be stored on a single-purpose storage device under the control of the study coordinator for the screening center.

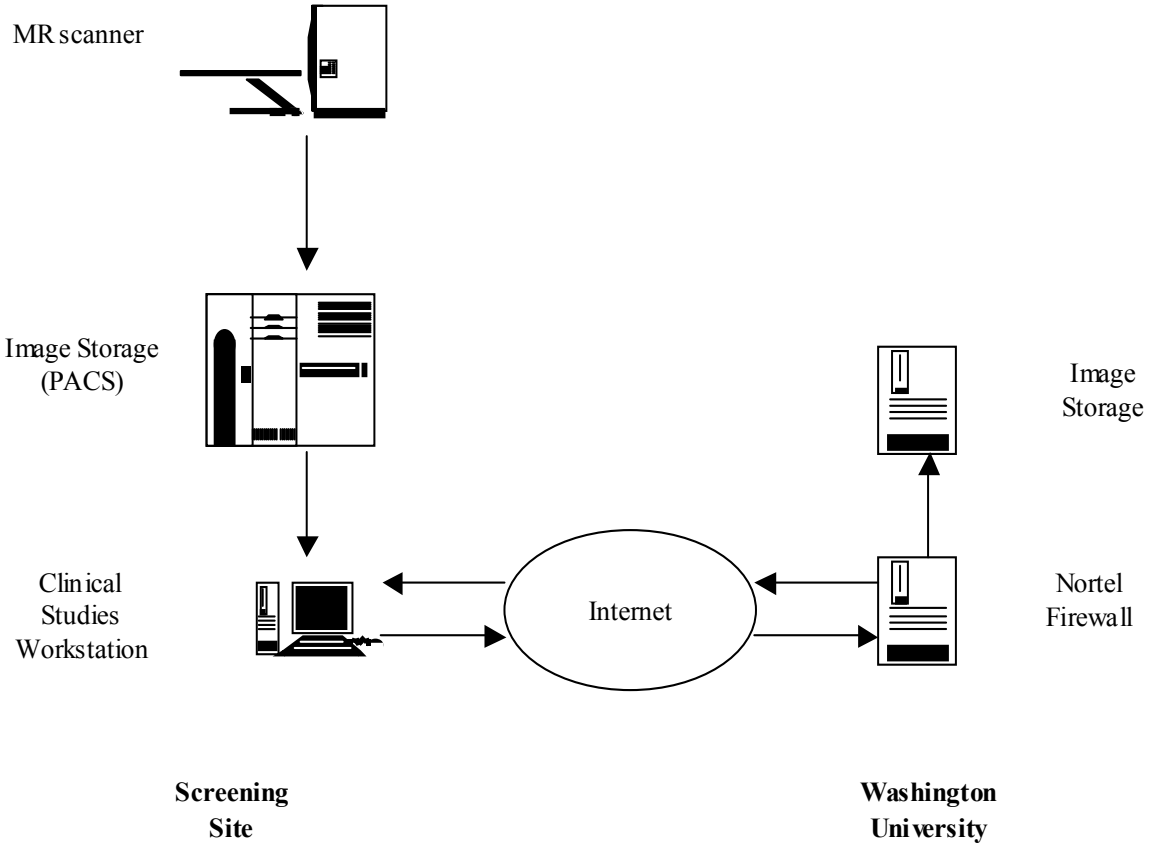


Figure 2.1 Block Diagram of Components at Screening Site and Washington University

After the studies are received at the CSW, another staff member (possibly the same staff member as above) modifies the demographics and transmits those studies to Washington University (WU) using a Virtual Private Network (VPN) over the Internet. No identifying information (PHI in HIPAA terms) is included in the transmission.

WU members perform a checkin process and translate the images into a format that is required for image measurement. As the WU members go through the checkin process, an email notification will be sent to the study coordinator confirming receipt of the data.

3 Site Installation

The CSW was configured and tested at the Electronic Radiology Laboratory at the Mallinckrodt Institute Of Radiology. This section describes those steps needed for site installation.

3.1 Administrator Changes

1. Logon to the system using the Administrator account. The system shipped to you has the administrator password set to _____. Change this password according to local convention.
2. The hostname of the system is _____. Please leave the hostname unchanged, but you should change the network settings for your institution. Use the Control Panel to get access to the Network Settings for this system, and change the following per your local configuration:
   a. IP address
   b. Subnet mask
   c. Default router
   d. DNS Service Search Order

   This PC will operate best with a fixed IP address. That can be managed through the network settings. If your site uses DHCP, you need to get a fixed IP address through your DHCP mechanism. This is because computer systems in Radiology (MR) will likely only understand a fixed IP address and will not be able to send images to this system if the IP address changes.
3. The system is shipped with a user account (Power User) under the name of the PI from your institution. That account name is _____ and password is _____. You are free to use this account for day to day activity or to create other accounts for individual users. To use the CSW software, these other accounts should be members of the Power Users group.
4. Some sites may want to reconfigure their PC and place it in a cluster with other systems. Do not do this with this PC. The VPN software that is used will cause problems with shared network drives, and the clustering software will disrupt the performance of the system. Use this PC as a standalone system as it was shipped.

3.2 Test the VPN Software

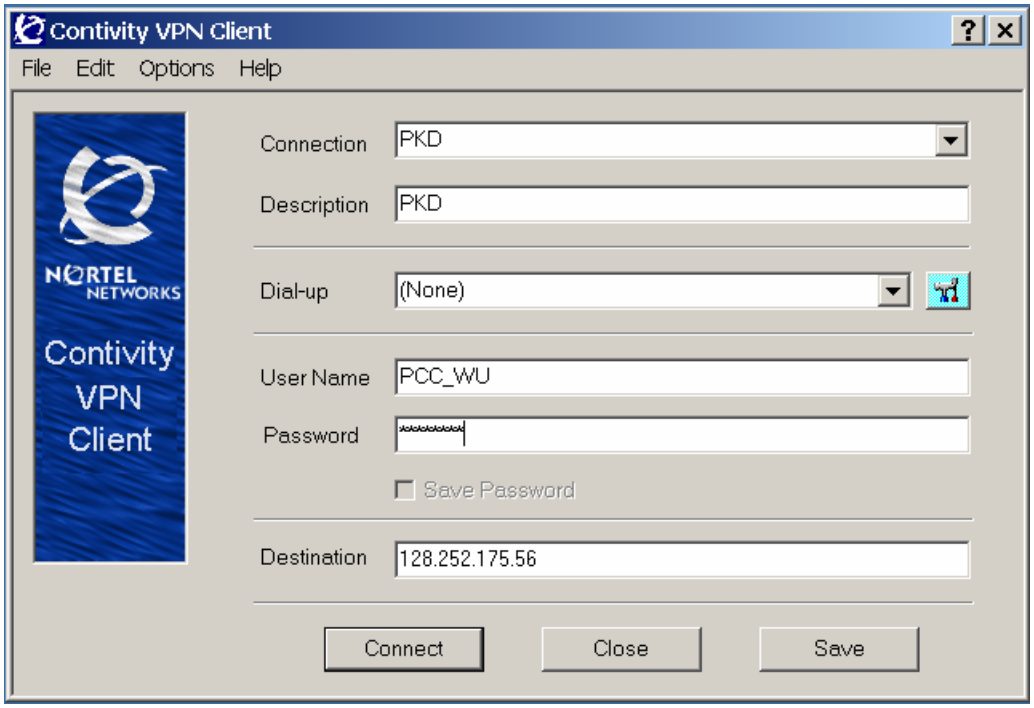
This test can be performed using the Administrator account or a user account.

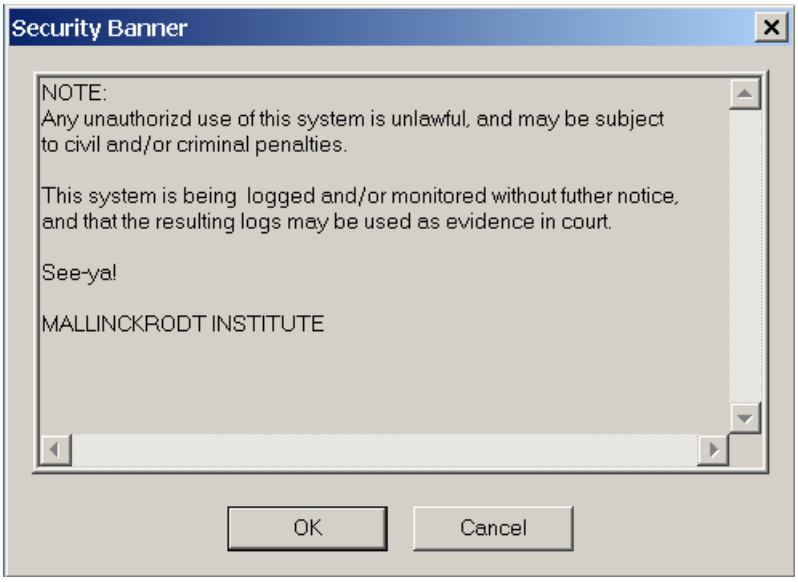
1. Make sure your system has network access to the Nortel firewall system at Washington University. Open a Command Prompt (DOS) window and ping the firewall system:

   ping 128.252.175.56

   The VPN software will not work if you cannot ping this system.

2. Activate the Nortel VPN client software. Use the desktop icon provided for the default user account or activate from the Start menu (Start->Programs->Nortel Networks->Extranet Access Client).
3. The Nortel client will present a display as shown in figure 3.1 below. The User Name and Password are fixed by Washington University. Your User Name is _____ and Password is _____. Leave the desination as is (128.252.175.56) and connect to the VPN. Upon success, you should see the window as shown in figure 3.2 below. Select the OK button to dismiss the success window.
4. Test connectivity to a system using the VPN software. Use the Command Prompt window and ping the system 128.252.219.64. If that succeeds, the VPN software if operational.
5. Disconnect the VPN connection. The Nortel VPN icon will be displayed in the tool tray in the lower right hand corner of your display. Double click that icon to bring the display to your screen. Select the Disconnect button.




Security Banner
NOTE:
Any unauthorizd use of this system is unlawful, and may be subject to civil and/or criminal penalties.
This system is being logged and/or monitored without futher notice, and that the resulting logs may be used as evidence in court.
See-ya!
MALLINCKRODT INSTITUTE
OK
Cancel

4 PACS/Modality Configuration Information

The CSW software includes a DICOM receiver that accepts images from a scanner (MR) or PACS and stores those images on local disk. The software starts when the system is turned on and remains active.

In order to receive images, you will need to inform the PACS manager of the parameters that describe this machine. These parameters include a port number, IP address and DICOM Application Entity title. The port number and DICOM Application Entity title are configured by Washington University. Your system administrator assigns the IP address at your institution.

1. Inform the PACS manager or appropriate person of your system parameters. These are listed below:

   Host Name: _____

   IP address: _____

   Port Number: _____**2301**_____

   DICOM AE Title: _____

2. Ask the manager to send a sample study from each system that will be used during the PKD study. We presume that these studies will be archived somewhere and then sent to the workstation. That is, even though the workstation supports this mode, we do not expect radiology to send studies directly from the scanner itself. (The workstation will operate properly if your department decides to send images directly from the scanner.)
3. Logon to the system, anonymize the images, and send them as test cases to Washington University. The contact person for testing is Steve Moore (moores@mir.wustl.edu).

