Manual of Operations (MOP)

NOVEL THERAPIES FOR RESISTANT FSGS
PHASE II CLINICAL TRIAL
PHASED INNOVATION AWARD (DK70341)

A MULTICENTER TRIAL IN CHILDREN AND ADULTS

NCT0081425

January 18, 2012
(Includes changes from Protocol Version 7)

FONTII MOP
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1. INTRODUCTION / GENERAL INFORMATION

1.1. General Information

The Manual of Operations (MOP) has been written to provide physicians, nurses, and others involved in the Novel Therapies for Resistant FSGS Phase II Trial (FONT II) with a detailed step-by-step description of the entire study. It is important that Study Coordinators and Principal Investigators (PI) in each of the participating sites become familiar with the entire contents of the MOP.

The sections have been designed to allow easy and prompt retrieval of essential information when the need arises. As with all multicenter collaborative studies, it is possible that you may be unclear about individual aspects of the study—despite our best efforts at clarity! If this happens, please do not hesitate to contact any of the people listed below. We welcome your calls and will do our best to be helpful. Thank you for your participation in this study. Listed below are some of the phone numbers, etc. that you may need.

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* For complete and updated contact information, please refer to the most recent FONT II Address Directory

2. GLOSSARY OF TERMS/LIST OF ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitor
ACS	American Cancer Society
AE	Adverse event
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
CBC	Complete blood count
CBL	Core biochemistry laboratory (Spectra)
CKD	Chronic kidney disease
CRF	Case report form
CSA	Cyclosporine
DCC	Data Coordinating Center
DM	Diabetes mellitus
ESRD	End stage renal disease
FSGS-CT	Focal Segmental Glomerulosclerosis Clinical Trial
GFR	Glomerular filtration rate
GI	Gastrointestinal
IRB	Institutional Review Board
MMF	Mycophenolate mofetil
PPAR	Peroxisome proliferator-activator receptor
SAE	Serious adverse event
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TSQM	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

3. BACKGROUND AND SIGNIFICANCE *

1. Clinical trials in FSGS

FSGS is a clinical entity with a distinctive histopathologic appearance, which may be either primary or secondary to other etiologies. This lesion may account for 10-20% of cases of primary nephrotic syndrome in children and 35% of cases in adults. In the majority of patients, the primary lesion is refractory to therapeutic interventions using traditional immunosuppressive agents. The final common pathway for advancing disease in primary FSGS is progressive fibrosis leading to ESRD in 50 to 75% of patients over a 10-year period (1,2,3,4,5). Consequently, the morbidity and mortality of patients with FSGS is compounded by that of superimposed ESRD. The life expectancy for a 10-year old child who is dialysis-dependent is approximately 29 years. Moreover, even if renal transplantation is performed, life expectancy is approximately 55 years compared to 84 years in the general US population. Following renal transplantation for FSGS, a high recurrence rate results in a 20-25% allograft loss and further diminishes the likelihood of long-term survival. Thus, the opportunity for patient survival is dependent upon success in achieving renal survival (6,7,8).

The lack of adequate randomized clinical trials has hindered clinical research in the treatment of FSGS. The majority of studies that have evaluated potential therapies for FSGS have either been uncontrolled, have not articulated well-defined end-points, or have been unable to incorporate sufficiently long treatment periods (1,9). This has engendered a great deal of controversy about optimal treatment of FSGS and variability in practice from the onset of the disease and throughout its course. For example, there is uncertainty about the advisability of administering corticosteroid therapy and how long this therapy should be maintained before categorizing patients as steroid resistant (9,10). Although there are some investigators that consider cyclosporine the best option for patients with steroid-resistant disease (11) this is not a universal opinion. The lack of effective agents after cyclosporine failure is underscored by the observation that only 1 out of 14 invited articles dealing with FSGS described alternative treatments, most of which had only been studied in small uncontrolled patient cohorts (12).

The R33 portion of this project will use a Phase II study design to evaluate the potential efficacy of two novel therapies, and to generate data upon which to more accurately estimate effect sizes. This staged approach to clinical research helps avoid large expenditures for serious diseases with unworthy and untested therapeutic agents.

2. Importance of reductions in proteinuria

The goal of therapy in proteinuric diseases such as primary FSGS is complete remission of proteinuria defined as a urinary protein:creatinine ratio <0.2. However, this is rarely achieved in patients with resistant FSGS (1,4). Instead, it is more likely that a reduction in proteinuria, albeit still in the abnormal range, can be accomplished. Long-term follow-up from the MDRD cohort and the REIN studies indicates that this is a worthwhile therapeutic objective because long-term renal outcome in patients with chronic glomerulopathies is directly related to the degree of reduction in proteinuria achieved in response to therapy (13,14). This finding has also been documented in cohorts of adults and children with FSGS (15,16). Thus, absent a therapy that is targeted at the putative cause of FSGS, it is still valuable to achieve a significant decline in proteinuria.

3. Progress in anti-fibrosis therapy for renal diseases

Great strides have been made in understanding renal fibrosis. Both TNF-α antagonists and PPARγ agonists can reduce renal fibrosis in experimental models of renal disease that have features in common with FSGS. Inhibition of the scarring process should be equally applicable in sporadic and genetic forms of FSGS (17,18,19,20). Moreover, fibrosis is an inviting target in patients who are resistant to immunosuppressive medications. Because concern that antifibrotic therapy may be ineffective in patients with FSGS whose disease has crossed a specific fibrosis threshold, only patients with an estimated GFR ≥40mL/min/1.73m^2 will be investigated. Response to antifibrotic treatment is not likely to be affected by age; however, racial background may be a confounding factor in evaluating efficacy of novel therapies because of differences in the incidence of FSGS (21,22,23) and enhanced expression of profibrotic cytokines in African Americans (24).

4. Role of conservative medical therapy

When specific therapy is unable to induce remission in patients with primary FSGS, a number of agents have been promoted as renoprotective with a potential to delay progression of CKD to ESRD. ACEi and ARB are two such drugs that reduce proteinuria when used alone and have been shown to have an additive effect on proteinuria reduction when prescribed in combination (25-34). Prescription of HMG-CoA reductase inhibitors in doses that lower hyperlipidemia is associated with stabilization of GFR and improved kidney function in chronic non-diabetic nephropathies (35). Combined use of all of these agents – an ACEi, an ARB, and a lipid lowering drug is likely to represent optimal conservative medical therapy in patients with resistant FSGS and has been advocated as renoprotective treatment (36,37,38,39).

5. Tumor necrosis factor-α (TNF-α):

TNF-α is an inflammatory cytokine that is produced by circulating or infiltrating mononuclear cells, macrophages, and kidney mesangial cells (40,41,42). Postulated mechanisms for TNF-α induced proteinuria in FSGS include recruitment of leukocytes to the site of glomerular injury, induction of cytokines and growth factors, generation of oxygen radicals including superoxide resulting in increased glomerular endothelial cell permeability to albumin, direct cytotoxicity to glomerular mesangial and epithelial cells, and induction of apoptosis (43,44,45,46).

In immune-mediated nephritis, there are elevated levels of TNF-α mRNA, high serum levels of TNF-α and subsequent renal injury (47). However, tubulointerstitial infiltration of macrophages and lymphocytes is also a prominent feature in non-immune renal diseases (48). For example, in the double-transgenic rat harboring human renin and angiotensinogen genes, early onset of hypertension, albuminuria, renal fibrosis and mortality are associated with increased entry of mononuclear cells into the renal interstitium. TNF-α antagonism with the soluble TNF-α receptor, etanercept, decreased albuminuria, nuclear factor-kB activation, and infiltration by immunocompetent cells (49). In the 5/6 nephrectomy model of CKD, progressive macrophage recruitment is paralleled by increased renal steady state levels of TNF-α mRNA (50). Upregulation of TNF-α is linked to higher levels of the profibrotic cytokine transforming growth factor-β (TGF-β) (51). Exposure of mesangial cells in vitro to the combination of TNF-α and TGF-β has a synergistic effect on fibronectin accumulation compared to incubation with each cytokine separately, suggesting that TNF-α is a key mediator of glomerulosclerosis (52).

TNF-α gene expression is increased in glomeruli and medullary tissue during the nephrotic and sclerotic phases of puromycin aminonucleoside nephropathy in rats, a model of FSGS (51). Enhanced production of TNF-α occurs in experimental diabetic nephropathy, a disease that like

FSGS is characterized by minimal inflammation. Urinary excretion of TNF-α is increased 3 days after induction of streptozocin-diabetes and injection of a soluble TNF-α receptor fusion protein reduced sodium retention and renal hypertrophy (53). Enhanced urinary excretion of TNF-α is paralleled by a rise in renal interstitial concentrations of the cytokine (54). TNF-α mRNA levels rise more than 4-fold in glomeruli and medullary tissue obtained from rats with streptozocin-diabetes for 24 weeks (56).

In patients with primary nephrotic syndrome including FSGS, elevated serum and urinary TNF-α levels at disease onset decline during remission (56,57,58). Circulating concentrations of TNF-α are higher in nephrotic patients compared with healthy controls with nearly a 20-fold increase in FSGS versus MCNS. Leukocyte cell surface expression of TNF receptors 1 and 2 is increased in steroid-resistant patients (59). Serum TNF-α levels rise just prior to the onset of a relapse, implicating TNF-α in the increased glomerular permeability (57). The increased urinary TNF-α excretion in patients with FSGS does not decline with cyclosporine therapy (58,59).

TNF-α release by cultured peripheral blood mononuclear cells is increased in patients with active nephrotic syndrome and normalizes during remission. Cytokine release correlates with the degree of proteinuria, mesangial hypercellularity, and glomerulosclerosis and a cut-off value of 50 pg/mL for TNF-α production is highly predictive of steroid resistance (58). Supernatants of cultured peripheral blood mononuclear cells obtained from patients with active FSGS syndrome have high TNF-α level. Infusion of this material into rats results in reduced density of anionic sites in the lamina rara externa and provokes albuminuria. (60). This indicates that peripheral blood mononuclear cell-derived TNF-α plays a role in the development of proteinuria in patients with FSGS.
In summary, the potential for TNF-α antagonism to reduce proteinuria in resistant FSGS is based on its role in promoting renal fibrosis, the finding of elevated TNF-α levels in experimental models of the disease and patients with FSGS, reduction in proteinuria with a TNF-α antagonist in the angiotensin II- induced renal injury model, and induction of proteinuria in animals by TNF-α produced by mononuclear cells taken from patients with FSGS.

6. Galactose

Published reports indicate that nearly 50% of patients with primary steroid resistant FSGS have elevated serum levels of a circulating factor that increases the permeability of glomeruli to albumin, P_{alb}, *in vitro* (76). P_{alb} testing provides a sensitive measure of the integrity of the permeability barrier. Experimental values vary from 0, normal, to 1.0, representing maximal loss of barrier function (77). The FSGS permeability factor is present in a fraction of plasmapheresis effluent obtained from patients with recurrent FSGS after renal transplantation (78,79). This fraction contains anionic sialoproteins with molecular weights in the range of 30 kDa (80) and a candidate molecule, cardiotrophin-like cytokine-1 has been identified (81). In plasma samples from healthy control patients, cardiotrophin-like cytokine-1 levels are below 10 pg/ml; in contrast, plasmapheresis effluents or plasma from patients with recurrent FSGS have levels exceeding 100 pg/ml. The active fraction of FSGS plasma is obtained by affinity chromatography using galactose coated agarose beads. The active substance(s) bind to the beads and can be eluted using a galactose solution; activity is evident only after removal of galactose by extensive dialysis.

A potential role for galactose in the treatment of resistant FSGS is suggested by the following observations. Addition of 10^{-12} M galactose inhibits the permeability effect *in vitro* and removal of galactose by dialysis restores activity. In contrast, extensive dialysis of sera obtained after prolonged oral galactose does NOT restore activity, suggesting that galactose supplementation may foster removal of active protein(s) from the circulation by enhancing clearance by hepatic galactose binding proteins. In one patient with recurrent FSGS in a second renal transplant, galactose was given intravenously and P_{alb} activity decreased immediately and remained low for several days. Oral administration of galactose at a later date resulted in a delayed decrease in P_{alb} that was evident within 2 weeks and persisted for 4 weeks after the final dose of galactose (82). In a recent case report, oral galactose treatment for over 1 year resulted in normalization of P_{alb}, a decline in proteinuria from 4.2 to 0.6 gm per 24 hr, without a decline in GFRe (83). Two other patients treated at the same center also had improvement in proteinuria (personal communication). Mild gastrointestinal bloating was the only side effect in the treated subjects.

Exposure of glomerular mesangial cells *in vitro* to serum containing the FSGS permeability factor results in inhibition of gene and protein expression of inducible nitric oxide synthase (84). Because nitric oxide inhibits net accumulation of extracellular matrix proteins in the glomerulus by reducing mesangial cell synthesis and enhancing degradation of these molecules (85,86), this provides another mechanism, in addition to a direct effect on glomerular permeability, by which a reduction in the circulating level of the FSGS permeability factor by galactose would diminish glomerulosclerosis and tubulointerstitial scarring. Taken together, these findings support the premise that galactose may be a safe and effective treatment to remove the FSGS permeability factor, lower proteinuria, and prevent renal fibrosis in patents with resistant FSGS.

In an open-label pilot study, galactose was administered to 23 patients with primary FSGS. Administration of the sugar was authorized by the FDA under IND #77,091. D-galactose, low endotoxin, purchased from Ferro Pfanstiehl (Ferro Corp., Waukegan, IL), was administered orally, 0.2 g/kg body weight per dose, twice a day for 28 days. The 4-week course of oral galactose was tolerated without any clinical adverse events. No patient developed hyperglycemia or any other abnormal laboratory test result. The pilot project was not intended to determine whether galactose treatment can effect a change in urinary protein excretion because the 28-day Treatment Period was too short to achieve this goal in the cohort of patients with resistant FSGS.

In summary, based on the safety and tolerability and anecdotal evidence that galactose can lower high Palb levels in patients with primary FSGS, we conclude that there is ample justification to proceed to a Phase II clinical trial evaluation of the efficacy of galactose as an antifibrotic renoprotective agent. A longer course of galactose treatment may reveal anti-proteinuric and renoprotective effects in resistant FSGS.

3.1. Preliminary Data: Summary of R21

Preliminary safety, patient tolerance, and PK data for the two novel therapies, rosiglitazone and adalimumab, were generated through the successful performance of a Phase I study.

In the Phase I study, a total of 21 patients were enrolled. 11 were assigned to receive rosiglitazone, and 10 were assigned to receive adalimumab. The patients were evenly divided by gender and pubertal stage. All patients had a GFR >50 mL/min/1.73 m^2.

There were no serious adverse events necessitating the withdrawal of study drug.

Rosiglitazone was stopped in one child due to a questionable allergy. The patients tolerated the experimental medications adequately based on the results of the Treatment Satisfaction Questionnaire for Medication (TSQM) which was administered at week 16.

The PK analyses indicated that the rosiglitazone dose needs to be increased to account for increased clearance and reduced area under the curve in patients with resistant FSGS and nephrotic range proteinuria. For adalimumab, clearance was also enhanced especially after receiving multiple doses. However, despite these results of the adalimumab PK analyses, no dose adjustment has been implemented to avoid the long-term side effects associated this antibody, i.e. malignancy and reactivation of TB.

The PK and safety data for each drug were presented in abstract form at the annual meeting of the American Society of Nephrology and published in Clin J Am Soc Nephrol 2009;4:379-47 (rosiglitazone) and Am J Kid Dis 2010;55:50-60 (adalimumab). A manuscript detailing the findings of follow-up observation for approximately 15 months after completion of the Treatment Period has been published in BMC Nephrology 2010 Jan 29;11:2.

This Phase II will again rely on the considerable investment of time and resources on the part of the study investigators and the NIH/NIDDK gained through the FSGS-CT (UO1-DK-63455) and the Phase I portion of the FONT study (DK70341). Steven and Alexandra Cohen Children's Medical Center of New York (CCMC) and University of Michigan resources including the GCRC and CTSA that were utilized in the R21phase of the study will be available for the R33 portion of the FONT project.

3.2. Specific Aims

A significant percentage of patients with primary FSGS are resistant to corticosteroids and other immunosuppressive medications. In view of the rising incidence of this disease and the grim prognosis for patients with resistant disease, it is imperative that new therapeutic approaches be evaluated in an efficient and systematic manner. This will enable accurate assessment of the risk-benefit ratio of novel therapies and guide the design of future Phase III randomized clinical trials.

Specific Aim #1: To evaluate two novel therapies for resistant FSGS -- anti-TNF-α antibody and galactose -- against standard therapy

Specific Aim #2: To identify one or more novel agents as candidates for future study in a Phase III randomized clinical trial

4. TIMELINES

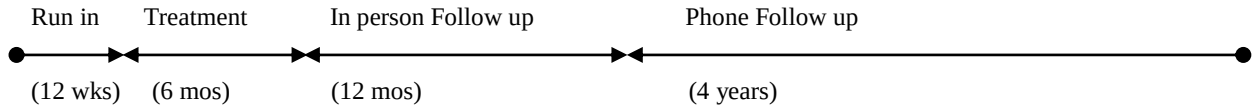
4.1. Project Calendar Timeline

03/2010	to	06/2010	Participating Site Training and IRB Approval
08/2010	to	06/2011	Subject Enrollment*
07/2011	to	10/2013	Data collection for efficacy
10/2013	to	03/2014	Data analysis for efficacy
10/2013	to	10/2018	Data Collection for late effects
After 11/2018			Final Study Closeout and Data analysis

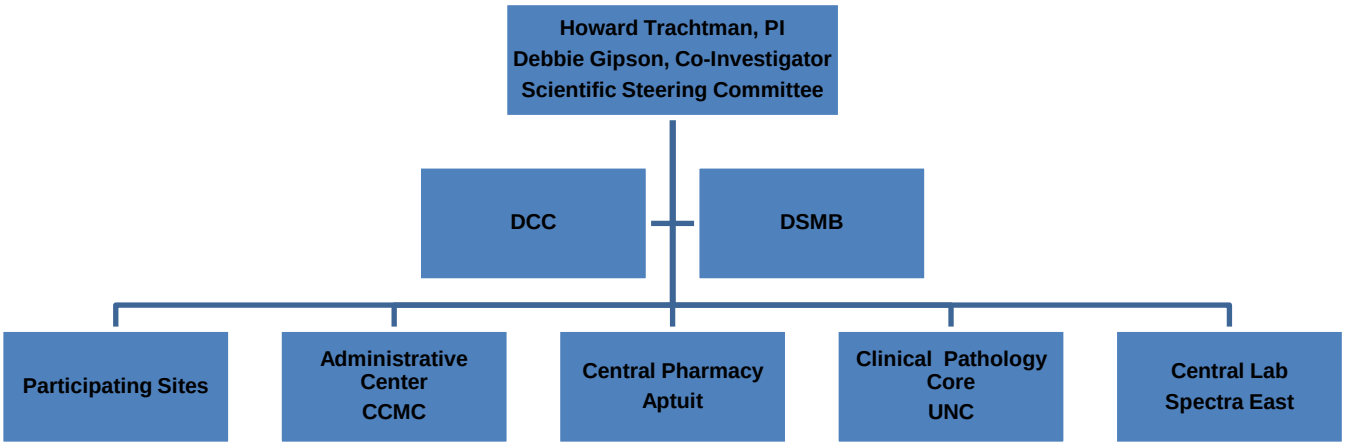
* During the Patient Enrollment Period, there will be a mandatory 6 month pause in enrollment after the first 17 patients are assigned into each treatment arm. This will be done in order to permit assessment of the therapeutic response in these subjects and to determine whether there is sufficient preliminary evidence of efficacy to justify proceeding to the target of 42 patients.