4.1 Reading Images from CD ROM

Because of network or other issues, some institutions may not be able to send DICOM images over a network to the CSW. Some institutions may have the ability to produce a DICOM Part 10 compatible CD ROM that can be read by software included with the CSW. These software was not designed as part of the GUI and is not an integrated part of the CSW application. This section of the document will describe the several steps needed to send images from a Part 10 CD ROM to the CSW application.

There is a set of one-time steps needed to modify the PATH variable for your account (or for the system) to include the CSW installation directory. You probably want assistance from a system administrator to perform these steps. The workstation shipped from MIR should have been shipped with an account with the PATH variable set as described below. Use that account or modify your account as follows:

1. Select the “Start” menu and then select Settings->Control Panel.
2. From the Control Panel folder, open the System icon.
3. A System Properties window should appear. Select the Advanced tab.
4. From the Advanced table, select the button for Environment variables.

5. You need to add a variable in the area reserved for User Variables (not system variables). In the User Variables area, select the button for New variable. Enter the name PATH for the variable and the following for the value: `%PATH%;C:\Program Files\CSW`
6. Close the system properties window (use the OK button)
7. Open a command prompt window (Start->Programs->Accessories->Command Prompt). In the window, type `dicom_echo <Enter>`. The system should tell you the parameters for the application. If the system tells you that it cannot find the application, then the %PATH% variable is not set properly.

Here are the instructions for sending the images to the workstation.

1. Insert the CDROM into your CD reader. Some CD ROMs have automatic software that starts a viewing application. Exit that application (this will leave the CD ROM mounted).
2. Use the Windows Explorer application on the workstation to open the CD ROM and search for files. If you try to open the CD using the drive designation from "My Computer", you are likely to launch the viewing application on the CD.
3. The CD contains DICOM images in files that are roughly 125 KBytes in length. The CD also contains other files used by the vendor to display the images or serve as an index for the images. Our software will try to open the non-image files and will have a problem. Copy all of the image files from the CD to a temporary folder on your hard drive. If you want, you can copy the entire CD and then go back and delete the non-image files on the local, temp directory.
4. Open a command prompt window. In that window, change directories to the temp directory where you just copied the image files. It could be that you created several sub-directories because the CD was formatted with sub-directories. That is OK; just change to the top-level directory that you created: (eg, `cd \cd-images`).
5. Type this command to make sure the local DICOM receiver is running:

   ```
   dicom_echo localhost 2301
   ```

   It should print a status message that looks like this:

   ```
   Echo context: Context
   Verification Response
     Message ID Responded to:    1
     Verification Status:     0000
   Echo Response
   Message ID Responded To: 1
   Data Set Type:           0101
   Status:                  0000  Status Information:-
        Successful operation
   Class UID:               1.2.840.10008.1.1
   ```

6. Send the images to the local workstation by typing the following command in the command prompt window:

   ```
   send_image -q -a CDROM -Z localhost 2301 .
   ```
   (that is a period)

This command tells the system to send all images in the current directory and below to the CSW server.

7. Assuming the transfers are successful, each image should be sent with the send_image program printing a success message. An example is included below.

```
Store Response
Message ID Resp:1
Data Set Type:  0101
Status:         0000  Status Information:-
      Successful operation
Class UID:      1.2.840.10008.5.1.4.1.1.2
Instance UID:   1.3.12.2.1107.5.1.4.24535.6.0.135608519411846
```

8. If any of the files cannot be tranmitted, *send_image* will stop with an error message. This normally indicates that one of the files was not a proper image file. Find the errant file, delete the file and invoke the *send_image* program again. It does not matter if you send the same images multiple times. The CSW software will discard duplicate copies of images.

5 User Login Instructions

These are the login instructions for users of the CSW. The Washington University group created one user account on your system. Your administrator may have created a separate account for you. Check with the administrator to determine the account name and password.

Account Name _____

Password _____

1. When no one is logged on the computer, you should see a screen as shown in figure 4.1 below. If the screen is dark (blank), press the Shift key or space bar.
2. As indicated in the figure, press the Ctrl, Alt and Delete keys simultaneously. This will bring you to the login screen. Use the login and password for your account.
3. To logout, use the mouse to select the Start menu (lower left corner of the screen). Select the Shutdown option and from there, select logoff (not shutdown or restart).

6 Washington University VPN Instructions

The Washington University Virtual Private Network (VPN) uses a hardware server from Nortel and client software on your PC to encrypt data sent across the Internet. The hardware server is located at Washington University. When the user wants to communicate with the imaging systems at Washington University, the VPN software must be enabled. The imaging functions include:

- Transmitting cases to the cooordinating center

Users should be able to login and log off the Washington University VPN using these instructions.

1. You should already be logged on to the PC using the instructions given in section 5. Your account can be a standard user account and need not be the Administrator account.
2. Activate the Nortel VPN client software. Use the desktop icon provided for the default user account or activate from the Start menu (Start->Programs->Nortel Networks->Extranet Access Client).
3. The Nortel client will present a display as shown in figure 6.1 below. The User Name and Password are fixed by Washington University. Your User Name is _____ and Password is _____. Leave the desination as is (128.252.175.56) and connect to the VPN. Upon success, you should see the window as shown in figure 6.2 below. Select the OK button to dismiss the success window.
4. When the VPN software is active, you will not be able to contact other computers on your local network or the Internet. This means that modality systems (MR) cannot send images to you, nor can you connect to public web servers such as www.rsna.org.
5. When you are finished using the CSW software, you need to disconnect the Virtual Private Network. The Nortel VPN icon will be displayed in the tool tray in the lower right hand corner of your display. Double click that icon to bring the display to your screen. Select the Disconnect button.
6. After the VPN software is disconnected, you may choose to log off the PC or perform other tasks.

7 Forwarding Studies to Washington Universitoy

The Clinical Studies Workstation application presents a graphical user interface (GUI) to the user to allow the user to modify demographic information in images and to forward those images to Washington University. To use this software, follow these instructions.

1. Log on to the computer using a standard user account; you do not need the Administrator account.
2. Activate the CSW application (Start Menu->Programs->CSW) as shown in figure 7.1 below.

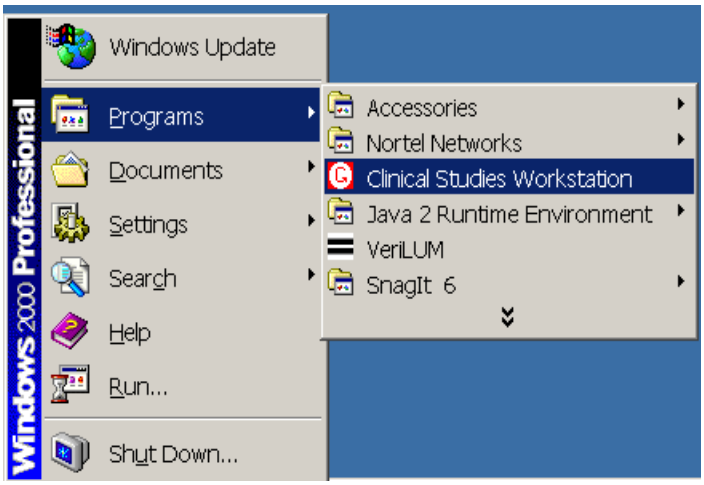


Figure 7.1: Launching CSW Application

3. The CSW application will present you with a list of studies stored on the workstation as shown in figure 7.2 below. The studies include demographics transmitted by the scanner or by the PACS. Select one study for transmission (single click).
4. Enter the Participant ID assigned by WU for the participant in the Patient ID box. Enter the Accession Number assigned by WU in the Accession Number box. You do not need to modify any other fields. The CSW software will automatically erase the Patient Name, Date of Birth and Sex.
5. Press the Commit button. This signals the workstation software to remember your changes in local memory; the images on disk are not changed.
6. Immediately after committing the changes, press the Enqueue button. This will place the study in a queue for transmission to the QACC.
7. In order to see what entries are in the queue to be transferred, select the “Queue” entry from the “Settings” pulldown.
8. The images stay in the queue until completely transmitted to Washington University. You will need to activate the Virtual Private Network software and leave that software active until all images are transferred. To make sure all images have been transferred, select the Study view and then Queue view again.

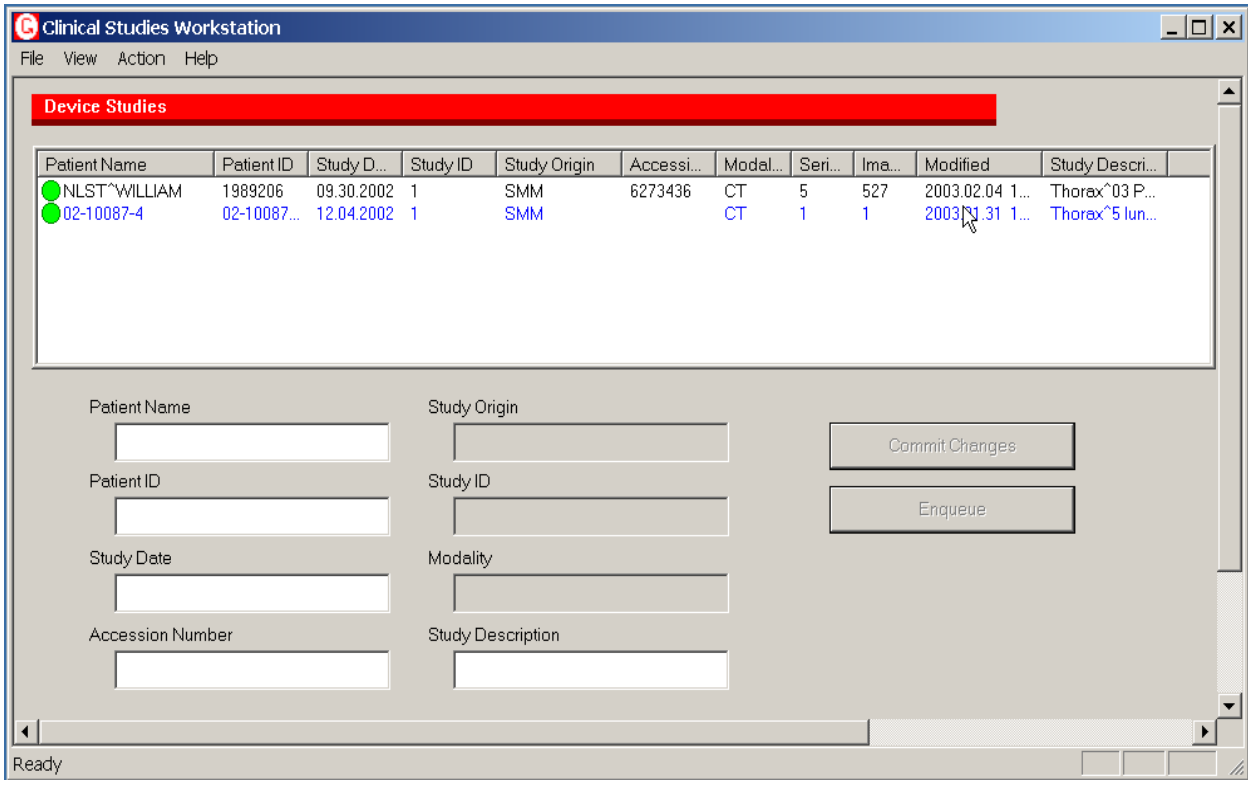


Figure 7.2: Study View of the CSW Application

8 Participant Anonymization Overview

The Clinical Studies Workstation is designed to operate under the control of sites participating in the PKD study. Imaging studies are sent directly from scanners or from a PACS to the workstation. The workstation stores the images with no modification on the local disk system.

The user of the CSW is assumed to be a study coordinator or other staff member at a screening site. Those staff members are assumed to have access to the demographics of participants in the study. The workstation software presents the participant name to the user to help ensure that the proper studies are forwarded to WU.

When the CSW user transmits a study to WU, the workstation software automatically replaces the following DICOM attributes with empty strings:

```
0010 0010 Patient Name
0010 0030 Patient Date of Birth
0010 0040 Patient Sex
```

Before transmitting the images, the user specifies a new patient identifier that is the Participant Identifier and the associate Accession Number. These numbers are required by the coordinating center to identify the proper study for quality assurance.

The CSW software is configured to remove a number of private groups from the DICOM images during the transmission process. This is done because some vendors copy patient demographics into those private groups. Screening sites that identify further attributes to be removed should contact the coordinating center for instructions on updating the CSW configuration.

The CSW system uses a commercial VPN solution to connect the workstation to computer systems at the QACC behind a firewall. This VPN solution uses 128 bit encryption software on the workstation and a firewall system at WU.

The coordinating center will only have the Participant ID and Accession Number to identify the images transmitted by the screening site. The coordinating center will have no mechanism to link these images to the human participant. It is expected that screening sites will have some mechanism to link the Participant ID to the participant.

The steps described above are designed to satisfy IRB or HIPAA requirements for participant anonymization. If a screening site requires further anonymization steps or documentation, please contact the WU data coordinator:

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A: Password Management

Using the CSW and associated services requires a number of different accounts and passwords used by various applications. This appendix describes the accounts and passwords.

A.1: CSW Computer Login

The CSW computer is a Windows 2000 computer system with normal user accounts. The coordinating center ships the CSW computer with one account established for users. Each site is free to add more accounts as they see fit. If any new accounts are added, the user must be a "Power User" to take advantage of software that must modify registry settings.

A.2: Virtual Private Network Software

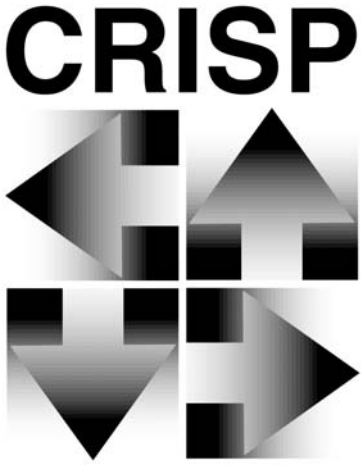
The CSW uses a Virtual Private Network solution from Nortel. A client application on the workstation requires a login and password that are assigned and managed by WU. Each screening center is given one login and one password that should be shared by users at that site. Screening centers are not allowed to modify passwords.

18 CRISP MOP Revision History

1. Section 1.1 Study Background and History - changed reference numbering.
2. Section 1.2 Study Organization - changed reference numbering.
3. Section 1.6 General Description of the Course of ADPKD - changed reference numbering.
4. Section 1.7 Factors related to End-Stage Renal Disease (ESRD) - changed reference numbering.
5. Section 1.8 Treatment of PKD - changed reference numbering.
6. Section 1.9 Specific Aims - changed first specific aim.
7. Section 6.2.3 Glomerular Filtration Rate - added guidelines regarding medications.
8. Section 6.2.3 Glomerular Filtration Rate - added List of Medications that should be avoided by CRISP Study Participants.
9. Section 6.2.4 24-hr Urine - changed toluene to boric acid, modified drug guidelines.
10. Section 6.2.5 Arterial Blood Pressure - added equation to calculate MAP.
11. Section 7.4 MR Scanning Procedure - updated scanning procedure.
12. Section 8.3 Ultrasound Assessment Methods - updated entire section.
13. Section 8.3.1 Component 1: Kidney Volume - revised section, added requirement to label kidney as right or left.
14. Section 8.3.3 Component 3: Transverse Scanning Series for Fractional Cyst Area - last sentence in first paragraph changed.
15. Section 10.4 Specialized Serum Collections Done on Demand for Archive - purple-top tube for serum TGFb needs to be spun for 10 min at 3000 rpm in a REFRIGERATED centrifuge immediately after it is drawn.
16. Section 10.6 Genetic Bloods - completed section on Utilization of CRISP Study Genetic Repository.
17. Section 11 Urine Handling Methods - toluene will not be used as a preservative, 10 grams of boric acid will be used instead.
18. Section 11.3 Subsequent Visits - corrected typo in urine pregnancy test requirement.
19. Section 11.4 Local Urine Labs - corrected typo in urine pregnancy test requirement, removed note to subtract amount of toluene added to urine sample as no toluene should be used.
20. Section 13.6 GFR Sample Collection - added reference to GFR Testing Manual.
21. Section 15.8 Web Site - added section.

22. Section 16.1.2 Follow-up Visits - Added specification on event patient is pregnant at Annual Clinic Visit.
23. Section 16.4.5 Data Processing on PCC Workstation - revised.
24. Section 16.6 Forms Audits - added section.
25. Section 16.10 GFR Procedures - replaced with updated version of GFR Testing Manual.
26. Section 16.11 Bar Codes - removed section.
27. Section 16.12 Incidental Disease - added section.

19 CRISP Study Directory



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20 Forms

CRISP

Identification Form

This form is to be completed at the participant's first clinic visit and kept in confidence at the PCC. Information on this form will NOT be sent to the DCIAC. This form is to be updated with each visit or telephone contact.

1. **Participant ID**: ___ ___ ___ ___ ___ ___

2. **Participant's Name**: _____, _____ _____
   Last First Middle

3. **Address**: _____ _____ _____
   Street P.O. Box Apartment

   _____ _____ _____
   City State/Province Zip

4. **Social Security Number**: ___ ___ ___ - ___ ___ - ___ ___ ___ ___

5. **Telephone**: Home: (_____) _____ - _____ Work: (_____) _____ - _____

   Fax: (_____) _____ - _____ Pager: (_____) _____ - _____

6. **Email**: _____

7a. Primary Care or Referring Physician information:

Name: _____

Phone: (_____) _____ - _____ Fax: (_____) _____ - _____

Address: _____ _____ _____
Street P.O. Box Suite

_____ _____ _____
City State/Province Zip

7b. Nephrologist or Other Physician caring for participant:

Name: _____

Phone: (_____) _____ - _____ Fax: (_____) _____ - _____

Address: _____ _____ _____
Street P.O. Box Suite

_____ _____ _____
City State/Province Zip

8. Contact Persons (NOTE: For participants under 18 years of age, you must list a parent or guardian):

A) Name: _____ _____
Last Name First Name

Phone: (_____) _____ - _____ Relationship to Participant: _____

Address: _____ _____ _____
Street P.O. Box Apartment

_____ _____ _____
City State/Province Zip

B) Name: _____ _____
Last Name First Name

Phone: (_____) _____ - _____ Relationship to Participant: _____

Address: _____ _____ _____
Street P.O. Box Apartment

_____ _____ _____
City State/Province Zip

9. Contact Notes for Participant: _____

_____

_____

_____

CRISP staff member completing this form _____ **Date form completed**: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

CRISP

Inclusion/Exclusion Criteria Form

This form is to be completed at the participant's first clinic visit and kept in confidence at the PCC. Information on this form will NOT be sent to the DCIAC.

1. **Participant's Name**: _____, _____ _____
   Last First Middle

2. **Participant's Gender** (circle)**:** Male Female

3. **Participant's Age: _____ years** **Is the age < 15 years** (circle)**?** **Yes No N/A**

   Is the age > 45 years (circle)**?** **Yes No N/A**

4. **Participant's Weight** (circle)**: _____ kg lbs.**

   Is weight > 158.76 kg (350 lbs) (circle)**?** **Yes No N/A**

5. **Has the participant ever had a partial or total nephrectomy** (circle)**?** **Yes No N/A**

6. **Does the participant have a congenital absence of a kidney** (circle)**?** **Yes No N/A**
   (i. e. Was the participant missing a kidney at birth?)

7. **Has the participant had a previous renal cyst reduction performed percutaneously, laparoscopically, or surgically** (circle)**?** **Yes No N/A**

8. **Has there been any documented presence of renal vascular disease** (circle)**?** **Yes No N/A**

9. **Does the participant have indwelling ureteric stents** (circle)**?** **Yes No N/A**

10. **Has the participant had a renal parenchymal infection within the last six months** (circle)**?** **Yes No N/A**

11. **Has the participant been hospitalized within the last 6 months for an acute illness (*not including elective admissions*)** (circle)**?** **Yes No N/A**

12. **Has the participant had a myocardial infarction or cerebral vascular accident within the last six months (*This includes transient ischemic attack, cerebral infarction, subarachnoid hemorrhage, or intracranial aneurysm rupture*)** (circle)**?** **Yes No N/A**

13. **Does the participant currently have unstable angina** (circle)**?** **Yes No N/A**

14. **Has the participant been diagnosed with non-insulin dependent or insulin dependent diabetes mellitus** (circle)**?** **Yes No N/A**

15. **Does the participant show the presence of systemic illness with renal involvement (systemic lupus erythematosis)** (circle)**?** **Yes No N/A**

16. **Does the participant have a history of or is malignancy currently present** (circle)**?** **Yes No N/A**

17. If the participant is female, is she currently pregnant or lactating (circle)**?** **Yes No N/A**

Has she delivered a child within the last 6 months (circle)**?** **Yes No N/A**

18. Does the participant have a history of significant diseases such as:

Pulmonary disease (circle)**?** **Yes No N/A**

Cardiac disease (circle)**?** **Yes No N/A**

Liver disease (not including polycystic liver disease) (circle)**?** **Yes No N/A**

19. Date of most recent Serum creatinine concentration: _____ / _____ / _____
Month Day Year

Most recent Serum creatinine concentration: _____ mg/dL

If the participant is female, is the concentration > 1.4 mg/dL (circle)**?** **Yes No N/A**

If the participant is male, is the concentration > 1.6 mg/dL (circle)**?** **Yes No N/A**

20. Is the estimate of GFR less than 70 ml/min either by the Cockcroft-Gault formula or by 24 hour creatinine clearance (circle)**?** **Yes No N/A**

Estimate of GFR:_____ ml/min via (circle)**: Cockcroft-Gault 24 hr creatinine clearance**

21. Date of most recent urinary protein excretion in a 24 hour period: _____ / _____ / _____
Month Day Year

Urinary Protein Excretion: _____ mg **Is this > 2000 mg** (circle)**?** **Yes No N/A**

22. Does the participant have significant anemia (determined by most recent hemoglobin reading):

Date of most recent Hemoglobin reading: _____ / _____ / _____
Month Day Year

Most recent hemoglobin: _____ gm/dL **Is hemoglobin < 10 gm/dL** (circle)**?** **Yes No N/A**

23. Does the participant have significant thrombocytopenia (determined by most recent platelet count):

Date of most recent platelet count: _____ / _____ / _____
Month Day Year

Most recent platelet count: _____,_____ platelets/µL
Is platelet count < 70,000 platelets/µL (circle)**?** **Yes No N/A**

24. Does the participant have significant neutropenia (determined by most recent absolute neutrophil count, ANC):

Date of most recent ANC: _____ / _____ / _____
Month Day Year

Most recent ANC: _____ neutrophil/µL **Is the ANC < 500 neutrophil/µL** (circle)**?** **Yes No N/A**

25. Does the participant have a current psychiatric or addiction non-compliance disorder that in the discretion of the principal investigator indicates that the subject will not successfully complete the study (circle**)?** **Yes No N/A**

26. Is the participant unable to provide written informed consent (circle**)?** **Yes No N/A**

27. Does the participant have a known claustrophobia to MRI scanners (circle**)?** **Yes No N/A**

If **YES** is circled in any of the above questions then the candidate is ***ineligible*** for the CRISP study.
DO NOT Continue.