4.2. Patient Timeline

Patient Timeline	Duration
Run In period to stabilize other treatments	2 -12 weeks
Treatment period	6 months
Follow-up after Treatment Period	5 years
In person follow-up	12 months
Phone follow-up	4 years



4.3. Organizational overview



4.4. Role of the PI and Co-Investigator:

The PI and Co-Investigator will share all responsibilities for study design, construction of the database, creation of clinical report forms, identification of participating sites and training of medical personnel and study coordinators in the proper performance of the protocols, and analysis and reporting of the study outcomes.

Howard Trachtman MD, PI of the project, working at NYU Langone Medical Center Clinical Coordinating Center, will oversee subject recruitment, monitor compliance with the protocol, and insure timely collection of experimental specimens and completion of clinical report forms. In addition, he will be responsible for reimbursement to participating sites for effort devoted to this

project. Dr. Sethna will oversee subject recruitment at Steven and Alexandra Cohen Children's Medical Center of New York (CCMC).

Debbie Gipson MD, Co-Investigator, working at the University of Michigan (Ann Arbor, MI) Clinical Coordinating Center will oversee the Central Pharmacy to make sure that drug supply is adequate and the participating centers are receiving medications on schedule. In addition, Dr. Gipson will oversee the activities of the Pathology Core to insure that there is prompt confirmation of the diagnosis of FSGS (within 2 weeks). This will enable efficient recruitment of subjects. She will assist with oversight of subject recruitment, compliance monitoring with the protocol, collection of experimental specimens, completion of clinical report forms and required regulatory procedures of all participating sites.

4.5. Scientific Steering Committee:

This group will assist in the oversight of the trial. Their roles include the following:

1. Assessment of the efficacy of the experimental treatments
2. Guidance on adverse event monitoring and discontinuation of the trial
3. Issues pertaining to subject recruitment and site selection
4. Modifications to the protocol
5. Recommendations of future novel agents to be tested in the FONT network

This group will include the following members:

- Howard Trachtman MD (PI), Chair and Debbie Gipson MD (Co-Investigator), Co-chair
- Daniel Cattran MD, University of Toronto Hospital, Toronto, Ontario, Canada,
- Jeffrey Kopp MD, NIDDK, and John Middleton, MD, Duke University Hospital, Durham, NC will provide expertise in internal medicine and clinical trials
- Aaron Friedman, University of Minnesota, Department of Pediatrics, Minneapolis, MN Chairman FSGS-CT Steering Committee, will provide expertise in pediatric nephrology
- Allison Eddy MD, Children's Hospital, Seattle, WA and Agnes Fogo MD, Vanderbilt University, Nashville, TN will provide expertise in nephropathology and renal fibrosis
- Mary Ann Dooley MD, University of North Carolina, Chapel Hill, NC will provide expertise in anti-rheumatic therapy and clinical trial design
- Melanie Joy PharmD, University of North Carolina, Chapel Hill, NC will provide expertise in pharmacology
- Jennifer Gassman PhD, Cleveland Clinic ,Cleveland OH , and Tom Greene, PhD, Utah Health Sciences Center, Salt Lake City, UT, will provide expertise in biostatistics and study design;
- Charles Jennette MD, University of North Carolina, Chapel Hill, NC will provide expertise in renal histopathology

Non-voting representatives of Glaxo Smith Kline, Philadelphia, PA and Abbott Laboratories, Chicago, IL will provide liaison between the Steering Committee and private industry.

4.6. Data Coordinating Center (DCC)

This unit will be directed by Jennifer Gassman PhD. She has supervised the DCC that is involved in the FSGS-CT and this expertise has facilitated rapid establishment of a database for the R33 phase of this project. They will assist in the identification of treatment and screen failures

throughout the trial and will interact with the PI, Co-Investigator and study coordinators to collect data, analyze the results, and provide reports to the DSMB in a timely manner.

4.7. Pathology Laboratory

Dr. Charles Jennette, who served as the FSGS-CT core pathologist for the UNC-Chapel Hill Core, will review existing renal biopsy material to confirm the diagnosis of primary FSGS for all patients who enroll in the R33 study. This will not be necessary in subjects who have already had a review of the renal histopathology by an FSGS-CT Core Pathologist. Dr. Jennette will conduct this assessment during the screening period for the phase II trial.

4.8. PROMIS Assessment team:

Darren DeWalt MD MPH, David Thissen, and Nan Rothrock will interact with the FONT Principal Investigators to integrate the Patient Reported Outcomes Measurement Information Systems (PROMIS) Survey into the Phase II clinical trial. They will assist in the implementation of this aspect of the project, collection of data, and analysis of the findings.

4.9. Data and Safety Monitoring Board (DSMB):

The DSMB is an independent Board comprised of physicians with expertise in nephrology, rheumatology, endocrinology, infectious diseases, clinical pharmacology and biostatistics. The DSMB is responsible for monitoring the project and for subject safety and adequacy of data quality. Details of DSMB activities can be found in the Charter Statement for the Safety and Monitoring Committee.

4.10. Independent External Monitor:

An independent external monitor will perform an independent external review of all activities related to research compliance to ensure that the FONT Clinical Trial is performed in accord with all federal and institutional regulations. This monitoring is mandated because Howard Trachtman is Principal Investigator and sponsor of the study and also holds the IND for the use of the experimental drugs.

5. STUDY POPULATION

5.1. Inclusion Criteria

1. Primary FSGS confirmed by renal biopsy OR documentation of a genetic mutation in a podocyte protein associated with the disease
2. Failure to respond to prior therapy at least one of the following immunosuppressive medications -- cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus – or other agents prescribed to lower proteinuria
3. Age 1-65 years at onset of proteinuria
4. Age 1-65 years at time of randomization
5. Estimated GFR $\geq$40 mL/min/1.73 m^2 using Schwartz (age <18 yr) or Cockcroft-Gault (age $\geq$ 18 yr) formula at screening and $\geq$30 mL/min/1.73 m^2 at the end of the Run-In Period and prior to randomization
6. Up/c > 1.0 g/g creatinine on first morning void
7. Steroid resistance defined as failure to achieve sustained Up/c < 1.0 following a standard course of prednisone/prednisolone/methylprednisolone prescribed for FSGS therapy, OR

contraindication/anticipated intolerance to steroid therapy defined as severe obesity, documented decreased bone density, family history of diabetes, or a psychiatric disorder.

8. Willingness to follow the protocol, including medications, baseline and follow-up visits, and procedures.

Rationale: The eligibility criteria for this project are modified from those used in the FSGS-CT based upon the collective clinical experience in that study and to overcome obstacles to enrollment of potential patients. FSGS can occur as a consequence of genetic mutations in structural proteins in the podocyte (84,85,86,87) The more widespread use of genetic testing provides an alternative method of establishing a diagnosis of primary FSGS and is a suitable criterion for enrollment, independent of the kidney biopsy findings. The wider age range will allow more patients to be considered without compromising the homogeneity of the disease cohort. The steroid resistance criterion has been revised to acknowledge the justifiable resistance of internal medicine nephrologists to administer a prescribed course of steroids in all patients because of potential life-threatening consequences that might result from this medication.

Although genetic screening for podocyte gene mutations will serve as a revised inclusion criterion, this testing is not mandatory because of a lack of data on expected response rates in the presence or absence of podocyte mutations. In addition, progressive renal fibrosis is similar in primary FSGS, regardless of whether or not there is a defined genetic mutation.

There is also no exclusion criterion based on obesity because antifibrotic agents should also be beneficial in patients with obesity-related FSGS. Therefore, all patients with resistant FSGS may benefit from the novel therapies being tested.

5.2. Exclusion Criteria

1. Lactation, pregnancy, or refusal of birth control in women of child-bearing potential
2. Participation in another therapeutic trial involving protocol mandated administration of a immunosuppressive medication concurrently or 30 days prior to randomization
3. Active/serious infection (including, but not limited to Hepatitis B or C, HIV)
4. History of malignancy
5. Abnormality in age appropriate cancer screening in accord with ACS 2003 guidelines (see appendix located in MOP-Manual of Operations) (103)
6. Patients with uncontrolled blood pressure >140/90 or >95th percentile for age/height at the end of the run in period
7. Diabetes mellitus Type I or II
8. Organ or bone marrow transplantation
9. Congestive heart failure
10. History of prior myocardial infarction
11. SLE or multiple sclerosis
12. Hepatic disease, defined as serum ALT/AST levels more than 2.5x the upper limit of normal
13. Hematocrit <27%
14. Immunosuppressive therapy with cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, rapamycin, or cyclophosphamide in the 30 days prior to randomization or Rituximab in the 90 days prior to randomization

15. Use of corticosteroids in the 30 days (prior to randomization) except for minimal dosage required for stabilization of edema. The site PI must consult with the PI or Co-PI to provide justification for this minimum dosage and reassurance that it will remain fixed for the duration of the treatment period.
16. Prior treatment with the study medications, galactose or adalimumab
17. Allergy to one of the study medications, i.e., galactose, adalimumab, lisinopril, losartan or atorvastatin
18. Abnormal Pap smear (more than CIN1) unless treated and follow-up indicates a normal Pap smear.

Rationale: The cardiovascular exclusion is expanded to insure patient safety in those who are assigned to either experimental treatment . Any prior history of malignancy is also an exclusion criterion to insure safety in those who are assigned to the adalimumab treatment arm.

5.3. Co-Primary Endpoint

This will be a co-primary endpoint in which a response will be assessed based on the following two clinical variables:

A subject will be classified as a "responder" if both of the following criteria are achieved:

- A reduction in proteinuria at 6 months by ≥ 50% of the value at the time of screening, AND
- An estimated GFR (GFRe) at 6 months ≥ 75% of the value at the time of randomization in those with an initial GFRe <75 mL/min/1.73 m^2 OR GFRe persistently ≥75 mL/min/1.73 m^2 in those who renal function was ≥75 mL/min/1.73 m^2 at the time of randomization.

Rationale: The proteinuria endpoint is a quantifiable variable that is represents an accepted intermediate outcome measure for studies of FSGS that can be achieved in a short-term study (87). In addition, ≥50% reduction in proteinuria is a large enough difference to justify further evaluation of a novel therapy. However, because of concerns that proteinuria alone may be an insensitive measure of efficacy in subjects with advanced resistant FSGS, stabilization of eGFR is included as a second component of a composite primary endpoint. Thus, the combined endpoint defined by the occurrence of either a ≥50% reduction in proteinuria or a stable eGFR value as defined above will define responders for the primary Analysis. The proteinuria at the time of screening will be used to determine eligibility and efficacy to enable determination of whether addition of the antifibrotic agents consolidates the benefits of conservative medical therapy. While a GFR ≥40 mL/min/1.73m^2 at screening will be used to determine eligibility, the GFR at the time of randomization will be used to determine efficacy to account for the hemodynamic impact of intensified combination therapy with ACEi and ARB agents.

5.4. Secondary Endpoints

- Adverse effect profile
- Patient satisfaction score using the TSQM questionnaire (88)
- Quality of Life and PROMIS scores
- Percent change in proteinuria (evaluated as a continuous variable)
- Change in or time to doubling of eGFR

- Response to the experimental treatments and long-term outcome in relationship to podocyte mutations

5.5. Statistical Considerations

Addition of galactose arm: When originally designed, the FONT Phase II trial included three treatment arms. A fourth experimental treatment arm, oral administration of galactose, was incorporated into the initial randomization Removal of the rosiglitazone arm will restore the project to a 3-arm study design. This will restore the statistical methods to the original set up. In order to accomplish this, the site investigators will initiate the process of obtaining IRB approval for the revised study, which will enable subjects to be assigned to any of the three arms in the revised Phase II trial as quickly as possible. When the three treatment groups have each reached 17 total subjects, this will initiate the mandatory 6-month pause that has been built into the design of the FONT II trial. At this time, each treatment arm will be independently assessed for the pre-defined retention criteria of at least 2 of 17 subjects demonstrate evidence of efficacy with Up/c reduction by at least 50% and preservation of GFRe.

Primary Analysis and Design Characteristics: FONT II is conceived as a Phase II clinical trial to choose which treatment or treatments are worthy of further study in a future randomized Phase III clinical trial. A hybrid Phase II design as described by Liu et al (89) will be used which incorporates a ranking/selection comparison (90,91) between the treatment groups as well as a minimum activity requirement within each treatment group. The ranking/selection component of the design compares the response rates between the treatment groups, and selects the treatment regimen with the best response rate, irrespective of how large or small the advantage over the others may be. The sample size in such a selection design is selected to assure that if one of the treatments has an underlying response rate which is clearly superior to that of the other treatments; it will be selected with high probability. FONT II includes a sample size of 42 subjects in each of the 2 treatment groups (standard therapy and adalimumab) for a total sample size of 84. With the addition of N=53 in the galactose arm, the total sample size for FONT III will be 137. This sample size will insure that the treatment with the best response rate will be correctly selected with a probability of 85% if one of the treatments has a response rate ≥40% and all the remaining treatments have response rates no higher than 25%.

This first stage of the study's conduct checks for a minimum activity threshold of each drug and provides a separate assessment of activity for each treatment group. This component of the design is based on the parameters p0, the estimated response rate to an "ineffective novel therapy", and p1, the projected response rate to an "effective novel therapy" that we would like to evaluate in a randomized clinical trial (RCT). Based on experience gathered from the Collaborative Glomerular Disease Network, we anticipate that optimal conservative medical therapy will result in response rate (≥50% reduction in proteinuria) of approximately 10%. Taking p0 = 10% and p1 = 30% (designating a 20% improved response for a successful novel therapy), the following two-stage procedure has Type I and Type II error rates of 2% and 10%, respectively.

The two-stage procedure will be conducted within each novel experimental treatment group as follows: Subjects will be enrolled until each of the three treatment groups has approximately 17 randomized subjects. At this point, randomization will be temporarily halted, and there will be a 6 month pause during which the first set of subjects assigned to each of the three arms will be

allowed to complete the treatment period and have their response to the therapy evaluated. This is the Stage 1 period for each experimental treatment group.

After the subjects in each of the treatment groups (standard therapy, adalimumab, and galactose) complete the Treatment Period their response to the therapy will be evaluated. If, in any of the adalimumab or galactose groups, there are no responders or there is only one responder, that group will be dropped from further consideration. After the 6-month pause, the study will continue to its second stage. Since we anticipate 6 months prior to the pause followed by a 6-month pause, it is anticipated that 8 months of the 20-month recruitment period will remain.

During the remaining 8 months of enrollment, randomization will continue until we meet the sample size goal of 42 subjects (for standard therapy, and adalimumab) and 53 subjects (for galactose) since it is anticipated that a total of 53 subjects will need to be randomized to the galactose arm to insure that at least 42 have a $P_{alb}>0.5$.

At the end of the second stage of the study, there will be a total of 53 subjects in the galactose arm (to provide a projected total of at least 42 with $P_{alb}>0.5$) and a total of 42 subjects in each other treatment group. For the primary analysis, only those galactose subjects with $P_{alb}>0.5$ will be considered. Any treatment with a total of at least 9 responses (out of 42 subjects) will be identified as having a response rate sufficiently greater than 10% and be considered to be "active" and worthy of further study. (The threshold for the number of responses to be classified as "active" in the galactose arm will be modified if necessary if the actual galactose arm sample size exceeds 42.)

The requirement of 2 or more responses for the two experimental treatments in the first stage reduces the risk of continuing to enroll subjects into a treatment group for which the early results indicate a low response rate. On the other hand, the 2-stage design has at least a 98% probability of proceeding to the second stage if the true response rate of either of the two initial experimental treatments is 30% or greater. The overall type I and II error rates of 2 and 10% indicate that for each treatment group, the proposed design has a probability of 2% of incorrectly designating a regimen with a 10% response rate as "active", and a probability of 90% of correctly designating a regimen with a 30% response rate as "active".

This hybrid Phase II design provides two types of information: The minimum activity assessment for each treatment group indicates whether that regimen is sufficiently promising for further study. The ranking/selection comparison provides a further indication of the single regimen with the best observed response rate, which has a high probability of being the regimen with the optimum response rate should one of the regimens be substantially superior to the two others. If no regimen attains the minimum threshold of required responses in the minimum activity component of the design, the ranking/selection component of the design will not be conducted and none of the regimens will be recommended for further study.

The three groups will each have a different percentage of Subjects with $P_{alb}>0.5$ but sufficient subjects will be assigned to the galactose arm to insure that there are at least 42 with $P_{alb}>0.5$, and the primary analysis of the galactose arm will be done on those with $P_{alb}>0.5$; secondary analyses will include all 53 galactose arm subjects. This Phase II trial design is not intended to provide a definitive comparison of the novel treatment regimens with each other or with standard medical therapy, but rather is designed to identify one or more promising agents for further study in a Phase III randomized clinical trial with a larger number of subjects.

In particular, if the underlying population response rates of the top two regimens differ by less than 15%, there may be a substantial probability that the ranking/selection procedure will miss the optimum treatment (91). Thus, if two or more treatment groups meet the minimum activity threshold, and resources are available, consideration should be given to testing each of these treatment regimens in Phase III trials. On the other hand, if resources are sufficient to test only a single regimen, the ranking/selection component of the design provides some guidance as to which regimen should be evaluated in a subsequent Phase 3 trial.

Other Statistical Analyses: In addition to the primary analysis described above, several secondary analyses will also be considered in the decision as to which agent(s) should be pursued in subsequent trials. These analyses will be carried out in treatment arms that proceed to Stage 2 and enroll 42 (or 53 galactose-treated) subjects. Race (black vs. non-black), baseline GFRe <70 vs >70 mL/min/1.73m^2, P_{alb} $\leq$0.5 versus >0.5, and presence or absence of podocyte gene mutations (analysis to be done at the NIDDK by George Nelson MD, a statistical geneticist) will be included as covariates in secondary analyses. Changes in log transformed proteinuria and estimated GFR (expressed as continuous variables) from baseline to the respective follow-up assessments will be evaluated using mixed effects models incorporating subject specific intercepts and slopes (and higher order terms if necessary) (92). In some but not all scenarios, analyses of these outcomes as continuous variables may have higher statistical power than analyses of the binary primary composite endpoint (93). Mixed effects models will also be used in the analysis of other biochemistry parameters and the subject satisfaction score. Transformations will be considered to make the continuous outcomes approach a normal distribution. Repeated binary outcomes, such as occurrence of adverse events (e.g., yes/no variables defined by occurrences of specific adverse events, decline in proteinuria by 50% at specific visits, or a >33.3% decline in estimated GFR to an estimated GFR < 75 mL/min/1.73m^2 at specific visits) will be analyzed using random effects logistic regression, with random effects for each subject. The effects of treatment assignment on ordered categorical variables (such as the ordered CTC severity categories) will be addressed with longitudinal models adapted for ordered categorical response variables (94,95). Changes in means or proportions (with 95% confidence intervals computed according to methods appropriate for Phase II trials) (96,97) will be estimated separately within each treatment group, and then compared between treatment groups using 2-sided statistical tests with a significance level of 5%. Analyses of secondary endpoints will be regarded as exploratory, and will be interpreted with the context of limitations in statistical power and the possibility of Type I errors due to multiple comparisons between treatment groups.