28. Does the participant have any problems that may interfere with, or be hazardous during, an MRI (circle**)? (See attached sheet for potential problems)** **Yes No N/A**

Specify Problem:_____

If YES is circled, then please review the participant's eligibility in the CRISP study with your PI and/or Radiologist.

_____

_____

If no is circled for every question above (the candidate *is* eligible for this study), then please answer the following questions to determine if the candidate is at high risk for progression to ESRD: (The goal is to recruit twice as many high risk as low risk individuals.)

29. Was hypertension diagnosed prior to age 35 (circle**)?** **Yes No N/A**

30. If participant is male, did he have gross hematuria with ADPKS prior to age 30 years (circle**)?** **Yes No N/A**

31. Did the participant at any time (including Baseline Visit) have > 300 mg urinary protein excretion in 24 hours in an adequate urine collection, where an adequate collection is defined as > 15 mg/kg/day and < 25 mg/kg/day creatinine excretion (circle**)?** **Yes No N/A**

32. Was the participant diagnosed with ADPKD in-utero or in the first year of life (circle**)?** **Yes No N/A**

If the answer to any **one** of these last four questions is **YES**, then the candidate is to be considered at **high risk**.

CRISP staff member completing this form _____ **Date form completed**: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Participant Name: _____ Date: _____ **CRISP -FORM #1a**

MRI Consent Attachment (see question 28)

This is an excerpt from a standard Radiology MRI consent form listing items that may interfere with, or may be dangerous to the participant when performing an MRI. If Yes is circled for any one of these, please indicate potential problem on question 28 and review eligibility with PI or Radiologist.

Cardiac Pacemaker or Pacer Wires	**Yes**	**No**
Aneurysm or Vascular Clip(s)	**Yes**	**No**
Gianturco Coil (embolus coil)	**Yes**	**No**
Heart Valve Prosthesis	**Yes**	**No**
Greenfield Vena Cava Filter	**Yes**	**No**
Orbital or Eye Prosthesis	**Yes**	**No**
Cochlear or Middle Ear Implant(s)	**Yes**	**No**
Neurostimulator (Tens Unit)	**Yes**	**No**
Biostimulator or Bone Growth Stimulator	**Yes**	**No**
Implanted Insulin or Drug Pump	**Yes**	**No**
Intraventricular Shunt	**Yes**	**No**
Wire Mesh or Sutures	**Yes**	**No**
Diaphragm or IUD	**Yes**	**No**
Penile Prosthesis	**Yes**	**No**
Artificial Limb or Joint	**Yes**	**No**
Any Orthopedic Item (pins, screws, nails, clips, plates, wire, or rods)	**Yes**	**No**
Shrapnel or Bullet	**Yes**	**No**
Tattooed Eyeliner	**Yes**	**No**
Dentures or Partials or any Removable Items	**Yes**	**No**
Any Dental Item Held in Place by Magnet	**Yes**	**No**
Hearing Aid	**Yes**	**No**
Any Other Implanted Item	**Yes**	**No**
Any Injury to the Eye Involving Metal	**Yes**	**No**
Surgical Procedure or Operation (resulting in the placement of an item that may interfere with an MRI)	**Yes**	**No**

CRISP

Registration Form

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's first clinic visit during baseline.

1. **Date of Baseline Visit**: _____ / _____ / _____
   Month Day Year

2. **Date the consent form was signed:** _____ / _____ / _____
   Month Day Year

3. **Gender** (circle): Male Female

4. **Date of birth**: _____ / _____ / _____
   Month Day Year

5. **Race/Population** (circle one):

   Caucasian African American Asian Hispanic Native American Pacific Islander Unknown

   Other (**Please specify**): _____

6. **Treating physician affiliation** (circle): CRISP physician Other nephrologist Other Physician

7. **Is the participant currently enrolled in another study in addition to CRISP** (circle)**?** Yes No

   If Yes, specify: _____

8. **Place of Birth**: _____ _____ _____
   City State/Province Country

9. **Education** (in total number of years) _____years

10. **Has the participant been enrolled at high risk or low risk for progression to ESRD?** See Enrollment Log Form 23 (circle)**:**

    High risk Low risk

11. **Diagnosis of PKD (please obtain information from Medical Records):**

    11a. Date when first diagnosed with PKD: _____ / _____ / _____
    Month Day Year

Clinical Center: _____

Participant ID: _____

Visit Number: _____

11. Diagnosis of PKD (continued)

11b. How was the diagnosis made (circle one**):** Ultrasound CT scan MRI IVP X-Ray Angiogram

Unknown Other, Specify: _____

11c. Why diagnosis was made (circle one**):**

Screening asymptomatic individual Symptomatic presentation/physical findings Unknown

If this is a symptomatic presentation, then specify reason: _____

_____

12. Is a family member a participant in this study? (circle one**):** yes no

13. Final Enrollment Status:

13a. Please indicate the final status of the potential participant (circle one**):**

Eligible and enrolled Eligible but failed to enroll (see 13b) Ineligible and withdrawn (see 13c)

13b. If failed to enroll is circled, indicate the primary reason participant failed to enroll (circle one**):**

unwilling to miss school/work unwilling to travel to clinics for visits unwilling to make follow-up commitment

Other (please specify): _____

13c. If ineligible is circled, check all reasons for which participant is ineligible:

Age less than 15 years or greater than 45 years	( )
Weight > 350 lbs. (158.6 kg)	( )
Total or partial nephrectomy	( )
Congenital absence of a kidney	( )
Previous renal cyst reduction	( )
Documented presence of renal vascular disease	( )
Indwelling ureteric stents	( )
Renal parenchymal infection within the past six months	( )
Hospitalized within the past 6 months for an acute illness	( )
Myocardial infarction or cerebral vascular accident within the last 6 months	( )
Unstable angina	( )

Clinical Center: _____

Participant ID: _____

Visit Number: _____

13c. (continued)

Diagnosed with non-insulin dependent or insulin dependent diabetes mellitus	( )
Presence of systemic illness with renal involvement	( )
History of or currently present malignancy	( )
Pregnant or lactating	( )
Delivered a child with the last 6 months	( )
History of significant diseases such as: pulmonary disease, cardiac disease or liver disease	( )
Serum creatinine is > 1.4 mg/dL for female or >1.6 mg/dL for male	( )
GFR less than 70 ml/min	( )
Urinary protein excretion >2000 mg	( )
Significant anemia	( )
Significant thrombocytopenia	( )
Significant neutropenia	( )
Unable to give written informed consent	( )
Contraindications to MR scan	( )

Other (Please specify): _____

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

Initial Screening Form

CRISP -FORM # 3

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's screening visit.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Specify Laboratory processing samples**: _____

3. **Participant weight:** (please circle the appropriate units used): _____ kg pounds

---

BLOOD WORK:

4. **Serum creatinine concentration**: _____ mg/dL **Date creatinine collected**: _____ / _____ / _____
   Month Day Year

5. **Date remaining blood samples were collected**: _____ / _____ / _____
   Month Day Year

6. **Hemoglobin**: _____ g/dL **Hematocrit**: _____ %

7. **White blood count (**circle units used**)**: _____ cell/µL K/µL

   ANC (circle units used**)**: _____ neutrophils/µL K/µL

8. **Platelet count (**circle units used**)**: _____ platelets/µL K/µL

9. **Serum (**circle units used**)**: mEq/L mmol/L

   Na _____ K _____ Cl _____ HCO3 _____

10. **Serum (in mg/dL)**: Ca _____ Uric Acid _____ BUN _____

    glucose _____ PO4 _____ Total bilirubin _____

11. **Serum (in U/L)**: SGOT (AST) _____ SGPT (ALT) _____ Alk Phos _____

Clinical Center: _____

Participant ID: _____

Visit Number: _____

URINE SAMPLES:

12. **Start time of urine collection: _____:_____** am pm **End time of urine collection: _____:_____** am pm

    Collection Date for start of 24 hour Urine Specimen: _____ / _____ / _____
    Month Day Year

13. **24 hour Urine Volume**: _____ mL

14. **Urine Protein Excretion**: _____ mg/24 h **or** **Urine Protein Concentration**: _____ mg/dL

15. **Urine Creatinine Excretion**: _____ mg/24 h **or** **Urine Creatinine Concentration: _____** mg/dL

16. **Eligibility Determination (Please enter NA if not applicable):**

    Collection Date: _____ / _____ / _____
    Month Day Year

    Urine Protein by Dipstick: _____ mg/dL

    Urine Protein/Osmolality Ratio: _____

    Predicted 24 hour Urine Protein: _____ mg/24 h

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

Baseline Visit Form

CRISP -FORM # 4

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot
U-Undetectable

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's baseline visit.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Specify Laboratory processing samples**: _____

3. **Participant Weight**: (please circle the appropriate units used) _____ kg pounds

---

BLOOD WORK:

4. **Serum creatinine concentration**: _____ mg/dL **Date creatinine collected**: _____ / _____ / _____
   Month Day Year

5. **Date remaining Blood samples were collected**: _____ / _____ / _____
   Month Day Year

6a. **Hemoglobin**: _____ g/dL **Hematocrit**: _____ %

6b. **Is sickle cell trait present (**circle one**)?** Yes No N/A **If yes,** indicate the percentages**:**

Hemoglobin A _____**%**
Hemoglobin S _____**%**
Hemoglobin C _____**%**
Hemoglobin F _____**%**
Hemoglobin A2 _____**%**
Misc. _____**%**

Has participant been diagnosed with sickle cell disease (circle one**)?** Yes No Unknown

Is participant symptomatic (circle one**)?** Yes No Unknown

7. **White blood count (**circle units used**)**: _____ cell/µL K/µL

8. **Platelet count (**circle units used**)**: _____ platelets/µL K/µL

9. **Serum (**circle units used**)**: mEq/L mmol/L

   Na _____ K _____ Cl _____ HCO3 _____

10. **Serum (in mg/dL)**: Uric Acid _____ BUN _____ glucose _____ Ca _____

    Mg _____ **mEq/L** ___ (check if used instead of mg/dL) PO4 _____ Total bilirubin _____