The frequency of adverse events and differences in subject satisfaction, two of the secondary end points, will be analyzed using the same criteria of drug feasibility that were used in the R21 Phase I studies. The other two secondary endpoints, percent change in proteinuria (evaluated as a continuous variable) and change in or time to doubling of GFRe, will be analyzed using standard methods.

Randomization schedules for the R33 Phase II trial will be prepared by the DCC prior to initiation of enrollment. Randomization will be performed online by an interactive tool programmed in the study database. After verifying that all baseline case report forms have been entered and enrollment criteria are met, the randomization assignment will be displayed on the screen and e-mailed to the participating site and the central pharmacy to arrange shipment of the assigned drug.

The treatments included in this Phase II clinical trial are at therapeutic equipoise and have a comparable *a priori* likelihood of achieving the primary outcome, namely a 20% increase in the proportion of subjects who experience ≥50% reduction in proteinuria and/or preservation of GFRe in response to the specific novel therapy compared to conservative medical therapy. The rationale for including a control comparison group is because there are few reliable data about the rate of remission (≥50% reduction in proteinuria) following rigorously applied conservative management as a consequence of the prevailing practice to continue aggressive immunosuppressive therapy in steroid resistant subjects with FSGS.

6. IRB AND INFORMED CONSENT

6.1. General Principles of Consent

1. To be eligible for the study, each participant must meet preliminary eligibility criteria and the subject or guardian must be willing to sign a statement of informed consent. This will document the agreement of the subject to take part in the study activities.
2. The time frame of a subject signing an informed consent to actually being randomized must be ≤ 6 months. If this time frame is greater than 6 months, it will be necessary to reconsent the subject before being randomized into the FONT II study.
3. Separate informed consent will be obtained for participation in the clinical trial and for obtaining and storing of biological samples (see Section 13 for Template Material Consent for Provision of Biorepository Samples). Although subjects will be permitted to join in the therapeutic trial without granting permission for collection and storage of biological samples, they will not be invited to provide biological specimens without being part of the clinical trial. (Note: NIH approval is required for *Repository Consents* before specimens can be taken out of the Repository.)
4. For each subject in the FONT II Study a de-identified copy of his/her informed consent signature page, specifying the assigned identification number, will be faxed to the DCC.
5. Subjects will be asked by study personnel not to participate in any other therapeutic research studies during the subject's follow-up period from baseline to the 18-month visit. A template informed consent form is provided below.

Privacy

1. At the beginning of the study, each participant is assigned an identification number and a study code.
2. In any individual tabulation, subjects will be identified only by number.
3. The medical records of subjects in the FONT II study will be confidential. Subject documentation and files will be stored in numerical order and stored in a secure and accessible place and manner.
4. Specific study related information may be made available to the Food and Drug Administration (FDA) and the National Institutes of Health (NIH).
5. All procedures will be in compliance with HIPAA (Health Information Portability and Accountability Act) regulations.

6.2. Study Consent Template

CONSENT FOR PARTICIPATION IN RESEARCH

TITLE: Novel Therapies for Resistant Focal Segmental Glomerulosclerosis (FSGS) A Phase II Clinical Trial

PRINCIPAL INVESTIGATOR: Howard Trachtman, MD

ROLE OF COLLABORATIVE SITES:
This is a multi-center collaborative research study. The Cleveland Clinic Foundation will be responsible for analyzing the clinical data collected from this study.

SPONSOR: National Institutes of Health (NIH)-National Institute of Diabetes and Digestive and Kidney Disease

Note: This consent form is written from the point of view of a research subject. If consent will be obtained from the parent or legal guardian of a minor, the words "you" and "your" should be read as "your child".

Introduction
You are being asked to participate in a research study because you are between 1-65 years of age and have a kidney disease known as focal segmental glomerulosclerosis (FSGS) and continue to have too much protein in your urine (proteinuria). You have had a kidney biopsy or genetic testing as part of your standard care, which confirmed the fact that your kidneys have this disease. You have already had some therapy to try to decrease the amount of protein in your urine. This has not been successful and therefore other therapy is needed.

It is important that you read this explanation of the study while you are deciding if you want to participate. This consent for research describes the study procedures, the study drugs involved, the risks and benefits, and the role you will have as a participant in this research study. Please read this information carefully and do not hesitate to ask the doctor any questions you may have about this consent form or about the study. You must sign this informed consent before you enter the study. Participation in this study is entirely voluntary. You will be told of any new findings that may change your decision to participate.

The investigator may also be your personal doctor. Before entering this study or at any time during the study, you may ask for a second opinion about the study from another doctor who is in no way associated with this study. You do not have to participate in this research study to continue to receive medical care.

Purpose of the Research Study
The purpose of this research study is to look at whether adalimumab (Humira®) and/or galactose can safely reduce proteinuria (abnormal amounts of protein in the urine) and protect kidney function better than standard treatment for patients with FSGS.

Researchers have not found the best treatment for the cause of FSGS. Decreasing the amount of protein in the urine in patients with FSGS may help their kidneys work better for a longer period of time. This is because a lower amount of protein in the urine may reduce kidney scarring.

Several different medicines have been used to treat patients with the disease that you have called focal segmental glomerulosclerosis or FSGS. You still have protein in your urine even after you were treated with steroids and other drugs that affect the immune system. These drugs may have included Cyclosporine, Tacrolimus (Prograf), Mycophenolate Mofetil (CellCept), and intermittent high doses of a steroid called methylprednisolone (Solumedrol) or dexamethasone (Decadron).

Background

Nephrotic syndrome is the name of the medical problem that occurs when the kidney leaks large amounts of protein into the urine. The standard treatment for this problem is to give prednisone, a steroid by mouth, for 8-12 weeks. In most cases, giving prednisone makes protein completely disappear from the urine. Those who do not get better with oral steroids usually undergo a kidney biopsy. Some patients are then found to have a disease called focal segmental glomerulosclerosis or FSGS. This disease has a poor outlook for kidney function and nearly 50% of patients will develop kidney failure.

The best treatment for people with FSGS is unknown, especially in patients who do not get better after receiving standard medicines. There is evidence that experimental drugs that prevent scarring in the kidney may be helpful in patients with FSGS. In this research study, investigators are testing two experimental (investigational) drugs. This means that the study drugs have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of FSGS. However, adalimumab has been approved for the treatment of other conditions noted below.

One experimental drug is called adalimumab (Humira®). Humira® is a drug called a monoclonal antibody. It attaches to and neutralizes a molecule that causes inflammation. Humira® has been approved by the FDA to treat adults with rheumatoid arthritis and is given as an injection under the skin every other week. Although Humira® has not been FDA approved to treat rheumatoid arthritis in children, there is evidence that it can be used safely and effectively for this purpose in children.

There is evidence from studies in animals that adalimumab can lower protein in the urine and prevent scarring in the kidney. This drug has been tested in a small group of patients with FSGS. This preliminary study suggests that the drug is generally safe and tolerated by patients with FSGS. However, the study was not large enough to determine if the drugs could lower protein in the urine in humans.

The second experimental treatment consists of the sugar, galactose. When galactose is chemically joined to glucose, it forms lactose, the main sugar in milk. It is closely related to glucose which is the type of sugar that is normally found in the body.

For the second agent, galactose, there is evidence from single patients with FSGS that the sugar lowers the level of a substance that circulates in the blood and that makes the filtering units in the kidney leak protein. This lowered the amount of protein in the urine. It has not been used as a treatment for FSGS or any other kidney disease.

This research study will test whether adalimumab and/or galactose can safely reduce proteinuria better than standard treatment for patients with FSGS.

Expected Duration of Participation

About 137 adults and children will be asked to participate in this study. This study will take place at about 25 centers across the country. About 10 -15 patients are expected to be eligible to participate at this institution. The expected duration of participation is 6 months of treatment, with follow-up every 6 months for 5 years.

Description of Procedures

Screening/Run-in Period

The screening period can last from 2-12 weeks and may include up to 2 visits (screening visit and baseline visit). Before you are given the study drug, you will be asked to have several screening assessments and tests done to make sure you are eligible to participate.

If you agree to participate in this study, you must stop taking medications you normally take to suppress the immune system.

Screening Visit Assessments

During the screening visit, you will have the following procedures and tests:

- Urine tests to check for protein. You will be asked to provide two urine samples and bring them for screening.
- If you are a female who is able to have children you will have a urine pregnancy test.
- Blood tests to check for protein, your kidney function, liver function, electrolytes (substances in the blood like sodium and potassium), glucose (tests your sugar level), uric acid (waste product in the blood that affects the kidneys), CPK (breakdown of muscle tissue) and cholesterol.
- CBC which checks your blood count, measures the number of your red and white blood cells (cells that fight infection) and platelets (cells which cause the blood to clot).
- ANA and C3 which tests for Systemic Lupus Erythematosus (lupus). SLE is an autoimmune disease which is an illness that affects the body's ability to tell the difference between harmful and healthy substances. If you are found to have SLE you will not be able to participate in this study.
- Tests for HIV (a serious disease that affects the immune system which is the body's ability to fight off disease) Hepatitis B and C (diseases that affect the liver).
    - If you have had a negative HIV or Hepatitis C test within the last 12 months, you may not have to be tested again. You will not be able to participate in this study if you have HIV, Hepatitis B or C.
    - HIV testing will require you to sign the New York State Dept. of Health consent form for HIV testing.
- Other blood tests (fructosamine, galactose, Hga1c, and PALB) will be done to make sure that you are healthy enough to participate. These tests will be explained later in this section.
- TB Test - TB (tuberculosis) is a serious infection of the lungs that is caused by a bacteria. The TB test is called a PPD. The PPD test involves an injection of a small amount of liquid directly under the skin of your forearm which will result in a small raised welt on your skin. You will need to have this checked in 48 to 72 hours. It can be checked by your own doctor if

this is easier for you. If you have not had a PPD in the past 12 months to determine whether you have had TB or been exposed to TB, the PPD will be done. If your TB skin test is positive you will not be able to participate in this study

- Physical examination to look for swelling, and to listen to your heart and lungs and to make sure you do not have a disease such as heart failure, diabetes, liver disease, or an infection that would make the study treatments too dangerous. Your height and weight and vital signs (blood pressure, heart rate, breathing rate and temperature) will be measured.
- Medical History and Cancer Screening Evaluation - You will be asked questions about any current or past illnesses (including tests you may have had that screen for cancer), surgeries and medications. You will also be asked about your family history.
- Medications - If you are not already taking lisinopril and losartan, these medications will be started during the screening period. Both of these are medications commonly given to people with kidney disease.

Note - A urine pregnancy test will be done because the study drugs study may harm a developing fetus (unborn baby) or a newborn baby. You will not be able to participate if you are pregnant or nursing a child. The results of pregnancy testing on a child subject will be discussed with parents only with the child's permission.

The total amount of blood that will be collected is about 3 ½ teaspoons or 17.5 mls.

Baseline Visit Assessments

The baseline visit is the second part of screening and can be done at a minimum of 2 weeks after the beginning of the Screening/Run-in Period, and must be completed within 12 weeks after the Screening Assessment Visit. Some of the procedures and tests that were done during the screening assessment visit will be repeated:

- Urine test to check for protein
- If you are a female who is able to have children, you will have a pregnancy test.
- Blood tests to check for protein, your kidney function, potassium (a type of electrolyte), uric acid, and glucose level.
- CBC (complete blood count)
- Interim history to find out if you have had any problems since your last visit. You will also be asked about any medications you are taking.
- Physical examination. Your height, weight and vital signs will be measured.
- Quality of Life Questionnaires (QOL) - You will be asked to complete QOL questionnaires. This will take about 20 - 30 minutes. QOL questionnaires will be completed by all subjects age 5 years and above. There is also a parent version for parents of subjects age 5-18 years.
- Patient Reported Outcome Measurement Information System (PROMIS) form will be completed by study subjects age 8 and above and parents for children age 5 to 18 years. The PROMIS form includes questions about how you feel and how the FSGS is affecting your life.

The total amount of blood taken at this visit will be about 1 teaspoon or 5 mls.

If you are already taking the full doses of lisinopril and losartan at the first visit, this second baseline visit will not be needed.

Study Treatment Groups

If you are eligible after the Baseline Visit Assessments, you will be randomized into one of the three treatment groups. Randomization is a procedure used to assign research subjects, by chance, to a study group in a clinical trial. It is used to make sure study results are not influenced by the selection of subjects in one group as compared to another. You or your study doctor will not be able to choose which treatment group you are assigned to.

All participants will receive active drug and no one will be given a placebo (either an injection or pill that contains no active medicine).

If you are eligible to participate, you will be randomly assigned by chance to receive one of the following three study treatment groups for 6 months:

1. Standard therapy with Lisinopril, Losartan and Lipitor
2. Adalimumab (Humira) and standard therapy OR
3. Galactose and standard therapy

If you are in the Standard Therapy group, you will not receive any experimental medicine. You will receive the maximum dose of standard therapy with lisinopril, losartan and lipitor. These medications are routinely given to patients with FSGS. The maximum dose for these drugs is based on your age and weight. If you are already taking lisinopril or losartan the dose may be increased to the maximum recommended dose while you are in the study. If you experience any side effects, the doses of lisinopril and losartan will be decreased.

Lisinopril is a drug that is FDA approved for use in pediatric and adult patients to treat high blood pressure. Lisinopril has also been shown to decrease the amount of protein in the urine. All patients on this study will be taking Lisinopril in doses that are based on weight.

Losartan is another drug commonly used to treat high blood pressure. It is FDA approved for use in adults and is frequently used in children as well. The FDA has not approved Losartan for use in children, but it is often given to them also, for high blood pressure. It has also been shown to reduce the protein in the urine.

Lipitor (atorvastatin) is a drug that is FDA approved in adults and children to lower cholesterol. Patients with FSGS and high levels of protein in their urine often have high cholesterol and are given Lipitor to treat this problem.

If you are in the Humira group, you will be asked to take the medicine as an injection (a shot) every other week for 6 months. The dose will be based on your weight, but may be changed based on any side effects you may have. You will also receive standard therapy with lisinopril, losartan and lipitor.

If you are in the Galactose group, you will be asked to take the sugar by mouth twice a day for 6 months. The dose will be based on your weight but may be changed based on any side effects you may have. You will also receive standard therapy with lisinopril, losartan and lipitor.

Treatment Period

Regardless of which group you are assigned, there will be a total of 6 or 7 visits during the Treatment Period. This will include the1 or 2 visits in the Screening/run-in period and 5 more visits during the 6 month treatment period. During the treatment period, there will be a visit at the

start (week 0) when you will be given the study medication. There will be 4 more visits (weeks 2, 8, 16, and 26) over the 6 month treatment course to check how you feel and whether the study medications are working.
You will be given instructions about how and when you should take the study medicine. All bottles of study drug must be returned to the study doctor whether or not the bottle is empty.
At all visits, you will have a physical exam and your vital signs will be measured.
You will also be asked how you feel, and about any other medicines you are taking.

At each visit, you will be asked to bring in a morning urine specimen to determine the amount of protein in the urine and blood tests will be done (about 1 teaspoon or 5 ml at each visit).

- Urine to test for protein.
- Blood tests to check for protein, your kidney function, electrolytes, glucose, uric acid, and liver function.
- CBC.
- Interim history to find out how you are doing on your study medication and if you have had any problems and other medications since your last visit.
- Physical examination. Your height, weight and vital signs will be measured.

The following will also be done at the visits listed below:

- Urine for protein will be done twice before your week 26 visit.
- Pregnancy test (weeks 8, 16 and 26)
- ANA, C3 and cholesterol (weeks 16 & 26)
- CPK (weeks 8 and 26)
- QOL Questionnaires (Week 26)
- PROMIS questionnaire (Week 26)
- TSQM questionnaire - You will also be asked to answer questions about how satisfied you are with the test medicine at the 26 week visit. This will take about 5 minutes. Quality of life questionnaires will be completed by all subjects ages 5 and above. There is also a parent version for parents of subjects age 1-18 years.

<u>Other Blood Tests</u> - If you are in the Galactose group, blood will be obtained to measure the galactose level and possible build up of sugar in the body, fructosamine and HbA1C (tests used to measure the sugar in your body) at weeks 8 and 26. In addition, the level of the permeability factor (PALB) that increases the leakiness of the kidney filtering units to protein will be measured at the start and end of the treatment period. A sample will also be collected at 8 and 26 weeks for this measurement and saved for future testing. All samples will be stored for future testing for molecules that may cause the leakiness of the kidney to this protein. (An additional 1 teaspoon or 5 ml of blood will be collected for this purpose.)
The total amount of blood drawn for the study is about 3 tablespoons.

<u>Follow-up Visits</u>
We will continue to collect information about you after the research study medication is completed. Your study doctor will see you 1 month, 3 months, 6 months and 12 months after you finish the 6 months of treatment. The following procedures and laboratory tests will be done:

- Urine to test for protein
- Blood tests to check for protein, kidney function, electrolytes, glucose, uric acid and liver function

- CBC
- Interim history
- Physical examination. Your height, weight and vital signs will be measured.

The amount of blood taken will be about 1 teaspoon or 5 ml at each visit.

The following will also be done at the visits listed below:
- Quality of Life Questionnaires (6 months after the end of study treatment)
- PROMIS questionnaire (6 months after the end of study treatment)

Extended Follow-up
During the extended follow-up period, study visits will occur every 6 months for about 5 years. After Month 18 (which is 12 months after the end of study treatment), study information can be collected by telephone, if you are not able to come in for visits.

If study visits are done by telephone, you will be asked for a list of medications that you are taking, if your kidneys are still working the same, or if you are on dialysis or have had a kidney transplant. We will also ask about your general health and if you have any new illness or symptoms.

We will ask for your permission to gather the results of your recent laboratory tests and an update on your health from your nephrologist or other medical care provider(s).

If your extended follow-up visits are done in person, you may also have the following tests and procedures:
- Urine to test for protein
- Blood tests to check your electrolytes and kidney function (about 1 teaspoon or 5 mls)
- Interim history
- Physical examination. Your height, weight and vital signs will be measured.
- QOL Questionnaires
- PROMIS questionnaire

You will also be asked to complete the QOL and PROMIS questionnaires which you can mail to your study doctor. The final QOL and PROMIS questionnaires will be done at month 24.