11. **Serum (in U/L)**: SGOT (AST) _____ SGPT (ALT) _____ Alk Phos _____

12. Lipid Panel (in mg/dL): HDL _____ LDL _____ total cholesterol _____ triglyceride _____

13. Serum sample saved for future studies: Collection Date: _____ / _____ / _____
Month Day Year

Number red top serum/plasma samples stored: _____ **Number green top serum/plasma samples stored**: _____

Number purple top serum/plasma samples stored: _____

URINE SAMPLES:

14. Start time of urine collection: _____:_____ am pm **End time of urine collection: _____:_____** am pm

Collection Date for start of 24 hour Urine Specimen: _____ / _____ / _____
Month Day Year

15. 24 hour Urine Volume: _____ mL

16. Creatinine Excretion: _____mg/24h **or** **Creatinine Concentration**: _____mg/dL

17. Albumin (Microalbumin) (circle units used if entering Concentration**)**

Albumin Excretion: _____ mg/24 h **or** **Albumin Concentration**: _____ mg/L mg/mL mcg/mL

18. Protein Excretion: _____ mg/24 h **or** **Protein Concentration**: _____ mg/dL

19. Urine Electrolytes (circle units used**)**:

Citrate Excretion _____	mg/24h	mmol/24h	**or**	Citrate Concentration _____	mg/dL	mmol/L
Oxalate Excretion _____	mg/24h	mmol/24h	**or**	Oxalate Concentration _____	mg/dL	mmol/L
Sodium Excretion _____	mEq/24h	mmol/24h	**or**	Sodium Concentration _____	mg/dL	mEq/L mmol/L
Potassium Excretion _____	mEq/24h	mmol/24h	**or**	Potassium Concentration _____	mEq/L	mmol/L
Calcium Excretion _____	mg/24h		**or**	Calcium Concentration _____	mg/dL	
Chloride Excretion _____	mEq/24h	mmol/24h	**or**	Chloride Concentration _____	mEq/L	mmol/L
Phosphorus Excretion _____	mg/24h	g/24h	**or**	Phosphorus Concentration _____	mg/dL	
Magnesium Excretion _____	mg/24h	mEq/24h	**or**	Magnesium Concentration _____	mg/dL	mEq/L

19. Urine Electrolytes continued (circle units used**)**:

Urea Excretion _____ mg/24h **or** Urea Concentration _____ mg/dL

Uric Acid Excretion _____ mg/24h g/24h **or** Uric Acid Concentration _____ mg/dL

20. Urine or Serum Pregnancy test (circle): positive negative test not performed

If test not performed, then specify reason: _____

21. Urine sample saved for future studies: Collection Date: _____ / _____ / _____
Month Day Year

Number of 5cc aliquots of urine saved: _____

22. Current Risk Status for progression to ESRD: (circle one) High risk Low risk

CRISP Member Completing this form _____ Date form completed_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

OTC/Prescribed/Other Drugs

CRISP -FORM # 5

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's first clinic visit during baseline physical exam.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Smoking and Tobacco:**

   2a. Do they currently smoke cigarettes (circle): no yes **2b. If yes, Cigarettes** (packs per year) _____

   2c. If no, Year Quit Smoking (n/a for never smoked): _____ / _____
   Month Year

   If they use any of the following products, please indicate below either the number of years used or the average number per year:

   2d. Pipe (number of years)_____ **2e. Cigars** (number per year) _____ **2f. Chewing tobacco** (number of years) _____

3. **Caffeinated Coffee/Tea/Other caffeinated beverage/Alcohol Intake:**

   3a. Average number of cups of caffeinated coffee/tea daily over the last month: _____

   Number of years (caffeinated coffee/tea use): _____

   3b. Average number of glasses of other caffeinated beverages daily over the last month: _____

   3c. Average number of alcoholic drinks daily over the last month:_____ **Number of years** (alcohol consumption): _____
   (drink = 1 bottle of beer, 4 oz. of wine, 1 shot of liquor)

   3d. N/A _____

4. **Analgesic Use History:** (**Complete** if at **least 100** analgesic tablets in **entire** life)
   Record the average number per month over the last year.

   4a. Acetaminophen tablets: _____ Avg. number / month **4b. Aspirin tablets**: _____ Avg. number / month

   4c. Combination analgesics: _____ Avg. number / month **4d. NSAID's**: _____ Avg. number / month

   4e. N/A (check if none of the above are applicable**)** _____

5. **Drug Use (**circle all that were in use in the last year**):**

   None Marijuana Cocaine Heroin Angel Dust Other
   If Other, Specify: _____

6. **Natural Product Use History:** (If yes is circled, please specify number of years of usage and products)

   6a. Protein supplement: yes no Number of years used: _____ Specify:_____

   6b. Other: yes no Number of years used: _____ Specify:_____

Clinical Center: _____
Participant ID: _____
Visit Number: _____

7. Current OTC and Prescribed Medication Use:

Does participant use over-the-counter or prescribed medications? (circle one): no yes

IF yes, then list the name of medications taken (not dosage):

#	Medication
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	

CRISP Member Completing this Form:_____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature):_____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person:_____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____

Participant ID: _____

Visit Number: _____

CRISP

Reproductive History Form

CRISP -FORM # 6

Missing Codes:
A-Patient refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the baseline visit for every female patient.

1. **Date of Visit**: _____ / _____ / _____ (Month / Day / Year)

2. **Please circle one response:** Male Female

3. **Have you had the following performed? Please circle the appropriate response:**

Hysterectomy: Yes No **If yes, then record the date performed**: _____ / _____ / _____ (Month / Day / Year)

Oophorectomy: Yes No **If yes, then record the date performed**: _____ / _____ / _____ (Month / Day / Year)

Tubal Ligation: Yes No **If yes, then record the date performed**: _____ / _____ / _____ (Month / Day / Year)

Menopause - Please circle one response:

4a. **Pre-Menopause:** Yes No **If yes, then record the age of onset of Menopause:** _____
Peri-Menopause: Yes No
Post-Menopause: Yes No

4b. **Use of hormone replacement therapy:** Yes No

If yes, please record name of hormone replacement: _____

Obstetrical History

5a. **Number of Pregnancies:** _____ 5b. **Number of Deliveries:** _____

6. **Is there a history of toxemia of pregnancy?** Yes No

7. **Date of first delivery:** _____ / _____ / _____ (Month / Day / Year) **Date of last delivery:** _____ / _____ / _____ (Month / Day / Year)

8. **Age of Menarche** _____

CRISP Member Completing this form _____ Date form completed: _____ / _____ / _____ (Month / Day / Year)

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____ (Month / Day / Year)

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____ (Month / Day / Year)

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

MR Session Information

CRISP -FORM # 7

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed during scan at the participant's clinic visits.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Start Time**: _____ :_____ (24 hour)

   End Time: _____ :_____ (24 hour)

3. **Machine name**: _____

   Technologist name: _____

   Radiologist name: _____

4. **Series information (see table on page 2)**

5. **Contrast Injection**: Duration of contrast injection: _____seconds Volume: _____mL

6. **Adverse events (**enter "None" for Event Description if no adverse events occurred**)**:

Series #	Event Description
_____	_____
_____	_____
_____	_____

7. **Omitted Series (**enter "None" for Reason if no omitted series occurred**)**:

Series #	Reason
_____	_____
_____	_____
_____	_____
_____	_____

CRISP Member Completing this form: _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Radiologist (signature required): _____

Date Radiologist signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

4. Series information: **Accession number**: _____

* For regular 3mm or heavy T2, if the kidney is too large to cover in a single breath-hold, use multiple breath-holds but as few breath-holds as possible. Have the 1st scan cover the posterior aspect of the kidney and then choose the 'shift-mean (starting point in GE)' of the 2nd scan as follows: For example, **the 1st shift-mean** = -60 mm. **Number of slices in the 1st set** = 23. (23-1)x3=66mm. **The 2nd shift mean** = -60 + 66 = 6 mm.

Series ID #	**Description/thickness or time** (circle one procedure and one thickness/time)							**Comments**	**#Slice**	**Scan Duration** (in seconds)	**FOV**
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				
	Pre T1	Reg-9mm	Reg-3mm*	T2 FatSat Reg-adj	Reg-adj-liver	Heavy-adj*	Post T1 120 180				

CRISP

US Session Information

CRISP -FORM # 8

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Please Use Missing Codes to indicate reason for absent information.

This form is to be completed during scan at the participant's clinic visit.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **US manufacturer**: _____ **Sonographer name**: _____ **Radiologist name**: _____

3. **Clinical Information (**circle am or pm**):**

   Time last hydration: _____:_____ (24 hour) Time last urination: _____:_____ (24 hour)

   Time study starts: _____:_____ (24 hour) Time study ends: _____:_____ (24 hour)

   Fasting (circle one): Yes No

4. **Scan Information: Fill out pages 2 (right kidney) and 3 (left kidney)**

5. **Comments:**

   _____

   _____

   _____

6. **Total Number of images (both kidneys) sent to DCIAC:_____**

CRISP Member completing this form: _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Radiologist (signature required): _____

Date Radiologist signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

4. Scan information: Accession number: _____

Right Kidney **Frequency of transducer**: _____MHz

Component #1: Right Kidney Volume **Measurements in cm**

Image #	Scan	Scanning Plane	Participant position	L/CC	L/AP	T/AP	T/ML
	Longitudinal	sagital coronal sag/cor	supine decubitus prone				
	Long #2*	sagital coronal sag/cor	supine decubitus prone				
	Transverse	Transverse	supine decubitus prone				
	Trans #2*	Transverse	supine decubitus prone				

*** if needed**

Comments:

Component #2: Individual Cysts in Right Kidney **If there are cysts, is the number ≤ 5 (**circle**)?** Yes No

If Yes, then please complete the table: **Measurements in cm**

Image #	Scan Cyst #	Location			L/CC	L/AP	T/AP	T/ML
	1	inferior mid superior	anterior mid posterior	lateral mid medial				
	2	inferior mid superior	anterior mid posterior	lateral mid medial				
	3	inferior mid superior	anterior mid posterior	lateral mid medial				
	4	inferior mid superior	anterior mid posterior	lateral mid medial				
	5	inferior mid superior	anterior mid posterior	lateral mid medial				

Comments:

Component #3: Transverse series – right kidney (Outline the kidney and measure its area at each frame - record on image**)**

Image #	Scan	**Scanning plane** (select one)	**Participant position**	AE**	Comments***
	1	transverse oblique intercostal	supine decubitus prone		
	2	transverse oblique intercostal	supine decubitus prone		
	3	transverse oblique intercostal	supine decubitus prone		
	4	transverse oblique intercostal	supine decubitus prone		
	5	transverse oblique intercostal	supine decubitus prone		
	6	transverse oblique intercostal	supine decubitus prone		
	7	transverse oblique intercostal	supine decubitus prone		
	8	transverse oblique intercostal	supine decubitus prone		
	9	transverse oblique intercostal	supine decubitus prone		
	10	transverse oblique intercostal	supine decubitus prone		
	11	transverse oblique intercostal	supine decubitus prone		
	12	transverse oblique intercostal	supine decubitus prone		