The following table summarizes the schedule of visits and tests that will be done:

Visit	**Urine test**	**Blood tests**	**Questionnaires**	**Pregnancy Testing**
Screening	X	X		X
Baseline	X	X	X	X
Week 0				
Week 2	X	X		
Week 8	X	X		X
Week 16	X	X		X
Week 26	X	X	X	X

Discomforts and Risks

Patients with uncontrolled nephrotic syndrome (high levels of urine protein and swelling) have greater risk of infections, blood clots, and death.

Adalimumab (Humira): Serious side effects that may occur include a lupus like syndrome with fatigue, rash and bone pain. There is a risk of confusion. Another serious risk is of getting multiple sclerosis (MS), which is a disease of the brain and spinal cord or other similar diseases. Symptoms include abnormal tingling sensations in the hands and feet (paresthesias), muscle weakness, numbness, difficulty seeing, loss of control of the bowels and/or bladder, difficulty with sexual function, and convulsions.

There is a risk of bleeding around the brain (subdural hematoma) which can cause death. There is a risk of tremor and reactivation of tuberculosis. There are cases in which people taking adalimumab have gotten serious infections with a tendency to spread that are caused by a fungus. Some of these patients have died.

There is also an increased risk of developing bacterial infections including Legionella and Listeria. These bacterial infections are not usually serious in healthy people but tend to lead to harmful symptoms only in those with a compromised immune system including people taking Adalimumab and similar drugs. Legionella is spread through the air and causes flu like symptoms including fever, chills, and dry cough. Advanced stages of the disease cause problems with the gastrointestinal tract and the nervous system and lead to diarrhea and nausea. Pneumonia may also present. Listeria is spread by eating food that is contaminated with the bacteria.Symptoms of Listeria include fever, muscle aches, nausea, or diarrhea. Some people may develop more severe symptoms such as meningitis, mental changes, brain abscesses, or death.

Adalimumab also increases the chances of developing leukemia, lymphoma (these are cancers of the blood), and other cancers. Some symptoms of cancer include unexplained loss of weight, fatigue, swollen glands in your neck, under your arms and in your groin, or easy bruising or bleeding.

Please contact your doctor immediately if you notice any of these changes or if you develop any other changes that you are concerned about.

Adalimumab may also increase the chance of getting psoriasis or making it worse if you already have it. Psoriasis is a skin disease that causes raised bumps or itchy red scaly patches on your skin. Please contact your doctor immediately if you notice any of these changes. The medication will be stopped immediately if they do occur. Common side effects include pain and redness at the injection site, local infections like colds, headaches, rashes, nausea, high cholesterol, and stomach or back pain. If they occur, they will, be treated to try lessen the symptoms, or the medication dose will be lowered.

Galactose: Side effects include nausea, vomiting, abdominal pain, and bloating. Less common problems are a rash or an allergic reaction. It is a natural sugar and has not been associated with any serious side effects.

Standard Therapy:
Lisinopril: Side effects noted in more than 3% of over 1,000 patients include: headache, dizziness, cough, low blood pressure, high blood potassium level, and decreased kidney function. If you experience these side effects, the dose of lisinopril will be decreased by 50%.

A serious condition known as angioedema has also occurred. This is swelling of the face, lips, tongue and or the larynx (voice box). Without treatment, this can lead to death. If you experience these symptoms, notify the investigator immediately and/or go to the nearest Emergency Room. If angioedema develops, the lisinopril will be stopped.

Lisinopril can also cause damage to the fetus and newborn if a woman becomes pregnant while taking this drug. Lisinopril may cause death of a fetus (miscarriage). It can also cause death of a newborn baby. It is important that while in the study and taking Lisinopril, women do not become pregnant. It is important that appropriate methods of birth control be used if you are sexually active.

Losartan: Side effects include headache, dizziness, weakness, fatigue, low blood pressure (hypotension), high blood potassium level (hyperkalaemia), diarrhea, abnormal results of liver function tests, pain in the muscles and joints and cough. If you experience these side effects, the dose of losartan will be decreased by 50%. Severe swelling of the lips, face or tongue (angioedema) can also occur. Without treatment, this can lead to death. If you experience these symptoms, notify the investigator immediately and/or go to the nearest Emergency Room. If angioedema develops, the losartan will be stopped. If you experience angioedema, the losartan will be immediately stopped.

Losartan can also cause damage to the fetus and newborn if a female participant becomes pregnant while taking this drug. It can also cause death of a fetus (miscarriage) or death of a newborn. It is important that while in the study and taking Losartan, female participants do not become pregnant. It is important that appropriate methods of birth control be used if you are sexually active.

Lipitor: The most common side effects of lipitor include cough, headache, chest pain, dizziness, insomnia, nausea, and arthritis, abdominal pain, gas, constipation, indigestion, and abnormal liver function tests. Less Common side effects include facial swelling, acne, loss of appetite, anemia, leg cramps, and abnormal liver function tests, and high blood potassium level (hyperkalaemia).

Blood Collection - When blood is withdrawn from the vein there may be some temporary discomfort, local bruising, blockage of the vein, or rarely, infection. Precautions will be taken to minimize these risks.

Questionnaires - Some of these questions may be of a personal and sensitive nature and may make you feel uncomfortable. You don't have to answer any questions you do not want to answer.

PPD - You will feel a brief sting as a needle is inserted just below the skin surface. There is a very small risk of severe redness and swelling of the arm in people who have had a previous positive

PPD test and who have the test again. There also have been a few cases of this reaction in people who have not been tested before.

Unknown Risks - We cannot predict all the risks or potential side effects of these medicines. There may be unknown or delayed risks that may occur months or years after treatment. As with all drugs, the study drugs may have interactions with other drugs, prescription drugs, nonprescription drugs and herbal remedies found at health food stores. Before any medicine or health product is taken, regardless of whether it is purchased by you, prescribed by a physician or purchased from a health food store, your study doctor needs to be called or notified. Other prescribed or "over the counter" drugs or herbals may cause increases or decreases in effectiveness of the study drugs and therefore may increase the risk of side effects or decrease the effectiveness of the study drugs.

As with all drugs there is a risk of allergic reaction to any drugs used in this study. Some allergic reactions can be serious. You should contact the investigator if you have any symptoms you are concerned about.

Female Subjects Able to Become Pregnant

There are definite risks, including risk of death, to an unborn baby and/or a newborn baby if you were to become pregnant during the study. Due to these risks, no one should participate in this study if she is pregnant, or plans to become pregnant during the research study period, or is breast-feeding a child.

If you are of childbearing potential (defined as having started menstrual periods):

- **By signing this form, you confirm to the best of your knowledge that you are not pregnant now do not plan to become pregnant during this study.**
- **By signing this form you agree that you should abstain from sexual activity or use two of the following contraceptive methods: barrier method including condoms and diaphragm, plus spermicidal foam, oral or implanted contraceptives including Norplant and Depo-Provera.**
- **A pregnancy test will be done before participation in this study and at weeks 8 and 16 to confirm that you are not pregnant.**
- **If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately for further instructions regarding participation in this study and follow-up.**
- **For child subjects, the results of the pregnancy tests will not be shared with the parents/legal guardians without the child's consent**

If you are a male with a partner who could become pregnant, you must use condoms and make sure your partner is also using effective birth control methods. If your partner becomes pregnant while you are in the study, let the investigator know right away.

Possible Benefits of Participation

The possible benefits to you from participating in this study include: decreases in protein in your urine, increase in level of protein in the blood, and reduction or even disappearance of swelling. This study may also benefit future patients by identifying which of the experimental drugs would be more helpful to patients with focal segmental glomerulosclerosis. You may receive no benefit by participating in this study. The protein in your urine may increase, may stay the same, or may

get worse. You will be informed of any new information about the study drugs that becomes known during the course of this study, which might affect your willingness to continue participation.

Alternative Treatments
You do not have to be in this study to be treated for FSGS. If you do not wish to participate in this study the following alternative treatments are available to you: other medications that suppress the immune system, or no treatment.

Reimbursement for Travel
You will receive $25 payment at the end of each study visit to reimburse you for your time and parking expenses.

Costs of Participating in the Study
The study drugs, study doctor's visits, and laboratory tests related to this study will be provided to you at no cost. Neither your insurance company nor you will be charged for any research procedure. Any standard care visits and medications that are not related to the study will be charged to you or your insurance company. After the study ends, you or your insurance company will be responsible for the cost of continued medications.

Compensation for Research-related injury
If you experience any side effect or injury, notify the investigator immediately so that you can receive appropriate medical treatment.

If you are hurt from being in the study, you will receive medical care and treatment as needed from the _____Health System. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance and/or other forms of medical coverage. No money will be given to you.

Contact for Questions
In the event that you have questions about the research study or if medical assistance is required, call Dr. _____at ( ) ___-____, or go to the nearest Emergency Room or call 911. Further information regarding your rights as a research subject can be obtained by calling the Office of the Institutional Review Board (IRB) at _____ at _____Health System. The IRB is the committee that oversees research at this institution.

Confidentiality
If you agree to participate in this study, we will collect health information that identifies you. We may collect the results of tests, questionnaires and interviews. We may also collect information from your medical record. We will only collect information that is needed for the research. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization.
The results of your tests will be stored in a centralized computer or data registry at the Cleveland Clinic Foundation for 7 years. Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside this hospital except as detailed below.

Investigators will share the results of your study tests and procedures with:

- National Institute of Health, NIDDK, the study sponsor and/or its agents,
- Clinical staff not involved in the study who may be involved in your standard treatment
- Governmental agencies in the United States such as the Food and Drug Administration (FDA)
- Collaborators at the Cleveland Clinic Foundation

In addition, your records may be reviewed in order to meet federal or state research regulations. Reviewers may include representatives from the FDA, representatives from the NIDDK and the _____ Institutional Review Board (IRB – the committee that reviews research at this institution), to make sure that the research was conducted properly. If your research record is reviewed by any of these groups, they may also need to see your entire medical record.

Please be aware that once private information is disclosed, it is subject to re-disclosure by the recipient and can no longer be considered protected.
If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records.

If you have a primary healthcare provider, then your study doctor will tell your primary healthcare provider about your participation in the study if you agree to that. Communication with your primary care physician will be documented in accordance with hospital policy as part of your permanent medical record. Please make your choice by initialing **one** of the lines below:

_____ Yes, you may contact my primary care doctor.

_____ No, you may not contact my primary care doctor.

If you change your mind about participating in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Dr. _____

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.
The information that is collected for research will be analyzed for many years and it is not possible to know how long this analysis and follow-up will take. Therefore, by signing this form, you are allowing access to this information indefinitely. Data from this study may be used in medical publications or presentations. The information will be de-identified so that individual subjects cannot be recognized and the information will no longer be considered Protected Health Information (PHI).

If the study reveals public health concerns or evidence of child abuse, it will be shared with the appropriate authorities.

Right to Withdraw and End of Study Procedures

You may withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. Your participation may be ended without your consent. Some reasons that your participation could be ended include: if you become ineligible to continue in the study, if you do not take the study drugs as instructed, if you consistently fail to come in for clinic visits, if the instructions of the study doctor are not followed, if you experience a study-related injury, if you are having unacceptable side effects or for any other reasons.

When your participation in the study ends, you will be asked to go through the end of study procedures the study doctor considers necessary for your safety. The procedures include a physical exam with blood pressure and heart rate measurements, and blood and urine sampling. You will also be required to return all study medications.

Voluntary Participation

Your participation in this research study is voluntary. You may choose not to participate or withdraw at any time from this research study without penalty or loss of benefits to which you are otherwise entitled.

Summation/Signatures

You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. Furthermore, you have been assured that a member of the research team will answer any future questions that may arise. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

A copy of this signed consent form will be given to you.

Subjects 18 years of age and over:

_____	_____	_____
Subject's Printed Name	Subject's Signature	Date
_____	_____	_____
Witness' Printed Name	Witness' Signature	Date

Witness Identification: _____

Minor subjects under 18 years of age:

_____
Subject's Name

_____	_____	_____
Parent's/Legal Guardian's Printed Name	Parent's/Legal Guardian's Signature	Date
_____	_____	_____
Witness' Printed Name	Witness' Signature	Date

Witness Identification: _____

PHYSICIAN'S STATEMENT

In addition to advising the above subject of other forms of treatment and therapy, which is appropriate, I have offered an opportunity for further explanation of the risks and discomforts, which are, or may be associated with this study and to answer any further questions relating to it.

_____	_____	_____
Physician's Printed Name	Physician's Signature	Date

ASSENT BY MINOR SUBJECT TO PARTICIPATE IN RESEARCH

TITLE: Novel Therapies for Resistant Focal Segmental Glomerulosclerosis (FSGS) A Phase II Clinical Trial

PRINCIPAL INVESTIGATOR: Howard Trachtman, MD

You have been asked to join this research study. You have the right to find out what will or might happen to you if you are in the study. You have the right to tell your parent(s)/guardian and the doctor whether you do or do not want to be in this study. Your parent(s)/guardian will also be asked to give permission for you to be in this study.

A research study is a way to find out about something. The study is being done to try to find out how to treat patients who have a disease called focal segmental glomerulosclerosis (FSGS) and who have not gotten better after receiving standard drugs. You have FSGS and have not gotten better after receiving steroids and several other drugs.

If you decide to be in this study, you will come back to see us 7 times over the next 26 weeks. We will ask you to tell us how you feel, what medicines you are taking, and what problems you are having, if any.

We want to tell you about some things that might happen to you if you are in this study. The study doctor will give you a physical exam and measure your height and weight. Your blood will be drawn with a needle and this may hurt a little. You may get a small bruise or a sore where the needle goes through your skin. We will take your vital signs (blood pressure, heart beat, breathing rate and temperature) at every visit. The blood pressure cuff will squeeze your arm and you may feel it as a pressure for a little while. We will ask you to give us some of your urine in a cup at each visit.

You will be assigned by chance to receive one of the three study medicines:
1. Standard therapy with Lisinopril, Losartan and Lipitor OR
2. Humira (an experimental medicine) and standard therapy OR
3. Galactose (a sugar) and standard therapy

.
You will be given instructions about how and when you should take the study medicine.

Lisinopril, losartan and lipitor are all given orally, once daily. If you receive Humira®, it will be given as an injection or shot every other week. If you receive Galactose, it is a sweet tasting powder that is mixed with water and taken twice a day. All study medications will be taken for 6 months.

It is important to remember that all medication can have side effects. If you do not feel well while taking the medication you should tell your parent and your study doctor right away. Some of the medications may make you feel dizzy or lightheaded when you stand up. Some people get back pain, headaches, nausea or just feel tired. If you have any pains, cough or increased swelling you should tell your parent and doctor.

FEMALES WHO ARE ABLE TO GET PREGNANT

There are definite risks to an unborn baby or a newborn baby if you were to become pregnant during the study. During pregnancy, some medications you would to be in the study can cause injury and even death to an unborn child. They could also cause injury or death to a newborn baby.

Due to these risks, you must not participate in this study if you are pregnant, plan to become pregnant or if you are breast-feeding a baby during the time of this research study.

If you are a girl who has menstrual periods:

- **A pregnancy test will be done to confirm that you are not pregnant before participation in this study at the screening and baseline visits and during the treatment period at week 8 week 16 and week 26 of the study. This is done by testing your urine.**
- **Your parents/legal guardian will only be told the results of the pregnancy tests with your permission. They will not be told if you don't want them to know.**
- **By signing this consent form, you are saying that to the best of your knowledge that you are not pregnant now. You are also saying you do not plan to become pregnant during this study.**
- **By signing this form you agree that you will not have sexual activity, or that you will use one of the following ways of trying to prevent pregnancy: barrier method (sponge, diaphragm or condom) plus spermicidal foam, oral ("the pill") or implanted contraceptives (Norplant)**
- **Every month throughout the study, the study doctor or nurse will ask you about your menstrual period and the possibility of pregnancy. If they feel it is necessary, the study doctor or nurse can request additional pregnancy tests.**
- **If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately. You will get instructions regarding your participation in this study and follow up.**

If you agree to be in this study, some good things might happen to you. The protein in your urine may not be as high while you are taking the study drug and you may have less swelling. But we do not know for sure that this will happen. The study might also find out things that will help other children some day.

Dr. _____ and my parent(s)/guardian have explained what you will have to do in the study.

Dr. _____ and my parent(s)/guardian have also explained any discomforts, risks and inconveniences you may experience if I am in the study.

Your parent (or legal guardian) must say it is okay for you to be in this study.

I have asked any questions I had, and all my questions have been answered.

_____ I do not want to be in this study.

_____ I want to be in this study.

If you want to be in this study, please sign your name. We will give you a copy of this form for you to keep.

I, _____, want to be in this research study.
(Print your name here)

_____ _____
(Sign your name here) Date

_____ _____ _____
Witness' Printed Name Witness' Signature Date

Witness Identification: _____

All procedures, risks and discomforts have been explained to the subject.

_____ _____ _____
Physician's Printed Name Physician's Signature Date

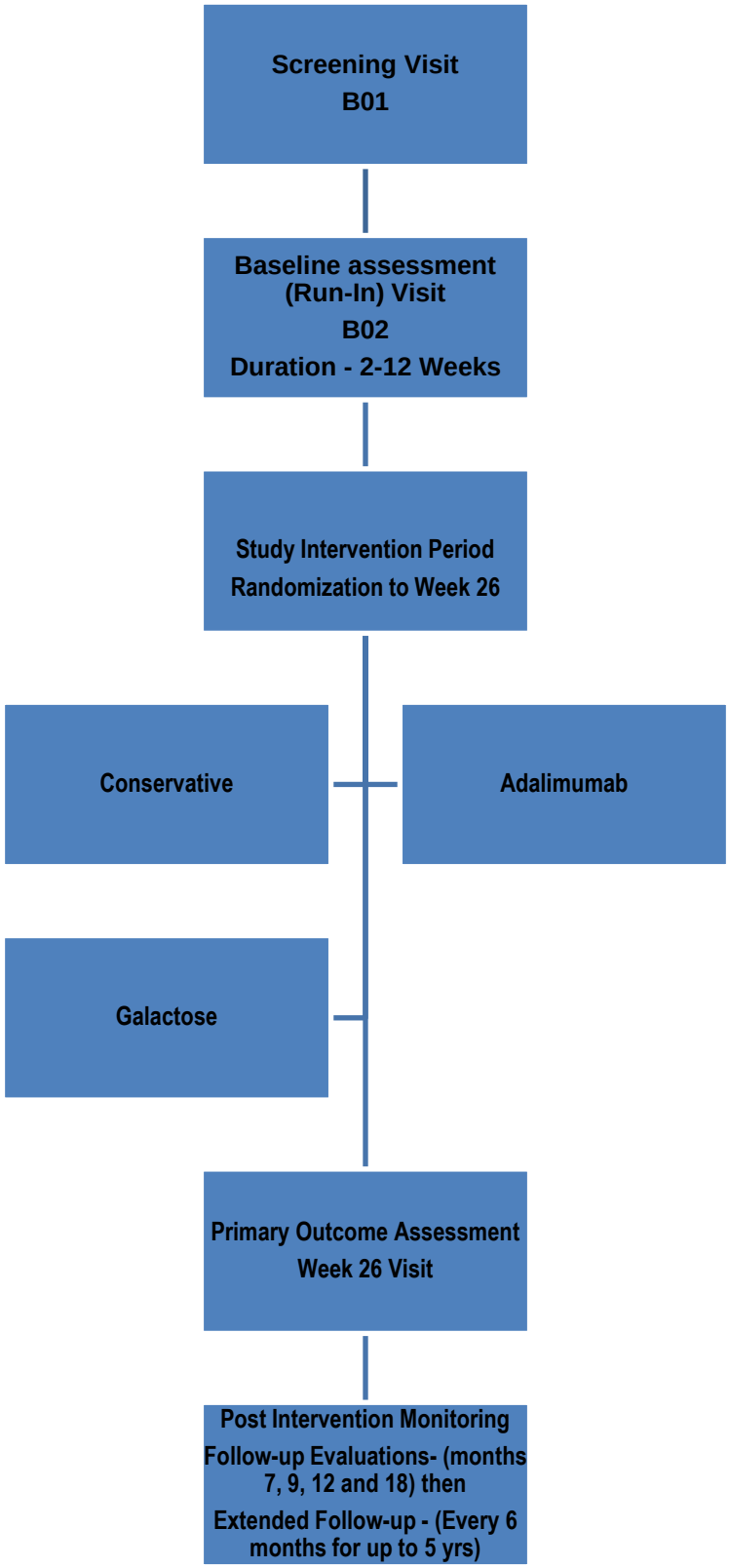
PHYSICIAN'S STATEMENT

In addition to advising the above subject of other forms of treatment and therapy, which is appropriate, I have offered an opportunity for further explanation of the risks and discomforts, which are, or may be associated with this study and to answer any further questions relating to it.

_____ _____ _____
Physician's Printed Name Physician's Signature Date

7. SUBJECT MANAGEMENT AND STUDY VISITS

The following figure outlines the course of the Phase II trial.



7.1. Purpose

This section describes the procedures that are to be performed during the study. These assessments are critical to the goals of this study and, therefore, must be carefully standardized across all of the Participating Sites.

Frequency of visits: After the screening period, subjects will be evaluated after 0, 2, 8, 16, and 26 weeks of treatment with the novel therapy or conservative medical therapy alone. This timing will coincide with the adalimumab dosing schedule and allow reinforcement of education about the technique of drug administration for subjects assigned to this medication. Thus, there will be a total of 7 visits including the screening/run-in period and the treatment period.

Visits will be performed within ±7 days of the target visit date. All visits should be scheduled as close as possible to the day defined by the protocol. If a visit must be rescheduled, make every effort to schedule the visit within 2 days before or after the designated date.

A follow-up evaluation will be performed at 1 month, 3 months, and 6 months after discontinuation of the novel therapy, and then every 6 months until the end of the funding period.

Baseline, follow-up, and final Treatment Period visits:

A request will be made to collect urine, plasma, serum, and DNA samples at baseline from all patients who are enrolled in the FONT Phase II clinical trial prior to initiation of novel therapy for storage in the NIDDK Biorepositories. Collection of biosamples and DNA will be fully coordinated with the FSGS-CT and FONT NIDDK sponsored Biorepositories. Samples for storage in the FONT Biorepository will also be collected at week 26 at the completion of the treatment Period. DNA will only be obtained once and will not be repeated in patients who participated in FSGS-CT.

Because of the potential risk of development of malignancy as a result of adalimumab treatment, eligible patients must have current cancer screening according to the American Cancer Society (ACS) 2003 guidelines (91), as appropriate to patient demographics and clinical status. Flowcharts outlining the ACS 2003 guidelines are provided in Section 15.4 of the MOP (Manual of Operations). A history of any type of cancer constitutes an exclusion criterion.
If an individual subject does not require the recommended cancer screening for a particular reason (a woman who had a total hysterectomy and no longer requires PAP smear, or a woman who had a double mastectomy and no longer requires mammography screening) documentation from the appropriate health care provider must be provided and discussed with Dr. Trachtman and/or Dr. Gipson. Circumstances such as these will be handled on case by case basis after review of the documentation by the PI and Co-PI.

Long-term follow-up visits after completion of the 6-month Treatment Period;
An in-person follow-up evaluation will be performed at 1 month (M07), 3 months (M09), and 6 months (M12) and 12 months (M18) after discontinuation of the novel therapy. At these visits, a history and complete physical examination will be performed. Laboratory tests will include a complete metabolic profile, CBC, and determination of proteinuria. These tests will be done in the

central laboratory. Testing at local labs will be utilized if adverse events occur that require urgent clarification and the patient cannot travel to the participating site.

After the completion of the 12 months of direct clinical follow-up after the treatment period, a phone or in-person questionnaire will be completed to document any new diagnoses in the past 6-12 months (i.e., lymph node enlargement, weight loss that was unanticipated, kidney failure, dialysis treatment, etc.) up to 5 years from end of participant's treatment period.

Patient safety: In assessing safety of the novel therapies and the frequency of adverse events careful consideration will be given to the frequency of these events in patients with resistant FSGS, as a consequence of their underlying disease. Thus, it is estimated that nearly 33% of the study patients may develop CTC Grade 2-3 anemia, more than 50% are likely to develop CTC Grade 3 hypertension, and 5-10% may develop CTC Grade 3-4 infectious complications.

Patient satisfaction: This will be assessed based on QOL surveys performed at week 0, prior to initiation of therapy and at week 26, after completion of the treatment period, and TSQM administered at week 26.

Procedures During Screening/Run-In (B01 and B02)

Screening/Run-In: There is no formal run-in period in the phase II trial because subjects with resistant FSGS who will be eligible for this study often have unstable kidney function and are prone to sudden decline in GFR. An effort will be made to achieve randomization between 2 and 12 weeks of the initial screening visit (B01).

In order to achieve a comparable baseline assessment prior to initiation of one of the novel therapies, the subjects must be off all immunosuppressive medications including corticosteroids (except for minimal dosage to control edema) for 30 days (prior to randomization). In addition, subjects will be placed on the maximal tolerated doses of an ACEi, and an ARB based upon measurements of blood pressure, serum K^+, and creatinine. Subjects will have to be on stable doses of the ACEi/ARB treatment for a minimum of 2 weeks prior to randomization into the FONT Phase II study to insure that the initiation of novel therapy does not coincide with a hemodynamically induced change in proteinuria. In order to implement this part of conservative medical therapy, a 2-12 week Screening/Run-In period will precede randomization. Blood pressure will be controlled in accord with published guidelines in pediatric and adult patients (104,105).

Rescreening will be necessary if subjects are not randomized to one of the three treatment arms within 12 weeks of the initial screening assessment. If the rescreening is done within 3 months, the participating site will need to repeat only those tests that excluded the subject plus a serum creatinine. Otherwise if time lapse is greater than three months, all tests for screening will need to be repeated. The participating site may rescreen a subject one time only.

7.2. Schedule of Events

The following table summarizes the evaluations during the Phase II Trial

	Screening Run-In		Wk 0	Wk 2	Wk 8	Wk 16	Wk 26	Mo 7	Mo 9	Mo 12	Mo 18	q 6mo[7]
	B 01	B 02										
Physical Exam [1]	X	X		X	X	X	X	X	X	X	X	X[8]
History	X	X		X	X	X	X	X	X	X	X	X
Pre-visit telephone contact [2]		X		X	X	X	X	X	X	X	X	
QOL and PROMIS		X					X			X		X[9]
TSQM							X					
Up/c	XX[3]	X		X	X	X	XX[3]	X	X	X	X	X[8][10]
GFR	X	X		X	X	X	X	X	X	X	X	X[8][10]
Serum Creatinine	X	X		X	X	X	X	X	X	X	X	X[8][10]
Serum Na, K, CO3, Cl, BUN	X	X[4]		X	X	X	X	X	X	X	X	X[8][10]
Serum fructosamine[5]	X				X[5]		X[5]					
Serum galactose[5]	X				X[5]		X[5]					
HbA1c [5]	X				X[5]		X[5]					
Palb [5]	X				X[5]		X[5]					
Glucose, Albumin	X	X		X	X	X	X	X	X	X	X	
Uric Acid	X	X		X	X	X	X	X	X	X	X	
AST/ALT/ alk phos	X			X	X	X	X	X	X	X	X	
LDH	X			X	X	X	X	X	X	X	X	
CPK	X				X		X					
CBC	X	X		X	X	X	X	X	X	X	X	
ANA/C3/Cholesterol	X					X	X					
Pregnancy test	X	X			X	X	X					
HIV[6]	X											
Hep B/C[6]	X											
PPD [6]	X											
Biorepository-blood	X						X					
Biorepository-DNA	X											
Biorepository-Urine	X						X					
Randomized Intervention			X	X	X	X	X					
Cancer screening	X											
Assessment of AE	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X

[1]Physical exam includes examination of lymph nodes, liver and spleen and measurement of height, weight and vital signs.
[2]Recommended.
[3]Two first morning urine samples to be submitted at the visit and collected a minimum of 24 hours apart
[4]Serum potassium only.
[5]Baseline samples for serum galactose levels, serum fructosamine, HbA1c and Palb will be done in all subjects. Samples at weeks 8 and 26 will only be collected in subjects randomized to galactose .The 26-wk Palb sample will be run in all galactose subjects and the 8 wk Palb sample will be stored for future assay.
[6]HIV, Hep B/C and PPD if not performed in the 12 months prior to screening
[7]Long term follow up after Month 18 may be conducted in person or by telephone interview
[8]Optional protocol procedure
[9]Final QOL assessment at month 24
[10]Local lab testing will be acceptable for these visits

7.3. Screening/run-in evaluation (Visits B01)

At the B01 visit, informed consent will be obtained and preliminary eligibility will be determined.

Study ID Number

The assigned ID number will have three parts – 123-001 AB. The first 6 digits will be composed of the 3 digit number assigned to each site by the FONT DCC followed by a consecutive number for each subject enrolled at the site beginning with 001. The last 2 digits will be a unique alpha code assigned to each subject.

Initial assessment

During the Screening Period, subjects with FSGS who are potentially eligible for the Phase II clinical trial should be evaluated to ensure that they satisfy the inclusion criteria. Special attention should be made to ensure that they have biopsy-proven primary FSGS that is resistant to steroids and a second immunosuppressant therapy, that their estimated GFR is greater than 40 mL/min/1.73 $m^{2,}$, and that their urine protein:creatinine ratio is greater than 1.0 g/g creatinine. This evaluation can be performed during a routine clinic visit.

Medications

Subjects should be queried about use of any of the immunosuppressive medication including steroids. Subjects must be off these drugs for 30 days prior to randomization in the study. If minimal doses of corticosteroids are considered necessary for subject stability, this should be discussed with Howard Trachtman, MD, Principal Investigator or Debbie Gipson, MD, Co-Investigator during the Screening/Run-in Period prior to randomization. Otherwise, they are disqualified from participating in the study. Subjects who are receiving concomitant treatment with an ACEi and ARB for control of blood pressure or to lower proteinuria will be allowed to continue these medications in doses prescribed by the protocol. The study doses of lisinopril, losartan, and atorvastatin are described in section 8. Subjects may receive vitamin E or diuretics.

Clinical Management

During the Screening/Run-in period, subjects who are not already on the medications should be started on a combination of the ACEi (lisinopril) and the ARB (losartan). By the end of the Screening/Run-in Period, subjects must be on the maximum tolerated doses of lisinopril and losartan combination. **For children <u>weighing less than 40 kg</u>, the maximum doses are 10 mg of lisinopril and 25 mg of losartan. For <u>subjects weighing 40 kg or more</u>, the maximum doses are 20 mg of lisinopril and 50 mg of losartan.** These are target doses and they can be adjusted downward for reasons of safety and/or tolerance. If a subject requires additional treatment for hypertension, the lisinopril or losartan dose may be increased at the preference of the study investigator. Additional antihypertensive agents should be used if blood pressure is not controlled on lisinopril and losartan. If a subject is intolerant of ACEi because of cough, then the losartan dose can be doubled if necessary.

There is no protocol-mandated escalation schedule for the lisinopril and losartan and this can be done at the discretion of the site investigator as long as the maximum doses are reached by the end of the Screening/ Run-in period or if escalation to full dose is prevented by signs of intolerance such as orthostasis or hyperkalemia. The doses of these medications should be left unchanged for the duration of the 6-month treatment.

PLEASE NOTE: During the course of the trial, subjects will be given a prescription for lisinopril and losartan and these medications will be provided via the subject's regular medical insurance coverage because these drugs are considered standard of care in patients with FSGS and persistent proteinuria.

Required Screening data (B01)

1. History and physical examination, including examination of lymph nodes, liver and spleen. Measurement of vital signs, height and weight.
2. Urine protein and creatinine excretion - Proteinuria (Up/c) will be expressed as the protein:creatinine ratio (mg:mg) in an early morning specimen. The value will represent the average of two samples collected during the week before this study visit.
3. B01 labs (see Schedule of Events in Section 6.5).
4. HIV, Hepatitis B and C serology, if not done in previous 12 months. In cases where there is a low clinical suspicion of HIV, serology results may be reported as negative within the previous 36 months.
5. TB skin test, if not done in the previous 12 months.
6. A urine pregnancy test will be obtained for females of childbearing potential.
7. A request will be made to collect urine, plasma, serum, and DNA samples from all subjects who are enrolled in the FONT Phase II clinical trial. These samples will be obtained from subjects who provide consent for collection and storage of repository samples. The repository samples should be obtained prior to initiation of novel therapy (at either visit B01 or B02) for storage in the NIDDK Biorepositories. See Section 6.4 for Repository Sample details.
8. Existing renal biopsy tissue will be assessed by the study pathologist for all subjects who have not had the diagnosis of FSGS confirmed by an FSGS-CT core pathologist.

*During the B01 visit – **KEY POINTS**:*

1. Review all prescribed medications and record on Medication Form
2. Ensure that the subject is not receiving medication that would result in exclusion
3. Screen for any condition that precludes the subject from being randomized to either of the study regimens. Any medication that does not result in the exclusion of the subject may be continued if it is required during the study.
4. If the subject is not yet taking an ACEi or ARB then these drugs should be started (see Clinical Management section above).
5. The Up/c must be > 1.0 mg/mg to be eligible for inclusion in the study.
6. Ensure that the subject has a negative cancer screening 2003 guidelines according to the American Cancer Society (ACS) 2003 guidelines (103), as appropriate to subject demographics and clinical status.

Because of the potential risk of development of malignancy as a result of adalimumab treatment, eligible subjects must have current cancer screening according to the American Cancer Society (ACS) 2003 guidelines (103), as appropriate to subject demographics and clinical status. Flowcharts outlining the ACS 2003 guidelines are provided in Section 15.4 of the MOP (Manual of Operations). A history of any type of cancer constitutes an exclusion criterion.

7.4. Screening/run-in evaluation (Visits B02)

The B02 assessment, which will be used as the pre-treatment values when assessing the therapeutic effect of the assigned medication regimen, must be obtained at the end of the Screening/Run-in period. The B02 assessment can be done at a minimum of 2 weeks after the B01 visit, and must be completed within 12 weeks after the B01 assessment. The duration of the Screening/Run-in period is left to the discretion of the site investigator but must be within the 2-12 week range.

The following procedures will be completed at the B02 visit

1. Interval History and physical examination, including examination of lymph nodes, liver and spleen. Measurement of vital signs sure, height and weight will also be done. .
2. B02 labs and urine protein:creatinine (see Schedule of Events in Section 6.5). These tests should be sent to the central laboratory (Spectra). They can be obtained and sent either from the participating site or from the office of a local physician provided the laboratory tests are sent to the central laboratory. These arrangements should be made in advance to make enrollment into the study and initiation of the Treatment Period as convenient as possible for the individual subject.
3. Quality of life assessment with PedsQL (children) or SF-36 (adults) and PROMIS (age 8 years and greater) (99,106, 07,108)
4. Adverse event assessment
5. Record concomitant medications

Abbreviated Screening Period

If a subject is already on medication and has reached target doses of ACEi and ARB for a minimum of 2 weeks at the time of the B01 visit, the B02 visit will not be required.

The B02 visit is held primarily for safety reasons. It is done to ensure that implementation of the combination of ACEi and ARB at the target doses does not cause a decline in GFR below 30 mL/min/1.73 m^2, the eligibility cut off. The subject will receive a screening GFR at B01 to ensure that a decline below 30 mL/min/1.73 m^2 has not occurred.

Assessment of Eligibility and Randomization

Subjects will be considered eligible for randomization if they provide consent to participate, if all of the required screening data is collected and validated, and no additional exclusion criteria are identified during the screening/run-in period.

A subject cannot be randomized until the results of the B02 assessments are available. For safety reasons, if the estimated GFR is less than 30 mL/min/1.73 m^2, at the B02 assessment, then the subject will not be eligible for randomization and will be excluded from further study. The urine protein:creatinine ratio at the time of the screening visit (B01) is the value used for trial eligibility.

Please note that the glucose, potassium, albumin, creatinine concentrations, CBC and pregnancy test **must be repeated** at the B02 Visit even if they were measured at the Screening Visit.

If the subject satisfies the inclusion criteria at the screening assessment (B01) and baseline studies (B02) confirm that enrollment is safe, then he/she will then be randomized to either:
(1) Conservative Medical Therapy (standard therapy),

(2) Adalimumab, or
(3) Galactose.

Subjects will be randomly assigned to one of the three treatment arms. The adalimumab vs. galactose vs. standard therapy 1:1:1 allocation scheme will be used to overcome subject heterogeneity caused by eligibility criteria that enable immediate or delayed enrollment. In addition, all study arms are at therapeutic equipoise and have a comparable *a priori* likelihood of being safe and acceptable to subjects.

Duration of novel therapy: Novel therapies will be administered for 6 months before assessing efficacy, i.e., ≥50% reduction in proteinuria. Although the novel therapies target renal fibrosis, it is anticipated that this period of treatment will be sufficient to document a beneficial effect on proteinuria.

Week 0 Visit:
Subjects will then return to the participating site at the Week 0 visit to receive their assigned study medications and will be instructed on the continuation of the Conservative arm or the appropriate method of administration of galactose (oral powder), and adalimumab (subcutaneous injection every other week). Atorvastatin will be dispensed at this visit and subjects will be given instructions on how to achieve the target dosage of the statin. For information on statin dosing see section 7.1 - Conservative medical therapy.