****Area Excluded: Enter Yes or No.** *****Comments: List all area measurements separated by commas.**

All images are transverse and cover the right kidney adequately for renal volume calculation?: Yes No
(i.e. yes = scanning planes are more or less consistently transverse)

4. Scan information: Accession number: _____

Left Kidney **Frequency of transducer**: _____MHz

Component #1: Left Kidney Volume **Measurements in cm**

Image #	Scan	Scanning Plane	Participant position	L/CC	L/AP	T/AP	T/ML
	Longitudinal	sagital coronal sag/cor	supine decubitus prone				
	Long #2*	sagital coronal sag/cor	supine decubitus prone				
	Transverse	Transverse	supine decubitus prone				
	Trans #2*	Transverse	supine decubitus prone				

***If needed**

Comments:

Component #2: Individual Cysts in Left Kidney **If there are cysts, is the number ≤ 5 (**circle**)?** Yes No

If Yes, then please complete the table: **Measurements in cm**

Image #	Scan Cyst #	Location			L/CC	L/AP	T/AP	T/ML
	1	inferior mid superior	anterior mid posterior	lateral mid medial				
	2	inferior mid superior	anterior mid posterior	lateral mid medial				
	3	inferior mid superior	anterior mid posterior	lateral mid medial				
	4	inferior mid superior	anterior mid posterior	lateral mid medial				
	5	inferior mid superior	anterior mid posterior	lateral mid medial				

Comments:

Component #3: Transverse series – left kidney (Outline the kidney and measure its area at each frame - record on image**)**

Image #	Scan	Scanning plane (select one)	Participant position	AE**	Comments***
	1	transverse oblique intercostal	supine decubitus prone		
	2	transverse oblique intercostal	supine decubitus prone		
	3	transverse oblique intercostal	supine decubitus prone		
	4	transverse oblique intercostal	supine decubitus prone		
	5	transverse oblique intercostal	supine decubitus prone		
	6	transverse oblique intercostal	supine decubitus prone		
	7	transverse oblique intercostal	supine decubitus prone		
	8	transverse oblique intercostal	supine decubitus prone		
	9	transverse oblique intercostal	supine decubitus prone		
	10	transverse oblique intercostal	supine decubitus prone		
	11	transverse oblique intercostal	supine decubitus prone		
	12	transverse oblique intercostal	supine decubitus prone		

****Area Excluded: Enter Yes or No.** *****Comments: list all area measurements separated by commas.**

All images are transverse and cover the left kidney adequately for renal volume calculation?: Yes No
(i.e. yes = scanning planes are more or less consistently transverse)

CRISP

GFR Collection Form

CRISP -FORM # 9

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed upon sending the GFR Testing materials to Mayo. Can be partially completed from the Patient Requisition Form provided by the Mayo Lab.

1. **Date of Visit (when sample was collected)**: _____ / _____ / _____
   Month Day Year

2. **Please circle appropriate units:**

   Weight: _____ kg pounds **Height**: _____ cm inches

3. **Initial Urine Collection Time (Uo)**: _____ : _____ (24 hour)

4. **Iothalamate Injection Time**: _____ : _____ (24 hour)

5. **Equilibrium Urine Collection Time (Ue)**: _____ : _____ (24 hour)

   Average Residual volume_____(<20ml or 10% of voided volume, no greater than 50 ml)

6. **Plasma Collection Time (P1)**: _____ : _____ (24 hour)

7. **GFR Testing Urine Collection Time (U1)**: _____ : _____ (24 hour)

   Average Residual volume_____(<20ml or 10% of voided volume, no greater than 50ml)

8. **Plasma Collection Time (P2)**: _____ : _____ (24 hour)

9. **U1 Collection Volume**: _____ mls

10. **Date Sample sent to Mayo lab**: _____ / _____ / _____
    Month Day Year

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

GFR Reporting Form

CRISP -FORM # 10

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed upon receipt of the GFR Mayo lab report.

1. **Date of Visit (when sample was collected)**: _____ / _____ / _____
   Month Day Year

2. **Date Sample was received at Mayo lab**: _____ / _____ / _____
   Month Day Year

Test requested: Short Renal Clearance

3. **Uncorrected Iothalamate Clearance**: _____ ml/min

4. **Corrected Iothalamate Clearance**: _____ ml/min/SA (1.73 m^2)

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Physical Findings Form

CRISP -FORM #11

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's visits for baseline and annual physical exams.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Please circle the correct units of measurement used (Use Height from Form 9):**

   Weight: _____ kg pounds **Height**: _____ cm inches

3. **Cardiac rhythm**: Regular _____ Irregular _____ Pulse Rate: _____

4. **Cardiac murmur** (circle one) yes no

5. **Abdominal Organ Evaluation** (circle one): **Palpable right kidney:** yes no **Palpable left kidney:** yes no

   Liver span: normal abnormal

6. **Hernia** (circle all that apply): umbilical ventral none

   left inguinal right inguinal

7. **Edema** (circle one): Yes No

8. **Other Findings**: _____

_____

_____

CRISP Member completing this form:_____ Date form completed_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Symptoms Form

CRISP -FORM # 12

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's baseline visit for physical exam.

1. Date of Visit: _____ / _____ / _____
Month Day Year

2. Symptoms: Please check yes or no for each symptom listed

Symptom	No	Yes	Date of Diagnosis _____ / _____ / _____ Month Day Year	Number of episodes
Hypertension			/ /	
			Date of First Diagnosis	
Gross Hematuria			/ /	
Ruptured/symptomatic ICA			/ /	
Nephrolithiasis			/ /	
Lower UTI			/ /	
Cyst or kidney infection			/ /	

3. History of Renal Pain: (In each category circle ONE option only**)**

3a) Frequency in the last year: never rarely sometimes often usually always

3b) Location: no pain right kidney left kidney both kidneys

3c) Severity: (Indicate on a scale from 0 to 10, where 0 = no pain and 10 = pain as bad as you can imagine)

0 1 2 3 4 5 6 7 8 9 10

CRISP Member completing this form: _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

ID of Data Entry Person: _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

Follow-Up Study and Events Form

CRISP -FORM # 13

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed for participant's 3-month follow-up, additional physician, or hospital visits.

1. **Date of Contact**: _____ / _____ / _____
   Month Day Year

2a. **Type of Event** (circle one)**:** scheduled follow-up visit SAE adverse events other events

2b. **Mode of Contact** (circle one)**:** office telephone fax email unknown

3. **Has the participant had any illnesses since last study contact (**circle one**)**: yes no

   If yes, please specify: _____

   _____

   _____

4. **Has the participant visited their primary care or any other physician since last study contact (**circle one**)**: yes no

   If the response is yes, then record 4a-c,g. Use 4d-f for additional visit (If 4e is identical to 4b, then enter SAME for Name in 4e)**:**

   4a. **Date of physician visit:** _____ / _____ / _____ **Check if there are multiple visits of this type:** ___
   Month Day Year

   4b. **Name and address of physician treating participant:** Name: _____

   Address:_____

   4c. **Specify reason for visit:** _____

   4d. **Date of additional physician visit:** _____ / _____ / _____ **Check if there are multiple visits of this type:** ___
   Month Day Year

   4e. **Name and address of physician treating participant:** Name: _____

   Address:_____

   4f. **Specify reason for visit:** _____

   4g. **Was there any renal surgery performed?** yes no

   If yes, was the intent cyst reduction: yes no

   For any renal surgery provide a date and short description:

   Date of intervention: _____ / _____ / _____ **Description:** _____
   Month Day Year

5. **Has the participant been hospitalized since the last study contact (**circle one**)**: yes no

   If the response is yes, then record the following 5(a-f)**:**

   5a. **Date admitted to hospital:** _____ / _____ / _____
   Month Day Year

5b. Date discharged from hospital: _____ / _____ / _____
Month Day Year

5c. Name and address of hospital: Name:_____

Address: _____

5d. Name and address of physician treating participant: Name:_____

Address:_____

5e. What was the diagnosis? _____

5f. If this hospitalization was unplanned, has it been reported to the local IRB? Yes No NA
(NA means this is **not** an SAE**)**

6. Prescribed medications changes:

6a. Have prescribed drugs been added (circle one**)**: yes no

If yes, then please record:

#	Prescribed Medications **added**	Date (month, day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

6b. Have prescribed drugs been stopped/discontinued (circle one**)**: yes no

If yes, then please record:

#	Prescribed Medications **discontinued**	Date (month, day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

7. Over-the-counter medications changes:

7a. Have OTC drugs been added (circle one**)**: yes no

If yes, then please record:

#	OTC Medications **added**	Date (month,day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

7b. Have OTC drugs been stopped/discontinued (circle one**)**: yes no

If yes, then please record:

#	OTC Medications **discontinued**	Date (month day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

8. Comments: _____

_____

_____

CRISP Member completing this form_____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Blood Pressure Form

CRISP -FORM # 14

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed in conjunction with the Physical Findings Form.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Blood pressure readings** (Please take BP readings as indicated. Each reading must be 3 minutes apart):

2a. Right Arm BP: **Sitting**

	mmHg:	MAP:	Pulse Rate BPM:	Time (24 hour):
1.	/			:
2.	/			:
3.	/			:

TOTAL _____ MAP

2b. Left Arm BP: Sitting

	MmHg:	MAP:	Pulse Rate BPM:	Time (24 hour):
1.	/			:
2.	/			:
3.	/			:

TOTAL _____ MAP

2c. Dominant Arm* BP Standing (circle one): **right** **left**

	mmHg:	MAP:	Pulse Rate BPM:	Time (24 hour):
1.	/			:
2.	/			:
3.	/			:

***The Dominant Arm is the arm with the highest total MAP.**

TOTAL _____ MAP

3. **Blood pressure machine**: Make: _____ Model: _____ Cuff size (circle): Ped Adult Large Thigh

CRISP Member completing this form:_____ Date form completed:_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ /_____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ /_____
Month Day Year

CRISP

Death Notification Form

CRISP -FORM # 15

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed for any participant who dies after enrollment in the study. As soon as CRISP clinic personnel are aware of a participant's death, this form must be completed. When available, send copy of autopsy report to the DCIAC. Any patient identifying information should be obliterated from the copies sent to the DCIAC and replaced with CRISP ID number.

1. **Date of Last Contact**: _____ / _____ / _____
   Month Day Year

2. **Date of Death:** _____ / _____ / _____
   Month Day Year

3. **Cause of Death** (circle): Cardiovascular Disease Septicemia Cancer Trauma Suicide
   Renal Disease Respiratory Disease Cerebrovascular Accident Unknown
   Other Specify: _____

4. **Has the autopsy been performed** (circle)**?** Yes No Unknown

5. **Location of Death** (circle): During hospitalization At home At work En route to Hospital Unknown
   Other Specify: _____

6. **How was information regarding participant's death confirmed?** Family Member Medical Record
   Other: Specify _____

7. **Comments:** _____

_____

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

ID of Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

Family History Form

Use Missing Codes to indicate reason for absent information.

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

This form is to be completed for any study participant during their first visit.