Week 02, 08 and 16 Visit:
Study Intervention Procedures:

1. Interval History and physical examination, including examination of lymph nodes, liver and spleen, measurement of vital signs, height and weight..
2. Labs and urine protein:creatinine (see Schedule of Events in Section 6.5). These tests should be sent to the central laboratory (Spectra).
3. Adverse event assessment
4. Record concomitant medications

7.5. Final Outcome Visit (Week 26)

1. History and physical examination, including documented examination of lymph nodes, liver and spleen, including the measurement of vital signs, height and weight.
2. Morning urine protein and creatinine excretion x 2 (The value will represent the average of two samples collected during the week before the visit.)
3. Labs (see Schedule of Events in Section 6.5)
4. Urine, serum and plasma for Biorepository
5. TSQM, age appropriate QOL and PROMIS questionnaires
6. Adverse event assessment
7. Record concomitant medications

7.6. Follow- Up Evaluations

7.6.1. Follow-Up Evaluations (Month 7, 9, 12, 18)

After completion of the 6-month Treatment Period, an in-person follow-up evaluation will be performed at 1 month (M07), 3 months (M09), and 6 months (M12) and 12 months (M18) after

discontinuation of the novel therapy. Testing at local labs may be utilized if adverse events occur that require urgent clarification and the subject cannot travel to the participating site.

1. History and physical examination, including documented examination of lymph nodes, liver and spleen and measurement of vital signs, height and weight.
2. Labs and urine protein:creatinine (see Schedule of Events in Section 6.5)
3. Age appropriate Quality of Life (Months 12 and 24)
4. Adverse event assessment
5. Record concomitant medications

7.6.2. Extended Follow-up Period Evaluations (After Month 18 Visit)

After Month 18, visits can be done by telephone collecting available information. Quality of Life forms may be completed at home and submitted by mail.

After the completion of the 12 months of direct clinical follow-up (after the treatment period) information can be collected in-person or by telephone to document any new diagnoses in the past 6-12 months (i.e., lymph node enlargement, weight loss that was unanticipated, kidney failure, dialysis treatment, etc.). This information will be collected for up to 5 years from end of subject's treatment period.

7.7. General Study Procedures

The following subsections describe the specific procedures for the FONTII study protocol.

First Morning Urine (FMU) Samples

1. First morning urine collections for measurement of the urine protein: creatinine ratio (Up/c) should be obtained at each protocol visit. The urinary protein and creatinine concentrations should be measured as mg/dl.
2. In order to obtain the most reliable estimate of urinary protein excretion and to eliminate any orthostatic component, this determination will be done in early morning specimens rather than random spot urine samples. The early morning urine sample should be collected as soon as the subject awakes in the morning prior to engaging in any activity. It is advisable to place a specimen cup in the bathroom in the evening prior to specimen collection.
3. A specimen should be collected on the morning prior to (urine should be less than seven days old when brought in for their visit) the screening and all follow-up visits. Subjects should bring these specimens in to the clinic. (Refrigerate specimens prior to visit for analysis)
4. The Up/c ratio at the Screening and week 26 outcome visit will be an average of 2 first morning urine samples. The intermediate follow-up visits will be calculated using a single value measured in one early morning urine sample. Subjects should be instructed to avoid drugs that interfere with creatinine excretion (e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, Tagamet (cimetidine), and NSAIDs for 48 hours prior to Up/c determination. Common NSAIDs include: Ibuprofen (Advil) and Naproxen (Aleve).
5. It is recommended that subjects be contacted prior to a scheduled visit to inquire if he/she has any of the following problems:
    a. Intercurrent illness
    b. Fever > 38º C (100.4º F)

c. Temporary use of a medication that interferes with creatinine excretion (see list of medications above). These conditions might cause a transient increase in proteinuria or alter the Up/c. If any of these circumstances apply, then reschedule the planned visit.

Note: All visits should be scheduled as close as possible to the day defined by the protocol. If a visit must be rescheduled because of illness or other problems such as school tests or transportation difficulties, make every effort to schedule the visit within 2 days before or after the designated date. This procedure will enable repeat testing, if needed, to be performed in a timely manner. If the subject is found to have fever or an intercurrent illness at a scheduled follow-up visit, then the urine sample should be discarded and a repeat sample should be obtained.

Blood Pressure Determinations

The normal values for blood pressure in pediatric age subjects are be based on the Second Task Force on Blood Pressure in Children (104) and in adults on the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (105). The blood pressure charts can be found in the MOP.

1. Blood pressure should be measured by trained personnel at each visit.
2. A sitting blood pressure should be recorded at each visit.
3. If possible, it is advisable that the same individual should measure the blood pressure in a subject at the baseline and follow-up visits to minimize inter-observer variability.
4. An appropriate size cuff should be used. This is defined as a blood pressure cuff containing a bladder, which covers at least 2/3 of the distance from the acromion to the olecranon. If there is any doubt about cuff size, then a larger rather than an inappropriately small cuff should be used. In adolescents or overweight adults, it may be necessary to use a large adult or thigh cuff to obtain an accurate measurement. If there is any doubt, it is preferable to err to the side of using a cuff that is too large rather than using a cuff that is too small.
5. The subject should be seated with arm extended at heart level for approximately 5 minutes prior to making the measurement.
6. Blood pressure can be measured using standard auscultatory methods or using an oscillometric device such as the Dinamapp. Auscultation is preferred. Try to use the same method throughout the study.
7. The method of measuring blood pressure should be recorded with each reading.
8. Investigators are encouraged to adjust antihypertensive agents to optimize blood pressure control throughout the trial. Lisinopril and Losartan doses will be optimized prior to study entry and should remain unchanged except for toxicity reasons.

Laboratory Tests

1. Blood will be collected at any time of the day.
2. Blood and urine assays will be conducted in the Central Laboratory. Although urinalysis is recommended as standard of care, it is not mandatory at the screening visit.
3. Pregnancy test, Human Chorionic Gonadotropin (HCG), should be assessed at B01, B02 and at the specified visits in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Urine pregnancy testing will be performed at the central lab.
4. Laboratory studies including glycosylated hemoglobin and fructosamine will be analyzed at the central laboratory, Spectra East. The blood sample for the in vitro glomerular permeability (Palb) assay will be sent to the laboratory of Virginia Savin MD (Kansas City, KS) and the blood for determination of serum galactose concentration will be sent to the laboratory of Daniel Stein PhD (Bronx NY).

5. Testing at local labs may be utilized if adverse events occur.

NOTE: Although there is a formal requirement to repeat a pregnancy test at specified follow-up visits, it is advised that the test be repeated as often as deemed clinically necessary to avoid unanticipated teratogenic effects of the drugs used in the treatment protocol.

See the Schedule of Events in Section 7.2 for the timing of laboratory tests.

Estimation of Glomerular Filtration Rate
The purposes of estimating glomerular filtration rate (GFR) are to:
1. Determine eligibility for the study AND
2. Provide an estimate of renal function for longitudinal analyses of the effects of the treatment intervention on GFR as a side effect of therapy or progression of disease.

To determine GFR:
1. The average of serum creatinine values at the Screening visits (B01 and B02) will be used for the calculation of the study estimated GFR baseline.
2. GFR will be estimated by the Schwartz formula for subjects age < 18 years and by the Cockcroft Gault formula for subjects age is ≥ 18 years.
3. The local investigator should use the formulas (see Manual of Operations for formulas) when calculating the GFR to determine eligibility during the Screening Evaluation.

Additional Samples for Special Studies at the Screening Assessment
Testing for HIV, Hepatitis B and C if not done in the previous 12 months. (The site must provide documentation of the result of these tests if they are not being repeated). In cases where there is a low clinical suspicion of HIV, serology results may be reported as negative within the previous 36 months.

Biorepository Samples:
Additional biological samples will be obtained at screening (B01 or B02) and Week 26. The biological samples will be stored for use in future studies of the pathobiology of FSGS. A separate materials consent will be obtained to specifically address the collection of these specimens. Among those subjects who consent for storage of biological specimens, urine, serum and plasma specimens will be shipped to the National Institutes of Health Biosample Repository at Fisher BioServices. In addition, whole blood specimens for DNA will be shipped to the National Institutes of Health Genetics Initiative at Rutgers University Cell and DNA Repository. In subjects who enroll in FONT who were participants in the FSGS Clinical Trial, DNA testing will **not** be repeated.
Collection of biosamples and DNA will be fully coordinated with the FSGS-CT and FONT NIDDK sponsored Biorepositories. DNA samples will be stored in the Rutgers University Biorepository under the auspices of the NIDDK under the direction of Rebekah Rasooly MD. Storage of materials in the NIDDK Biorepository will facilitate future studies into the mechanism of action and laboratory correlates of response to novel therapies. Sample storage and investigational use will be conducted under the Ancillary Studies Protocol of the FSGS-CT (see section 14 of the FSGS-CT Protocol).

PPD (tuberculosis skin test)
Potential subjects without a history of a previously positive PPD skin test (tuberculosis skin test) must receive a PPD test during the screening period unless the subject has a documented negative

PPD test in the 12 months prior to enrollment. PPD must be negative. In the case of a historically positive PPD, confirmation of previous therapy for tuberculosis and a negative chest radiograph is an acceptable alternative.

Kidney Biopsy Review
The existing kidney biopsy that documents the diagnosis of FSGS will be reviewed by the FONT study pathologist unless previously reviewed and approved by an FSGS clinical trial pathologist. See detailed description of pathology procedures in Section 9.

History and Physical Examination
A full history and physical examination should be done at all required visits (see the Schedule of Events in Section 6.5) including measurement of including height, weight, and vital signs.

Participant Questionnaires
The TSQM questionnaire should be administered at the Week 26 visit. Satisfaction with the novel therapy regimen will be assessed using the Treatment Satisfaction Questionnaire for Medication (use authorized by S. Colman, Quintiles Late Phase, San Francisco, CA). It yields valid information in four areas – effectiveness, side effects, convenience and global satisfaction. This index contains 14 questions, scored on a Likert scale and requires approximately 10 minutes to complete. The results are scored on a 0-100 scale.

Quality of life questionnaires will be self administered at the B01or B02 visit, week 26, week 52 and year 2 visits.

a. The SF-36 is a 36 item quality of life questionnaire self-reported for adults age 18 and above (108).
b. The PedsQL is a 23 item quality of life questionnaire self-reported for children ages 5 to 18 years and parent proxy-reported for ages 2-18 years (107)
c. The Patient Reported Outcome Measurement Information System (PROMIS) (17.9) will be completed by study subjects age 8 and above (98). This permits the assessment of patient reported outcomes across the life span.

Validated translations of the SF-36 and the PedsQL will be provided in English, Spanish, and French. PROMIS is an English only instrument

PROMIS
The operations manual for PROMIS can be found in section 15.8 of the MOP. The PROMIS assessments are to be completed by patients ages 8 years and older who are able to speak and read English and are cognitively capable of doing QOL assessments. This is a self-administered questionnaire, study coordinators/parents are not to read the PROMIS questions to pediatric participants. PROMIS uses two websites, one for adults and one for children.

Pediatric participants (participants age 8-17):
https://www.assessmentcenter.net/ac1/Assessments/PROMIS2_Pediatric_Kidney
Adult participants (participants age 18 and above):
https://www.assessmentcenter.net/ac1/Assessments/PROMIS2_Adult_Kidney

Additional QOL assessment will be conducted at study year 2 if additional funding is acquired.

General Standard of Medical Care

The study protocol does not define the specific care to be provided for the following problems that are likely to arise in the subjects identified during the Screening Period or the Treatment and Follow-up Periods: (1) hypertension; (2) hyperlipidemia; (3) edema. All participating PIs are encouraged to treat these problems in the best manner possible, in accordance with the prevailing practice patterns at their institution. The therapy for these problems can be initiated during the Baseline period.

i. For hypertension medications should be prescribed to maintain the blood pressure below the 90th percentile for gender by age and height for children and ≤ 130/80 for adults. Additional medications to control blood pressure can be prescribed if needed, after maximizing the ACEi and ARB dosing in the screening phase.
ii. Modification of diet and the use of cholesterol lowering medications are encouraged to achieve target lipid levels. These can include statins or cholesterol binding agents, whatever is deemed appropriate for the specific subject.
iii. It is anticipated that edema may be a persistent or recurrent problem in subjects enrolled in the clinical trial. This may be managed using dietary sodium restriction, diuretics as single agents or in combination therapy, and/or alternative medication supplements. It is advised, if possible, that diuretic medication should not be changed within one week of a scheduled visit.
iv. Dietary advice and the use of antacids and H2 blockers to prevent gastritis will be left to the discretion of the Participating Site PI. However, cimetidine must be held for 48 hours before each follow-up visit in order to enable accurate measurement of the serum creatinine concentration and Up/c ratio. Therefore an alternate H2 Blocker may be more compatible with trial subjects.

8. STUDY MEDICATIONS

8.1. Drug Supply and Allocation

In July 2008, IND # 103,147 was issued authorizing the performance of the complete protocol including the use of the two experimental drugs, rosiglitazone and adalimumab and the three components of standard medical therapy, lisinopril, losartan, and atorvastatin. An application was submitted to the FDA on 3/29/10 for an IND to authorize the administration of all study agents including galactose that would be administered in this modified Phase II clinical trial. The four arm protocol modification has been approved by the FDA and is incorporated into the existing IND #103,147 that currently is active for the three arm protocol. No new IND number was issued. In August 2010, a second major revision was made in the protocol to remove the rosiglitazone arm and revert to a 3-arm study (standard conservative therapy, adalimumab, and galactose). This revision has been submitted to the FDA along with an updated IND application. No new IND number has been issued.

Aptuit, Inc. will serve as a central pharmacy and drug distribution system. This facility will receive the drug assignments after randomization from the DCC and ship the appropriate study drug to participating sites for provision to the subject.

Drug Returns
The Participating Sites should use their own approved local procedures for disposal of any unused study medications.

8.2 Therapeutic Interventions:

8.2.1. Conservative Medical Therapy

All subjects will receive optimal conservative medical therapy consisting of a combination of the following three agents: (1) ACEi, lisinopril: (2) ARB, losartan; and (3) statin, atorvastatin. The doses of the ACEi and ARB will be maximized during the Screening/Run-In period (2-12 weeks).The maximum target doses for subjects weighing <40 kg are: lisinopril 10 mg and losartan 25 mg. For subjects weighing >40 kg, the maximum target doses are: lisinopril 20 mg and losartan 50 mg. A steady state dose for each of these agents must be achieved by the end of the Screening/Run-in period and remain unchanged for the duration of the Treatment Period barring any clinical or laboratory side effects.

DRUG	WT ≤ 40 KG Maximum Dose	WT > 40 KG Maximum Dose
Lisinopril	10 mg	20 mg
Losartan	25 mg	50 mg
Atorvasatin	10 mg	20mg

These target doses can be adjusted downward for reasons of safety and/or tolerance. If a subject requires additional treatment for hypertension, additional antihypertensive agents may be used for blood pressure control as needed. If a subject is intolerant of lisinopril because of cough, then the losartan dose can be doubled if necessary.

Subjects who have a documented intolerance to any of the standard therapy medications can still be eligible for FONT and need to maintain the maximum tolerated doses of each drug throughout the treatment period. It is not mandated that subjects take all three drugs to be eligible for inclusion. The doses listed in this protocol are suggested doses. Please speak with Dr. Trachtman or Dr. Gipson for clarification if your participant is not able to take all three of the standard therapy medications.

Treatment with the HMG CoA reductase inhibitor, atorvastatin, will be at a dose of 0.5 mg/kg/day, maximum 40 mg/day. This third component of conservative medical therapy will be initiated at the Week 0 visit, which constitutes the start of the treatment period. The site investigator should instruct the subject to achieve the target dose by the first visit after 2 weeks of the Treatment Period.

Subjects who require steroid treatment to maintain clinical stability will have the dose tapered to the lowest effective level, preferably given every other day, during the Run-In Period. All medication doses defined at the end of the Run-In Period will be unchanged during the 6-month Treatment Period except for safety indications.

Preparation of liquid formulations of lisinopril and losartan

Participants who require a liquid formulation of lisinopril will need to have this prepared at the Participating Site using the tablets that are provided by the study. The shelf life of the dissolved tablet is 30 days.

DIRECTIONS FOR PREPARATION OF A LIQUID LISINOPRIL SUSPENSION

Add 10 mL of purified water USP to a polyethylene terephthalate (PET) bottle containing twenty (20) 10-mg tablets of lisinopril and shake for at least one minute. Add 30 mL of Bicitra® diluent and 160 mL of OraSweet SF™ to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients. The resulting suspension (1 mg/mL) should be stored at or below 25°C (77°F) and can be stored for up to four (4) weeks. Shake the suspension before each use.

Participants who require a liquid formulation of losartan will need to have this prepared at the participating site using the tablets that are provided by the study. The shelf life of the dissolved tablet is 28 days.

DIRECTIONS FOR PREPARATION OF A LIQUID LOSARTAN SUSPENSION

Add 10 mL of purified water USP to an 8 ounce (240 mL) amber polyethylene terephthalate (PET) bottle containing ten (10) 50-mg COZAAR tablets. Immediately shake for at least two minutes. Let the concentrate stand for 1 hour and then shake for 1 minute to disperse the tablet contents. Separately prepare a 50/50 volumetric mixture of Ora-Plus™ and Ora-Sweet SF™. Add 190 mL of the 50/50 Ora-Plus™/Ora-SweetSF™ mixture to the tablet and water slurry in the PET bottle and shake for 1 minute to disperse the ingredients. The suspension should be refrigerated at 2 - 8ºC (36-46ºF) and can be stored for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.

The following are common toxicities for lisinopril:

a. Decline in eGFR which is 30% or more below the baseline value and ≤100 mL/min/1.73m^2 which is repeated and confirmed in a well-hydrated participant will require modification of study medications.
b. Hyperkalemia: If serum potassium concentration is 5.5-6.0 mmol/L the value will be confirmed then, alterations in diet and administration of diuretics should be attempted. If hyperkalemia persists with serum potassium greater than 6 mmol/L, dosage modification should be instituted.
c. Hypotension or orthostasis
d. Cough: Persistent cough unrelated to other causes.
e. Angioedema: Lisinopril and losartan should be discontinued and a Serious Adverse Event Form should be completed. A Study Medication Termination Form should be filed for lisinopril. The Clinical Coordinating Center should be informed. Losartan can be reintroduced at the discretion of the site investigator.

Dosage Modifications for Lisinopril / Losartan Toxicity:

If a, b, or c above pertain, the dose of lisinopril should be reduced to 50% of the original dose for 2 weeks. If the indication for dosage modification persists, the lisinopril should be discontinued.

If the toxicity persists, the losartan should be reduced to 50% of the original dose for 2 weeks.

The dose of lisinopril or losartan at which the toxicity is corrected should be maintained for the remainder of the study. If lisinopril is discontinued because of toxicity of cough (see dosage modification above), treatment with ARB may be continued (see table below) and toxicity monitored.

If lisinopril or losartan have to be discontinued to achieve resolution of toxicity a, b or c, then the drug may be restarted at a lower dose at the discretion of the local investigator with monitoring for return of toxicity**.**

8.2.2. Adalimumab

Adalimumab (Humira®): *TNF-α antibody*

This medication will be provided by Abbott Laboratories and will be available as a liquid in single use vials. It will be administered as a subcutaneous injection every other week. The therapeutic dose of adalimumab will be 24 mg/m^2 to a maximum of 40 mg/dose every other week for the entire treatment period. Although the PK data from the FONT I Study indicated enhanced clearance of adalimumab in subjects with FSGS and nephrotic-range proteinuria the dose will not be increased above the standard amount given to treat rheumatoid arthritis because of safety concerns related to malignancies that might be associated with the administration of anti-TNF agents.

Subjects should be instructed to rotate the site of injection. In order to reduce the pain associated with the biweekly adalimumab injections, subjects can apply EMLA crème or steroid inhaler spray prior to administration of the medication. After the injection is completed, the subject can take Tylenol as needed or apply ice to the site for symptomatic pain relief.

Subjects receiving Humira® will be required to write down dates and times of drug administration and bring the administration log to each study visit (see Manual of Operations for administration log). In addition, when a subject is assigned to the Humira® arm, a per protocol dose schedule listing the week and the optimal date of drug administration will be sent with the medication to the site. This sheet can be used to facilitate scheduling of visits and it can be shared with the subject.

<u>Instructions for Administration of Humira® to Pediatric Subjects</u>

Children participating in this study may require less than the contents of the vial of Humira® (40 mg/0.8 mL) provided by Abbott. In order to calculate the correct dose of study drug to be administered, obtain the subject's height and weight and calculate body surface area. The treatment dose is 24 mg/m^2 and the maximum dose is 40 mg. For children who require less than the contents of the complete vial of Humira®, the following procedure should be followed. Using a 1 cc tuberculin syringe with a 25 or 27 gauge needle, draw back the syringe to the mark indicating the correct dose of study medication. Place the needle of the syringe into the vial of Humira® and inject the air into the vial. Holding the vial and syringe upright, withdraw the required amount of medication. Before removing the needle from the bottle, check the syringe for any air bubbles which may reduce the amount of medication in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose. Administer this dose as a subcutaneous injection immediately. Discard any unused drug immediately after giving the injection using standard hospital procedures for drug waste. Discard the used needle and syringe in a "Sharps" container.

<u>Dose adjustment protocols</u>

The following Tables outline the expected adverse events for the novel therapies and the responses that will be taken to each adverse event.

Adalimumab (Humira®): Event rate is based on dose of 24 mg/m^2 or maximum 40 mg

ANTICIPATED ADVERSE EVENT	SEVERITY GRADE CTC 0-5	EXPECTED FREQUENCY % OF PTS	TREATMENT OR ACTION TO BE TAKEN
Lupus-like syndrome	4	Rare	D/C drug
Confusion	4	Rare	D/C drug
Multiple sclerosis	4	Rare	D/C drug
Subdural hematoma	4	Rare	D/C drug
Serious infection/Sepsis	4	1%	D/C drug
Malignancy/lymphoma	4	<2%	D/C drug
Tuberculosis	4	Rare	D/C drug
Antibodies (ANA)	3	12%	D/C drug
Paresthesia	3	Rare	Reduce dose by 50%
↑alkaline phosphatase	2	Common	Symptomatic Rx, continue drug
Hypertension	2	Common	Symptomatic Rx, continue drug
Allergic reaction	1-2	<1%	Hold drug, try to restart
Tremor	1-2	Rate	Reduce dose by 50%
Injection site reaction	1-2	20%	Symptomatic Rx, continue drug
Local Infection	1-2	Common	Symptomatic Rx, continue drug
Headache	1-2	Common	Symptomatic Rx, continue drug
Rash	1-2	Common	Symptomatic Rx, continue drug
Nausea	1-2	Common	Symptomatic Rx, continue drug
Hyperlipidemia	1-2	Common	Symptomatic Rx, continue drug
Abdominal pain/ Back pain	1-2	Common	Symptomatic Rx, continue drug

8.2.3. Galactose

Galactose: *sugar*
This medication will be purchased from Ferro Pfanstiehl (Waukegan, IL).It will be dispensed as a powder and each jar will contain 500 g. The sugar will be administered orally in two divided daily doses. The therapeutic dose of galactose will be 0.2 g/kg per dose administered twice a day. The maximum single dose will be 15 g. The sugar will be dissolved in 15-30 ml of water and the solution will be ingested 15-30 minutes before breakfast and dinner. Scoops (in mL) to measure the galactose will be provided to the study site by NYU. 4g of galactose is equal to 5mL of galactose.

Galactose. Event rate is based on a dose of 20 grams per day

ANTICIPATED ADVERSE EVENTS	SEVERITY GRADE CTC 0-5	EXPECTED FREQUENCY % OF PATIENTS	TREATMENT OR ACTION TO BE TAKEN
Hepatotoxicity	4	Rare	Discontinue drug
Hyperglycemia	4	Rare	Discontinue drug
Abdominal pain, bloating, flatuence	1-3	Common	Reduce dose by 50%
Diarrhea	1-3	Common	Reduce dose by 50%
Headache	1-2	Common	Symptomatic Rx, continue drug
URI	1-2	Common	Symptomatic Rx, continue drug

9. ADVERSE EVENTS AND DEVIATIONS FROM ASSIGNED TREATMENT

Serious Adverse Events

All serious adverse events (SAE) will be documented on the Adverse Event Report Form. This form will request that the participating site note whether or not the SAE was related to the study medication.

The 7 items listed below constitute the definition of an SAE:

a. Death
b. Life-threatening
c. Requires or prolonged hospitalization
d. Results in disability significant, persistent, or permanent
e. Pregnancy with or without resultant in a birth defect
f. Causes cancer
g. Overdose of a study medication. Overdose is retained as an SAE and is defined as ingestion of a study medication in a dose that requires hospitalization for evaluation or treatment.

If an SAE or unanticipated adverse effect occurs during the FONT study or in a post-study period of reasonable duration, the participating site investigator is required to inform the Study Principal Investigator (H Trachtman, telephone number 646-501-2663) and an official at the local IRB within 2 business days (or within 72 hours if a weekend intervenes) of occurrence or knowledge of the event. If you are unable to reach Dr. Trachtman then please inform Dr. Gipson (telephone number 734-232-4852) of the SAE within the 48-72 hour allowable time window.

After this initial notification is done, the Adverse Event Report Form should be completed and Faxed to the Study Principal Investigator, FAX #212-263-4053. The Principal Investigator will report the SAE to the FONT Steering Committee and the DCC, which will inform all participating sites of the occurrence. In addition, if it is necessary to inform officials from the NIDDK or FDA, the Study Principal Investigator at the NYU Medical Center Clinical Coordinating Center will do this.

Other Adverse Events

These events will be recorded at each follow-up visit on the Adverse Event Report Form. These events will be reviewed by the FONT Steering Committee and summarized on an annual basis for the Data Safety Monitoring Board (DSMB).

Please note that information about all adverse events may be shared with the pharmaceutical companies that are supplying the study medication if they request this data.

Study Mandated Deviations from Assigned Treatment: Medication Stop Points

Definition

A stop point can only occur after the participant is randomized to a treatment arm and denotes the occurrence of an event, which necessitates altering the interventions of the study, i.e., cessation of galactose or adalimumab. Before a stop point is declared, all possible measures will be taken to reverse the problem necessitating the stop point. If there is a necessary deviation from the

randomized intervention, we will minimize the degree if at all possible. If possible, the participant will resume the intervention at a later time.

The Participating Site will complete an Adverse Event Form noting the date and reason for discontinuation of the study medication. The FONT Steering Committee will confirm the indications for stopping the study medication.

Stop points for novel therapy

- >50% decline from baseline eGFR and >60mL/min/1.73m^2 OR a final level <20 mL/min/1.73m^2
- ESRD, i.e., initiation of dialysis or receipt of a renal transplant
- SAE, i.e. grade 4 CTC toxicity
- Increase in ALT/AST to >2.5x the upper limit of normal
- Onset of congestive heart failure
- Clinical onset of SLE and/or positive ANA $\geq$ 1:160
- Serious infection/sepsis
- Malignancy
- Pregnancy

If any of these events occur, the Participating Site PI will complete an SAE form and notify Dr. Howard Trachtman as outlined earlier in this section.

NOTE: If a study subject becomes pregnant during the course of the clinical trial, then the study medication should be discontinued immediately. Second, the PI at the New York University Medical Center **Administrative Center should be informed of this event. Third, the patient must be followed until the time of delivery (premature or full-term) to determine the outcome of the pregnancy and if there are any birth defects in the infant.**

Follow-Up after reaching a Stop Point

If the study medication is stopped, effort should be made to follow the patient according to the study protocol to permit adequate safety monitoring and intent to treat analysis. During these visits, a history and complete physical examination will be performed. Laboratory testing should follow the study protocol. If the patient progresses to CKD 5 and is receiving dialysis, or has received a kidney transplant, this date should be recorded and long term follow up schedule should be followed.

10. LABORATORY SECTION

Note: Please make sure you use the appropriate barcode on the study requisition. The barcode labeled "Requisition" must be placed on requisition form only. Please use the correct label on the appropriate tube. If you have any questions regarding the new barcode sheets, please contact your dedicated Spectra Team @ 800-517-7157 option 2.

Labels are tube specific

This barcode label is for the requisition form **only**

Specimen collection and processing
General Information

10.1. Supplies

Supplies for the FONT II clinical trial will be supplied by Spectra. Start up supplies will be sent to your site prior to the start of your site in this clinical trial. Should you need additional supplies at any point during this clinical trial please call your Customer Service Representatives at 800-517-7157 Ext 5226.

10.2. Safety Laboratory Sample Collection

Safety Laboratory Kit Components:

Screening Visit (B01): KIT 3164-4

1 2mL Lavender top tube
2 8.5mL Serum Separator Tube (SST)
2 3.5mL Serum Separator Tube (SST)
2 Urine Collection Kit
2 Cryovial
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
3 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Week 2 : KIT 3165-5

1 2mL Lavender Top Tube
1 3.5mL Serum Separator Tube (SST)
1 Urine Collection Kit
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
2 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Baseline Visit (B02): KIT 3165-5

1 2mL Lavender Top Tube
1 3.5mL Serum Separator Tube (SST)
1 Urine Collection Kit
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
2 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Week 8 Visit: KIT 3167-7

1 3.5mL Serum Separator Tube (SST)
1 8.5mL Serum Separator Tube (SST)
1 2mL Lavender Top tube
1 Cryovial
1 Urine Collection Kit
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
2 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Week 16 Visit: KIT 3166-6

2 3.5mL Serum Separator Tube (SST)
1 2mL Lavender Top tube
1 Urine Collection Kit
1 Cryovial
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
2 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Week 26 Visit: KIT 3168-8

2 3.5mL Serum Separator Tube (SST)
1 8.5mL Serum Separator Tube (SST)
1 2.0mL Lavender Top Tube
2 Urine Collection Kit
2 Cryovial
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
3 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Month 7, 9, 12 and 18 Visit: KIT 3165-5

1 2mL Lavender Top Tube
1 3.5mL Serum Separator Tube (SST)
1 Urine Collection Kit
1 LifePak Plastic Tray
1 Research Safety Bag
1 Small Ziplock Bag
1 Tube Holder
1 23G Butterfly Needle
2 Sheets of Spectra Barcodes
1 Refrigerant Pack
1 IATA Approved Shipping Box

Freeze Ice Packs the day before Blood Draw

Prior to Blood Draw

1. Call FedEx to schedule a pickup
2. Complete serum and urine form for each patient
3. Affix accession number labels to test tubes and form

Please note that you will not need to use all of the barcode labels on each sheet. Please discard all unused barcode labels.

Order of Blood Draw

1. Serum Separator Tubes (SST) (gel barrier)
2. Lavender Top Tubes (EDTA additive)

10.3. Blood Draw of Safety Laboratory Specimens (Serum)

1 Using proper technique, collect specimen in the Serum Separator Tube
2. Fill tube(s) completely. Tubes are vacuum tubes and will fill to the correct amount, once the tube top is punctured
3. Invert tube 5-10 times gently to mix
4. Stand tubes upright to allow the specimens to clot at room temperature for 20 to 30 minutes, but no longer than 60 minutes
5. Centrifuge SST (within 60 minutes of collection) for 15 minutes at 3000rpm, to separate the cells from the serum. Unless indicated, send sample in original tube.
6. Unless otherwise indicated, refrigerate specimen in LifePak™ tray, prior to same day shipment
7. Snap to close LifePak. Secure lid closure by snapping 3 press indicators

10.4. Specialty Testing

For ANA by IFA and Complement C3, Serum, a 3.5mL SST is provided. Remove serum after centrifugation and transfer to plastic cryovial provided. Remember to affix "miscellaneous" accession label to plastic transport tube. Ana and C3 samples get sent to Spectra for processing.

<u>Palb</u>

For Palb an 8.5 ml SST is provided. Remove serum after centrifugation and transfer to plastic cryovial provided. Remember to affix Palb label to plastic transport tube. These labels are not barcodes. One sheet of labels was sent to each site. Palb samples get sent to Spectra.

<u>Galactose levels</u>

Collect 1mL of serum at the baseline visit from the 8.5mL SST and aliquot into a cryovial. Label this sample with the "galactose" labels that have been sent to your site. This is the **ONLY SPECIMEN THAT DOES NOT GET SENT TO SPECTRA**. PLEASE STORE THIS SAMPLE AT YOUR SITE IN A -70 FREEZER. We will batch and ship galactose levels to Dr. Stein. For subjects randomized to galactose, this level will be repeated again at week 8 and week 26.

10.5. Whole Blood Samples (Lavender top tube)

1 Using proper technique, collect specimen into Lavender top tube

2. Allow tube to fill completely to ensure proper mix of anticoagulant to blood. Tube is a vacuum and will fill to correct amount once top is punctured
3. Invert 5-10 times gently to mix
4. Label tube lengthwise with corresponding bar-coded accession label and patient's initials
5. Unless otherwise indicated, refrigerate specimen in LifePak™ tray, prior to same day shipment
6. Snap to close LifePak™. Secure lid closure by snapping 3 press indicators

All samples are sent to Spectra on a frozen ice pack unless otherwise specified

Visit	Kit	Sample	TEST	Label	Instructions
Screening Visit (B01)	KIT 3164-4	1 2mL Lavender	Hematology (CBC,Diff,Platelet)	Lavender	**Do not centrifuge**
		1 8.5mL SST	Chemistry, Serology	SST Gel	Centrifuge
		1 3.5mL SST	HIV	SST Gel	Centrifuge
		1 3.5mL SST	ANA/C3	Miscellaneous	Centrifuge, pipette into cryovial
		1 8.5mL SST	Galactose level	Galactose*	Centrifuge, pipette into cryovial*, store at -70*F at site.
			PALB	PALB*	Centrifuge, pipette into cryovial
		2 Yellow conical tubes	Urine Chemistry	Urine Chemistries	Draw one from each urine cup
Baseline Visit (B02) Week 2 Month 7,9,12,18	KIT 3165-5	1 2mL Lavender	Hematology (CBC,Diff,Platelet)	Lavender	**Do not centrifuge**
		1 3.5mL SST	Chemistry	SST Gel	Centrifuge
		1 Yellow conical tube	Urine Chemistry	Urine Chemistries	Draw from urine cup
Week 8	KIT 3167-7	1 2mL Lavender	Hematology (CBC,Diff,Platelet)	Lavender	**Do not centrifuge**
		1 3.5mL SST	Chemistry	SST Gel	Centrifuge
		1 8.5mL SST	Galactose level (if necessary)	Galactose*	Centrifuge, pipette into cryovial*, store at -70*F at site.
			PALB	PALB*	Centrifuge, pipette into cryovial
		1 Yellow conical tube	Urine Chemistry	Urine Chemistries	Draw from urine cup
Week 16	KIT 3166-6	1 2mL Lavender	Hematology (CBC,Diff,Platelet)	Lavender	**Do not centrifuge**
		1 3.5mL SST	Chemistry	SST Gel	Centrifuge
		1 3.5mL SST	ANA/C3	Miscellaneous	Centrifuge, pipette into cryovial
		1 Yellow conical tube	Urine Chemistry	Urine Chemistries	Draw from urine cup
Week 26	KIT 3168-8	1 2mL Lavender	Hematology (CBC,Diff,Platelet)	Lavender	**Do not centrifuge**
		1 3.5mL SST	Chemistry	SST Gel	Centrifuge
		1 3.5mL SST	ANA/C3	Miscellaneous	Centrifuge, pipette into cryovial
		1 8.5mL SST	Galactose level (if necessary)	Galactose*	Centrifuge, pipette into cryovial*, store at -70*F at site.
			PALB	PALB*	Centrifuge, pipette into cryovial
		2 Yellow conical tubes	Urine Chemistry	Urine Chemistries	Draw one from each urine cup

*Labels are not included with the Spectra barcoded kit labels. They have been sent separately to each site. Galactose cryovials are separate from the kit.

10.6. Packaging and Shipment of Safety Laboratory Specimens to Spectra

1. Make sure Federal Express has been called to schedule pick up
2. Place tubes in specimen trays (refer to Tray Packaging System)
3. Place tray in zip lock bag
4. Place the zip lock bag into RESEARCH SAFETY BAG along with a completed serum and urine mailing form(s)
5. Seal bag
6. Place bag in Spectra box
7. Fold box divider over and place ice pack in box
8. Close the box and seal with tape
9. Complete airbill addressed to SPECTRA by filling in box # 1 with your site information including site number
10. Affix airbill addressed to SPECTRA to box
11. Make sure airbill is marked PRIORITY OVERNIGHT
12. Mark weight in box #7 as <2lbs, with no declared value

GOOD SAMPLE PREPARATION MEANS ACCURATE RESULTS
USE THE *INSIST* METHOD

INVERT……gently, DO NOT SHAKE
NOTE …….. any special handling instructions
STAND ……SST to clot at least 30 minutes no more than 60 minutes
INSPECT……. tubes before centrifuging to assure a clot has formed
SPIN…….centrifuge SST for 15 minutes
TRANSPORT…..refrigerate/freeze sample as required. Follow shipping instructions

UNSPUN – clotted blood remains on top of gel barrier. Spin specimen in centrifuge for at least 15 minutes (this should be done no longer than 1 hour after drawing the specimen).

INCOMPLETE SEPARATION- serum is not completely separated from the red cells. Centrifuge again for 10-15 minutes. Cells left in serum can affect certain results.

HEMOLIZED SPECIMEN- serum is red or pinkish. If possible redraw specimen. Cells left in serum can affect certain results.

INSIST on quality specimens for quality results

Invert-	shaking the specimen can cause hemolysis
Note-	special instructions, i.e. freezing
Stand-	specimen must be clotted before spinning to achieve good . separation
Inspect-	make sure the specimen has clotted
Spin-	centrifuge specimen for 15 minutes at 3000rpms for good separation, if necessary re-spin
Transport-	follow instructions from central lab

spectra clinical research

Customer Service
(800) 517-7157 ext 5330

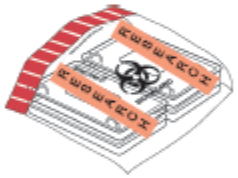
Tray Packaging System

Small Tray Shipper

1. Assemble shipping box.

2. Place tubes into tray(s).

3. Place up to 4 trays and ALL paperwork into the clear poly bag and seal the bag.



4. Place the sealed bag in the box.

5. Fold over cardboard separator, and place 1 ice pack on top.

6. Seal box with tape and affix airbill to box.

10.7. Reporting

General Information

Reference Ranges
Most reference ranges for tests performed at Spectra are those reported by the manufacturer of the assay reagents for the particular methodology used. For ranges that vary by gender or age, the applicable range will be indicated based on the patient demographic information provided to Spectra. Values outside the reference range will be automatically flagged as High or Low.