										Y=Yes; N=No; U=Unknown			
Line#	Relation**	First Name	Last Name	Blood relative (Y/N)	Gender (M/F)	Year of Birth	Living or dead (L/D)	If dead, age at death	If dead, cause of death***	PKD (Y/N/U)	Dialysis (Y/N/U)	Kidney transplant (Y/N/U)	Participant in this NIH study (Y/N/U)
------	(A)	(B)	(C)	(D*)	(E)	(F*)	(G*)	(H*)	(I*)	(J*)	(K*)	(L*)	(M*)
1.													
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.													
10.													
11.													
12.													
13.													
14.													
15.													
16.													
17.													
18.													

For **relation and ***cause of death legends see page 2. *Please use U if the information is unknown in columns D, and columns F through M.

**Relation: List Family Members in the following order:

1 = biologic children;
2 = mother;
3 = father;
4 = full sisters; Include half-sisters and indicate common parent as follows:
4-M = half-sister with mother as common parent;
4-F = half-sister with father as common parent;
5 = full brothers; Include half-brothers and indicate common parent as follows:
5-M = half-brother with mother as common parent;
5-F = half-brother with father as common parent;
6 = nieces;
7 = nephews;

8 = maternal grandparents;
9 = maternal aunts;
10 = maternal uncles;
11 = maternal cousins;

12 = paternal grandparents;
13 = paternal aunts;
14 = paternal uncles;
15 = paternal cousins;

16 = maternal great grandparents;
17 = maternal great aunts;
18 = maternal great uncles;
19 = children of maternal great aunts/uncles;

20 = paternal great grandparents;
21 = paternal great aunts;
22 = paternal great uncles;
23 = children of paternal great aunts/uncles

***Causes of Death:

1 = ESRD;
2 = myocardial infarction;
3 = congestive heart failure;
4 = CVA (stroke);
5 = aortic dissection;
6 = sepsis/infection;
7 = transplantation complication;
8 = other cause;
U = Unknown

CRISP Member completing this form _____ **Date form completed:** _____ / _____ / _____
Month Day Year

Contents of form reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Renal Blood Flow

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's clinic visit during the MRI scan.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Field of View** (circle one)**:** 14 cm 16 cm Other, Specify: _____cm

3. **Matrix Size** (circle one)**:** 512x512 256x256 Other, Specify: _____

4. **Renal Blood Flow Measurement in Right Kidney:**

Right Renal Artery	Peak Systolic Velocity (cm/sec)	End Diastolic Velocity (cm/sec)	Blood Flow (cc/min)	Min Area (cm^2)	Max Area (cm^2)
1					
2					
3					

5. **Renal Blood Flow Measurement in Left Kidney:**

Left Renal Artery	Peak Systolic Velocity (cm/sec)	End Diastolic Velocity (cm/sec)	Blood Flow (cc/min)	Min Area (cm^2)	Max Area (cm^2)
1					
2					
3					

6. **Total Number of Cardiac Phases measured per RR Interval:** _____

7. **Recorded Heart Rate at time of Exam:** _____

CRISP Member Completing this form: _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of form reviewed by Radiologist (required signature): _____

Date Radiologist signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Transfer Form

CRISP -FORM #18

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed by the Study Coordinator whenever a participant transfers between clinics. The destination clinic should complete this form. Please contact the clinic of origin to coordinate date of transfer and other participant information.

1. **Original Participant ID:** ___ ___ ___ ___ ___ ___

2. **Original Clinic (**circle one**):** Emory KUMC Mayo UAB

3. **Destination Clinic (**circle one**):** Emory KUMC Mayo UAB

4. **Date of transfer:** _____ / _____ / _____
   Month Day Year

5. **Modified Participant ID (Provided by data entry system):** ___ ___ ___ ___ ___ ___

CRISP Member completing this form _____ Date form completed_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

ID of Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

CRISP

Study Withdrawal Form

CRISP -FORM # 19

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed if the participant has decided to drop out of the study.

1. **Date of Last Follow-up Visit Attended:** _____ / _____ / _____
   Month Day Year

2. **Are the reasons for the participant's withdrawal known? (**circle one**):** yes no

If yes, then please complete items 3-11.

3. **The participant has moved to a location which is not near a CRISP Clinical Center (**circle one**):** yes no
4. **The participant's physician has asked him or her to withdraw from the study (**circle one**):** yes no
5. **The participant is unwilling to have additional GFR measurements (**circle one**):** yes no
6. **The participant is unwilling to have additional MRI sessions (**circle one**):** yes no
7. **The participant is unwilling to have additional Ultrasound sessions (**circle one**):** yes no
8. **The participant is unhappy about the frequency of the follow-up visits (**circle one**):** yes no
9. **The participant has a new job or a new work situation which makes participation burdensome (**circle one**):** yes no
10. **The participant has an illness or hospitalization of self or family (**circle one**):** yes no
11. **Other (Please specify briefly):** _____

_____

CRISP Member completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

ID of Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Clinical Center: _____
Participant ID: _____
Visit Number: _____

Screening Log

This form is to be kept by the Study Coordinator as a record of all patients who were screened and found to be ineligible to participate in the CRISP Study or who chose not to participate in the study. This form is to be kept at the Clinic and **not** sent to the DCIAC.

Date	Name	Date of Birth	Gender	Reason for Exclusion

Date	Name	Date of Birth	Gender	Reason for Exclusion

CRISP

Enrollment Log

This form is to be kept by the Study Coordinator as a log of CRISP Study participants.
This form is to be kept at the Clinic and **not** sent to the DCIAC.

ID Number	Participant Name	Date of Birth	Date of Enroll.	Gender	Race	High/Low Risk

ID Number	Participant Name	Date of Birth	Date of Enroll.	Gender	Race	High/Low Risk

CRISP

Missed Visit Form

CRISP -FORM # 24

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed if, despite the best efforts of CRISP personnel, a follow-up clinic visit or telephone interview cannot be completed within the time window specified by the appointment schedule.

1. **Date of scheduled follow-up visit or telephone interview:** _____ / _____ / _____
   Month Day Year

2. **Date of last contact with participant or family member:** _____ / _____ / _____
   Month Day Year

3. **Are the reasons for the participant's missed follow-up visit known? (**circle one**):** yes no

If yes, then please complete items 4-9.

4. **There were scheduling difficulties, personal or job related (**circle one**):** yes no

5. **There were scheduling difficulties within the clinic (**circle one**):** yes no

6. **The participant refused (**circle one**):** yes no

7. **The participant had transportation problems (**circle one**):** yes no

8. **The participant was ill or incapacitated (**circle one**):** yes no

9. **Other (please specify briefly):** _____ yes no

   _____

10. **Is it likely the participant will return for the next scheduled annual clinic visit?** yes no

    If no, please explain: _____

CRISP Member completing this form _____ Date form completed_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

Medical Information Document for the CRISP Study Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

Name _____ Date of Birth ____/_____/_____

S.S.N. _____

1. Date of Diagnosis of PKD: _____/_____/_____

2. Method of Diagnosis of PKD (please check one): US _____CT Scan _____

   MRI_____ IVP_____ Angiogram _____

3. Reason for Diagnosis (please indicate): Family Screening _____
   Incidental Finding _____
   Symptomatic: please specify _____

   _____

4. Hypertension (please check one): Yes _____ No _____

   If yes, date of diagnosis of hypertension: _____/_____/_____

5. Gross hematuria (please check one): Yes _____ No _____

   If yes, date of first occurrence: _____/_____/_____

6. Most Recent Serum Creatinine Concentration: ____ mg/dl
   Date _____/_____/_____

7. Latest 24 hour urine collection: Date _____/_____/_____

   Protein excretion _____ mg/day

Doctor's Printed Name _____

Doctor's Signature _____ Date ____/_____/_____

CRISP

Annual Visit - Labs

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot
U-Undetectable

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's annual visit.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Specify Laboratory processing samples**: _____

3. **Participant Weight**: (please circle the appropriate units used) _____ kg pounds

---

BLOOD WORK:

4. **Serum creatinine concentration**: _____ mg/dL **Date creatinine collected**: _____ / _____ / _____
   Month Day Year

5. **Date remaining Blood samples were collected**: _____ / _____ / _____
   Month Day Year

6. **Hemoglobin**: _____ g/dL **Hematocrit**: _____ %

7. **White blood count (**circle units used**)**: _____ cell/µL K/µL

8. **Platelet count (**circle units used**)**: _____ platelets/µL K/µL

9. **Serum (**circle units used**)**: mEq/L mmol/L

   Na _____ K _____ Cl _____ HCO3 _____

10. **Serum (in mg/dL)**: Uric Acid _____ BUN _____ glucose _____ Ca _____

    Mg _____ **mEq/L** ___ (check if used instead of mg/dL) PO4 _____ Total bilirubin _____

11. **Serum (in U/L)**: SGOT (AST) _____ SGPT (ALT) _____ Alk Phos _____

12. **Lipid Panel (in mg/dL)**: HDL _____ LDL _____ total cholesterol _____ triglyceride _____

13. **Serum sample saved for future studies**: Collection Date: _____ / _____ / _____
    Month Day Year

    Number red top serum/plasma samples stored: _____ **Number green top serum/plasma samples stored**: _____

    Number purple top serum/plasma samples stored: _____

URINE SAMPLES:

14. Start time of urine collection: _____:_____ (24 hour) **End time of urine collection: _____:_____** (24 hour)

Collection Date for start of 24 hour Urine Specimen: _____ / _____ / _____
Month Day Year

15. 24 hour Urine Volume: _____ mL

16. Creatinine Excretion: _____mg/24h **or** **Creatinine Concentration**: _____mg/dL

17. Albumin (Microalbumin) (circle units used if entering Concentration**)**

Albumin Excretion: _____ mg/24 h **or** **Albumin Concentration**: _____ mg/L mg/ml mcg/ml

18. Protein Excretion: _____ mg/24 h **or** **Protein Concentration**: _____ mg/dL

19. Urine Electrolytes (circle units used**)**:

Citrate Excretion _____	mg/24h	mmol/24h	**or**	Citrate Concentration _____	mg/dL	mmol/L	mg/L
Oxalate Excretion _____	mg/24h	mmol/24h	**or**	Oxalate Concentration _____	mg/dL	mmol/L	mg/L
Sodium Excretion _____	mEq/24h	mmol/24h	**or**	Sodium Concentration _____	mg/dL	mEq/L	mmol/L
Potassium Excretion _____	mEq/24h	mmol/24h	**or**	Potassium Concentration _____	mEq/L	mmol/L	
Calcium Excretion _____	mg/24h		**or**	Calcium Concentration _____	mg/dL		
Chloride Excretion _____	mEq/24h	mmol/24h	**or**	Chloride Concentration _____	mEq/L	mmol/L	
Phosphorus Excretion _____	mg/24h	g/24h	**or**	Phosphorus Concentration _____	mg/dL		
Magnesium Excretion _____	mg/24h	mEq/24h	**or**	Magnesium Concentration _____	mg/dL	mEq/L	
Urea Excretion _____	mg/24h		**or**	Urea Concentration _____	mg/dL		
Uric Acid Excretion _____	mg/24h	g/24h	**or**	Uric Acid Concentration _____	mg/dL		

20. Urine or Serum Pregnancy test (circle): positive negative test not performed

If test not performed, then specify reason: _____

21. Urine sample saved for future studies: Collection Date: _____ / _____ / _____
Month Day Year

Number of 5cc aliquots of urine saved: _____

22. Current Risk Status for progression to ESRD: (circle one) High risk Low risk

CRISP Member Completing this form _____ Date form completed_____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Annual Clinic Visit - Meds and Events

CRISP -FORM # 28

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed for participant's annual clinic visits.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Has the participant had any illnesses since last study contact (**circle one**)**: yes no

   If yes, please specify briefly: _____

   _____

3. **Has the participant visited their primary care or any other physician since last study contact (**circle one**)**: yes no

   If the response is yes, then record 3a-c,g. Use 3d-f for additional visit (If 3e is identical to 3b, then enter SAME for Name in 3e**):**

   3a. Date of physician visit: _____ / _____ / _____ **Check if there are multiple visits of this type:** ___
   Month Day Year

   3b. Name and address of physician treating participant: Name: _____

   Address:_____

   3c. Specify reason for visit: _____

   3d. Date of additional physician visit: _____ / _____ / _____ **Check if there are multiple visits of this type:** ___
   Month Day Year

   3e. Name and address of physician treating participant: Name: _____

   Address:_____

   3f. Specify reason for visit: _____

   3g. Was there any renal surgery performed? yes no

   If yes, was the intent cyst reduction: yes no

   For any renal surgery provide a date and short description:

   Date of intervention: _____ / _____ / _____ **Description:** _____
   Month Day Year

4. **Has the participant been hospitalized since the last study contact (**circle one**)**: yes no

   If the response is yes, then record the following**:**

   4a. Date admitted to hospital: _____ / _____ / _____
   Month Day Year

   4b. Date discharged from hospital: _____ / _____ / _____
   Month Day Year

4c. Name and address of hospital: Name:_____

Address: _____

4d. Name and address of physician treating participant: Name:_____

Address:_____

4e. What was the diagnosis? _____

4f. If this hospitalization was unplanned, has it been reported to the local IRB? Yes No NA
(NA means this is **not** an SAE**)**

5. Smoking and Tobacco:

5a. Do they currently smoke cigarettes (circle): no yes **5b. If yes, number of packs per year** _____

5c. If they quit smoking since the last clinic visit, please indicate when (n/a for never smoked): _____ / _____
Month Year

During the past year if any of the following products were used, please indicate below:

5d. Pipe yes no

5e. Cigars (number in the last year - enter 0 if none smoked) _____

5f. Chewing tobacco yes no

6. Caffeinated Beverage/Alcohol Intake since the last clinic visit (please check a single time period for 6a, 6b, and 6c if a number is given):

6a. Average number of cups of caffeinated coffee/tea: _____ daily in the last month _____
weekly in the last month ___
monthly in the last year ____

6b. Average number of 12 oz portions of other caffeinated beverages (e.g. soda): _____ daily in the last month _____
weekly in the last month ___
monthly in the last year ____

6c. Average number of alcoholic drinks:_____ daily in the last month _____
(drink = 1 bottle of beer, 4 oz. of wine, 1 shot of liquor) weekly in the last month ___
monthly in the last year ____

6d. Enter N/A if none of the above are applicable: _____

7. Analgesic Use History: Record the average number per month over the last year.

7a. Acetaminophen tablets: _____
Avg. number / month

7b. Aspirin tablets: _____
Avg. number / month

7c. Combination analgesics: _____
Avg. number / month

7d. NSAID's: _____
Avg. number / month

7e. Enter N/A if none of the above are applicable _____

8. Drug Use (circle all that were in use in the last year):

None Marijuana Cocaine Heroin Angel Dust Other
If Other, Specify: _____

9. Natural Product Use History: (If yes is circled, please specify products)

9a. Protein supplement: yes no Specify:_____

9b. Other: yes no Specify:_____

10. Comments: _____

_____

_____

_____

11. Prescribed medications changes:

11a. Have prescribed drugs been added (circle one**)**: yes no

If yes, then please record:

#	Prescribed Medications **added**	Date (month, day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

11b. Have prescribed drugs been stopped/discontinued (circle one**)**: yes no

If yes, then please record:

#	Prescribed Medications **discontinued**	Date (month, day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

12. Over-the-counter medications changes:

12a. Have OTC drugs been added (circle one**):** yes no

If yes, then please record:

#	OTC Medications **added**	Date (month,day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

12b. Have OTC drugs been stopped/discontinued (circle one**):** yes no

If yes, then please record:

#	OTC Medications **discontinued**	Date (month day, year)
		/ /
		/ /
		/ /
		/ /
		/ /

13. Indicate the best way to contact the participant for the 3 month telephone interview (check all that apply**):**

regular mail _____ email _____ telephone _____
Best time to contact: _____

Please review all contact information on the Identification Form including phone number and email address.

CRISP Member completing this form_____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Current Reproductive History

Missing Codes:
A-Patient refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the annual visit for every female patient.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Has the participant had the following performed in the past year? Please circle the appropriate response:**

   Hysterectomy: Yes No **If yes, then record the date performed**: _____ / _____ / _____
   Month Day Year

   Oophorectomy: Yes No **If yes, then record the date performed**: _____ / _____ / _____
   Month Day Year

   Tubal Ligation: Yes No **If yes, then record the date performed**: _____ / _____ / _____
   Month Day Year

Menopause

3a. Has the menopausal status of the participant changed?: Yes No

If yes, then please indicate the current state: Peri-Menopause Post-Menopause

If yes, record the age of onset of Menopause: _____

3b. Does the participant use hormone replacement therapy?: Yes No

If yes, name of hormone replacement therapy: _____

Obstetrics

4a. During the past year was the participant pregnant?: Yes No

4b. Was it a live birth?: Yes No

If Yes, date of delivery: _____ / _____ / _____ **Is the participant still breast feeding?:** Yes No
Month Day Year

If No, date pregnancy ended: _____ / _____ / _____
Month Day Year

4c. Did the participant have toxemia during pregnancy? Yes No N/A

CRISP Member Completing this form _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Current Symptoms Form

CRISP -FORM # 30

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed at the participant's annual visit for physical exam.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Symptoms: Please check yes or no for each symptom which has been observed since the Baseline Visit. *Do not input Date of First Diagnosis if the symptom has been observed in a previous Clinic Visit and the Date was given previously.**

Symptom	No	Yes	Date of Diagnosis this year _____ / _____ / _____ Month Day Year	# of episodes this year
Hypertension			/ /	
			Date of First Diagnosis*	
Gross Hematuria			/ /	
Ruptured/symptomatic ICA			/ /	
Nephrolithiasis			/ /	
Lower UTI			/ /	
Cyst or kidney infection			/ /	

3. **Renal Pain:** (In each category circle ONE option only)

   3a) **Frequency in the last year:** never rarely sometimes often usually always

   3b) **Location:** no pain right kidney left kidney both kidneys

   3c) **Severity:** (Indicate on a scale from 0 to 10, where 0 = no pain and 10 = pain as bad as you can imagine)

   0 1 2 3 4 5 6 7 8 9 10

CRISP Member completing this form: _____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person: _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

Medication Status

CRISP -FORM # 31

Missing Codes:
A-Participant refused
B-Reading not possible
C-Investigator forgot

Use Missing Codes to indicate reason for absent information.

This form is to be completed for participant's annual clinic visits.

1. **Date of Visit**: _____ / _____ / _____
   Month Day Year

2. **Medication Summary:** **Has the participant used prescribed/otc meds since the last clinic visit? (**circle one**)**: yes no

If yes, then please record:

#	Medications	Ongoing prior to study start	Start Date (month, day, year)	Currently Ongoing	Stop Date (month, day, year)	PRN? (circle)
1		yes no	/ /	yes no	/ /	yes no
2		yes no	/ /	yes no	/ /	yes no
3		yes no	/ /	yes no	/ /	yes no
4		yes no	/ /	yes no	/ /	yes no
5		yes no	/ /	yes no	/ /	yes no
6		yes no	/ /	yes no	/ /	yes no
7		yes no	/ /	yes no	/ /	yes no
8		yes no	/ /	yes no	/ /	yes no
9		yes no	/ /	yes no	/ /	yes no
10		yes no	/ /	yes no	/ /	yes no
11		yes no	/ /	yes no	/ /	yes no
12		yes no	/ /	yes no	/ /	yes no
13		yes no	/ /	yes no	/ /	yes no
14		yes no	/ /	yes no	/ /	yes no
15		yes no	/ /	yes no	/ /	yes no
16		yes no	/ /	yes no	/ /	yes no
17		yes no	/ /	yes no	/ /	yes no
18		yes no	/ /	yes no	/ /	yes no
19		yes no	/ /	yes no	/ /	yes no
20		yes no	/ /	yes no	/ /	yes no

#	Medications	Currently Ongoing	Ongoing prior to study start	Start Date (month, day, year)	Stop Date (month, day, year)	PRN? (circle)
21		yes no	yes no	/ /	/ /	yes no
22		yes no	yes no	/ /	/ /	yes no
23		yes no	yes no	/ /	/ /	yes no
24		yes no	yes no	/ /	/ /	yes no
25		yes no	yes no	/ /	/ /	yes no
26		yes no	yes no	/ /	/ /	yes no
27		yes no	yes no	/ /	/ /	yes no
28		yes no	yes no	/ /	/ /	yes no
29		yes no	yes no	/ /	/ /	yes no
30		yes no	yes no	/ /	/ /	yes no
31		yes no	yes no	/ /	/ /	yes no
32		yes no	yes no	/ /	/ /	yes no
33		yes no	yes no	/ /	/ /	yes no
34		yes no	yes no	/ /	/ /	yes no
35		yes no	yes no	/ /	/ /	yes no
36		yes no	yes no	/ /	/ /	yes no
37		yes no	yes no	/ /	/ /	yes no
38		yes no	yes no	/ /	/ /	yes no
39		yes no	yes no	/ /	/ /	yes no
40		yes no	yes no	/ /	/ /	yes no

CRISP Member completing this form_____ Date form completed: _____ / _____ / _____
Month Day Year

Contents of Form Reviewed by Principal Investigator (required signature): _____

Date Principal Investigator signed: _____ / _____ / _____
Month Day Year

Data Entry Status: Please check to indicate that the above information has been entered ☐

Data Entry Person _____ Date Form Entered: _____ / _____ / _____
Month Day Year

CRISP

CHECKLIST FOR THE ANNUAL CLINIC VISIT

Please use the following checklist to be certain all necessary information has been obtained and all required tests completed.

		Please Check	
		Yes	N/A
1.	Form 1 - Review and Update Identification Form -- Double check Identification Form to make sure you have the address, email or telephone number for the best way to contact the participant.		
2.	Complete the following forms:		
	Form 27 – Annual Visit -Labs		
	Form 28 – Annual Clinic Visit - Meds and Events		
	Form 29 – Current Reproductive History		
	Form 7 – MR Session		
	Form 8 – US Session		
	Form 9 – GFR Collection		
	Form 10 – GFR Reporting		
	Form 11 – Physical Findings		
	Form 30 – Current Symptoms		
	Form 14 – Blood Pressure		
	Form 17 – Renal Blood Flow		
3.	Form 16 – Review and update Family History Form		