Alert/Exception Values
Alert and Exception values are meant to flag important deviations from the normal range. These values appear on the Alert /Exception report.

Panic values require immediate attention and are returned to the site via fax as soon as they are available in the laboratory. A follow-up telephone call is made to confirm receipt of the fax.

Reports
Reports are returned to the site via fax. The fax consists of the following:

- Cover page
- Alert/Exception Report
- Patient report(s)
- Report Summary

Turn-Around-Time
Routine chemistry and hematology tests are performed within 24 hours of Spectra's receipt of a specimen. If you have any questions regarding reports or failed transmission please call any member of your Spectra team.

Test Cancellation
Tests will be cancelled by Spectra when specimens are received in a condition that does not allow accurate testing. These include the following:

Unspun: Uncentrifuged serum samples are only suitable for BUN, Creatinine, Albumin and Serology testing. All other tests will be cancelled. The listed tests will only be performed if, after centrifuging the specimen, it is found to not be hemolyzed.

Gross Hemolysis: Glucose, Electrolytes and Enzymes are affected by gross hemolysis and will not be performed.

Moderate hemolysis: Specimens received in this condition will be tested and the results reviewed. In many cases the results will be reported with a comment indicating the specimen condition.

Clotted, Hemolyzed or Grossly under filled: Hematology tests (CBC) will be cancelled on specimens with these conditions.

T.C.	TEST NAME	REF RANGE	Gender	UNITS
200	**CBC**			
204	**WBC**	4.80 - 10.80		1000/mcL
207	**RBC**	4.20 - 5.40	F	mill/mcL
		4.70 - 6.10	M	mill/mcL
200C	**HGB**	12.0 - 16.0	F	g/dL
		14.0 - 18.0	M	g/dL
200D	**HCT**	37.0 - 47.0	F	%
		42.0 - 52.0	M	%
	MCV	81 - 99	F	mcm3
		80 - 94	M	mcm3
	MCH	27.0 - 31.0		pg/cell
	MCHC	33.0 - 37.0		g/dL
202	**WBC Differential**			
	Neutrophils	40.0 - 74.0		%
	Lymphocytes	19.0 - 48.0		%
	Monocytes	3.4 - 9.0		%
	Eosinophils	0.0 - 7.0		%
	Basophils	0.0 - 1.5		%
	LUC	0.0 - 4.0		%
201	**Platelets**	130 - 400		1000/mcL
115S	**Albumin**	3.8 – 5.2		g/dL
111	**ALT/GPT**	7 - 52		U/L
110	**AST/GOT**	13 - 39		U/L
101	**BUN**	6 - 19		mg/dL
106	**Bicarbonate**	22 - 29		mEq/L
105	**Chloride**	96 – 108		mEq/L
118	**Cholesterol**	0 - 199		mg/dL
102	**Creatinine**	0.4 - 1.1	F	mg/dL
		0.5 - 1.2	M	mg/dL
136	**Creatinine Kinase**	30-223		U/L
116	**Glucose, Serum**	70 - 105		mg/dL
112	**LDH**	118 – 273		U\L
103	**Potassium, Serum**	3.5 - 5.1		mEq/L
104	**Sodium**	136 - 145		mEq/L
117	**Uric Acid**	2.4 - 5.7	F	mg/dL
		3.4 – 7.0	M	mg/dL
114U	**Urine Protein**	0.0 – 12.0		mg/dL
102U	**Urine Creatinine**	**		mg/dL
174	**Urine Protein/Creat Ratio**	<0.2		gm/gm
320	**Urine HCG**	Negative		**
	HIV 1 and 2	Non-reactive		
	Serum C3 (Performed at Reference Lab)	90 - 180		mg/dL

CENTERS FOR MEDICARE & MEDICAID SERVICES

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS

CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS

SPECTRA EAST INC
8 KING ROAD
ROCKLEIGH, NJ 07647

CLIA ID NUMBER
31D0961672

EFFECTIVE DATE
08/03/2011

LABORATORY DIRECTOR
MASSOUD S KASHANI MD

EXPIRATION DATE
08/02/2013

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

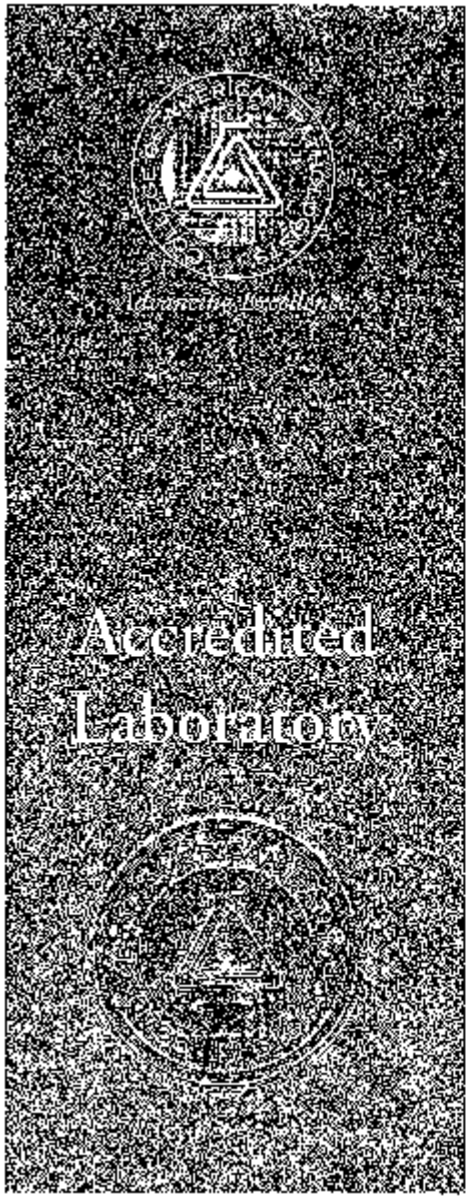
Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations

29 certs2_070911

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective date:

LAB CERTIFICATION (CODE)	EFFECTIVE DATE	LAB CERTIFICATION (CODE)	EFFECTIVE DATE
BACTERIOLOGY (110)	09/16/1999		
MYCOLOGY (120)	11/01/1999		
SYPHILIS SEROLOGY (210)	11/07/2001		
GENERAL IMMUNOLOGY (220)	11/07/2001		
ROUTINE CHEMISTRY (310)	08/03/1999		
URINALYSIS (320)	11/08/2001		
ENDOCRINOLOGY (330)	11/07/2001		
TOXICOLOGY (340)	11/07/2001		
HEMATOLOGY (400)	08/03/1999		
ABO & RH GROUP (510)	11/08/2001		

FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.HHS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.



The College of American Pathologists

certifies that the laboratory named below

Spectra East, Inc.
Laboratory
Rockleigh, New Jersey
Massoud Kashani, MD

LAP Number: 1204501
AO-ID: 1177386
CLIA Number: 31D0961672

has met all applicable standards for accreditation and is hereby fully accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur prior to February 10, 2012 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Frank R Rudy
Chair, Commission on Laboratory Accreditation

Steven H Bauer MD FCAP
President, College of American Pathologists

11. PATHOLOGY SECTION

In order to confirm participant eligibility for the FONT trial, a biopsy review will be done by the FONT Pathologist, Charles Jennette, MD.

Renal biopsy
The following materials should be sent to the FONT Pathologist:

- Representative light microscopy slides containing a minimum of 1 glomerulus demonstrating segmental sclerosis on light microscopy will be required to confirm the diagnosis. A minimum of one H & E and one PAS slide or unstained slide is required. An H&E optimal shipment will include one of each:
  A. 1 Hematoxylin & eosin (H&E) slide
  B. 1 Periodic acid-Schiff (PAS) slide
  C. 1 Silver stain slide
  D. 1 unstained slide if possible

- A copy of the immunofluorescence and electron microscopy reports (describing the staining pattern and appearance of at least 1 glomerulus)

- Representative photomicrographs (1-5 per participant) of the electron microscopy containing at least 1 glomerulus and demonstrating the FSGS lesion)

If electron microscopy cannot be performed at a participating site, then arrangements can be made by the FONT pathologist to process and review electron microscopy from an existing specimen prior to randomization. The FONT Pathologist will store these materials until completion of the study.

Renal histopathological slides and photographs should be sent by courier and Labeled:

FONT II RESEARCH STUDY

Attention: Dr. J. Charles Jennette
University of North Carolina
Department of Patholgoy
409b Brinkhous-Bullitt, CB # 7525
Chapel Hill, NC 27599-7525
TEL: 919-966-2421

The FONT Pathologist will review all biopsy specimens within 5 business days of receipt. The review will be communicated to the local site Principal Investigator. Reports of the FONT Pathologist review will be completed and returned to the Participating Site's PI and DCC. Participants with a history of biopsy confirmed FSGS from the NIH Sponsored FSGS Clinical Trial Pathology Committee will not require additional biopsy review. The FSGS Clinical Trial identification number or FSGS Clinical Trial Biopsy Report will need to be submitted to FONT for confirmation of biopsy eligibility.

12. CENTRAL PHARMACY

The Central Pharmacy (Drug Distribution Center) for the FONT II Study will be set up by Aptuit. They will be responsible for storage of all study medications and shipping them to participating sites once a patient is enrolled and randomized. All shipments will be secure and designed to insure stability of the individual medications during transport.

The contact information for the Central Pharmacy is listed in the Address Directory.

Drug Returns
The Participating Sites should use their own approved local procedures for disposal of any unused study medications. A copy of the local policy for disposal of unused medications should be placed in the site's regulatory binder.

13. REPOSITORIES

Biosamples (plasma, serum and urine) will be stored in the Repository at Fisher Bioservice, while DNA samples will be stored in the Rutgers Cell & DNA Repository. Both sites are under the auspices of the NIDDK under the direction of Rebekah Rasooly MD. Potential investigational use of samples from patients enrolled in the FONT II clinical trial will be conducted under the Ancillary Studies Protocol of the FSGS-Clinical Trial. IRB consent forms for the repositories from each participating institution must be reviewed by Dr. Rasooly at study site initiation.

Kits containing supplies for obtaining the serum, plasma, urine, and DNA specimens will be shipped to each participating site by the respective Repository prior to collection of specimens. **Please provide at least 5 working days notice to one of the Project Coordinators prior to scheduling the Baseline Visit for a new patient to enable shipping and receipt of the Biorepository sample kits in time for the initial comprehensive evaluation.**

13.1. DNA Repository

Rutgers Cell & DNA repository

Attention:	Dr. Douglas Fugman
Address:	604 Allison Avenue Piscataway, NJ 08854
Contact number:	732-445-1498

For DNA sample collection, 2 types of kits will be used. For participants ≤12 years of age, the kit will contain three 2.6 mL ACD tubes. For participants ≥13 years of age, the kit will contain two 8.5 mL ACD tubes. Two 2.6 mL tubes should be filled for participants age 6 years or less. All 3 of the 2.6 mL tubes should be filled for participants age 7-12. Both 8.5 mL tubes should be filled for age 13 or greater. **Tubes should be filled completely and must be mailed to the Rutgers Cell & DNA Repository at ambient temperature**.

Sites will be informed if there is a need to redraw a blood specimen for Cell & DNA storage because of technical problems (e.g. problems in shipping, inadequately filled tubes of blood) in establishing the immortalized cell line for DNA extraction.

Volume of Blood Samples for Rutgers Cell & DNA Repository

Type of Blood Sample	**Study Visit**	**Tubes to be utilized**	**Age(Years)**		
			Age 2-6	Age 7-12	Age ≥ 13
Whole blood for DNA (mL)	Week 0	ACD (yellow top)	5.2	7.8	17

NOTE: Patients, for whom DNA was sent to the Biorepository as part of the FSGS-Clinical Trial, will not have to send a second DNA sample when they enroll in the FONT study.

13.2. DNA Flow Sheet Sample Collection

The following page entitled, "FONT Study: Flow Sheet for Blood Sample Collection," provides instructions for collection of the DNA samples that will be sent to the Rutgers Cell & DNA Repository.

FONT STUDY

FLOW SHEET FOR BLOOD SAMPLE COLLECTION

YELLOW TOP TUBES FOR NIDDK GENETICS INITIATIVE AT RUTGERS UNIVERSITY

1) Complete and attach I.D. labels to the tubes. **DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**

2) Collect adult blood specimen in the two 8.5mL yellow top (ACD tubes). In pediatric case use 2 to 3 pediatric 2.6mL ACD tubes. For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above "Exp" in the lower right corner of theBD label is equal to or later than the current month. **Be sure to invert each tube gently 6 times to mix blood with additives and keep them at room temperature. DO NOT CENTRIFUGE THE SAMPLES GOING TO RUTGERS.**

3) Double check NIDDK ID #, verify that ID information on tube matches that on the enclosed NIDDK Phlebotomy Collection Form (Form #296).

4) Date and sign the NIDDK Phlebotomy Collection Form (Form #296).

5) Package the blood tubes in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red tape (water resistant).

6) Place the collection form (NIDDK Phlebotomy Collection Form # 296) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.

7) Use the enclosed Fed Ex shipping label to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.

8) For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650."

9) **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**, and a courier will be dispatched to pick up the samples. **Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination. DO NOT, UNDER ANY CIRCUMSTANCE, PUT MAILER IN FED-EX DROP BOX!**

10) **Notify the Rutgers University Cell and DNA Repository** that blood is being shipped and provide the Federal Express tracking number(s) _____ and NIDDK ID #(s) _____. This can be done through the Web Portal at http://rucdr.rutgers.edu/shippingblood), by fax (1-732-445-1149) or phone (1-732-445-1498).

Assembly instructions for one Polyfoam Packers Model 472 Thermosafe® Safety Mailer System

Read all instructions thoroughly before starting assembly.

Required Components:

One Model 470 Safety Mailer (body and lid)
One 2-1/2" x 9" pre-cut section of absorbent material
One roll waterproof tape
One press-lock plastic bag
One corrugated shipping carton with locking tabs

Assembly Procedure:

1) Place tubes and other diagnostic test components in body of the Safety Mailer, as usual.

2) Tear off one section of absorbent material along the perforations (Fig. 1) and place it so it exactly covers the cavity of the Safety Mailer, including all diagnostic test components (Fig. 2).

3) Place the lid of the Safety Mailer over the body and absorbent material (Fig. 2), and press down firmly until the sides of the lid meet the sides of the body.
NOTE: If absorbent material is pinched between the lid and the body, the lid will not close properly. In this case, reposition absorbent material and then refit the Safety Mailer lid.

4) Cut two 18" long pieces of red, waterproof tape. Peel the backing from one piece of tape and begin sealing the Safety Mailer lid to the body (Fig. 3). Then peel the backing from the second piece of tape and continue sealing the mailer, overlapping the first piece of tape about two inches on both ends.

5) Place the sealed Safety Mailer into the press-lock plastic bag. **DO NOT SEAL THE BAG YET** (air trapped in the sealed bag will prevent it from fitting into the corrugated shipping carton).

6) Slide the Safety Mailer and open press-lock bag into the corrugated carton (Fig. 4). Then seal the press-lock bag, close the carton using the locking tabs, and place sealing tape (not included) over them.

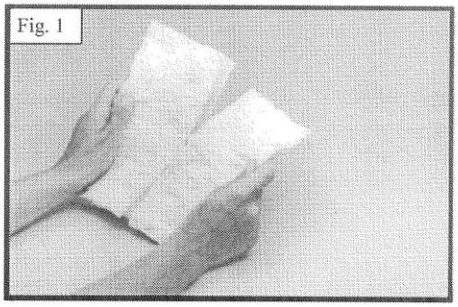


Fig. 1

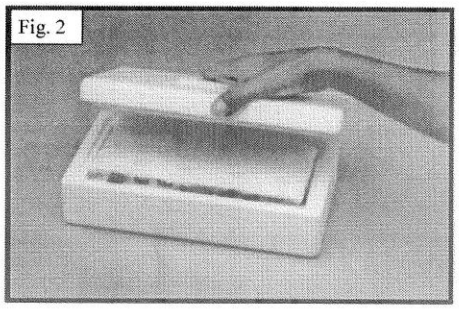


Fig. 2

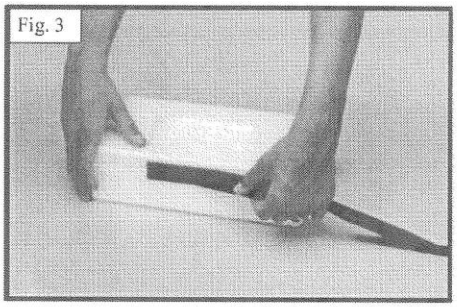


Fig. 3

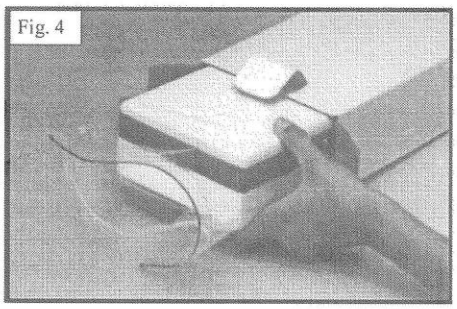


Fig. 4

POLYFOAM Packers
Division of Tuscarora Incorporated
Part of SCA Global Packaging

2320 Foster Ave, Wheeling, IL 60090-6572
800-323-7442 • 847-632-9600 • FAX 847-398-0653
www.polyfoam.com

LIT 127-08/02

13.3. Biosample Repository

NIDDK Biosample Repository at Fisher Bioservice
Attention Heather Higgins
20301 Century Blvd.
Bldg. 6-Suite 400
Germantown, MD 20874
Email: NIDDKRepository@thermofisher.com
Phone: (240) 686-4702 (Rich)
Phone: (240) 686-4703 (Heather)
Fax: (301) 515-4049

Volume of Blood Samples for Fisher Biosamples Repository

Type of Blood Sample	**Study Visit**	**Tubes to be utilized**	**Age(Years)**		
			Age 2-6	Age 7-12	Age ≥ 13
Serum (mL)	Weeks 0, 26	SST (yellow)	4	8	16
Plasma (mL)	Weeks 0, 26	PST (light green)	4.5	9	18

The urine samples for the Biosample Repository at Fisher Bioservice will be obtained from fresh urine collections at the clinical visits, and are to be a minimum of 10 mL, but up to 90 mL will be shipped if provided by the participant.

Below is a sample (template) consent for the biorepository which contains approved language for the both repositories.

13.3.1. Fisher Biosample Repository Procedure Instructions

1. Complete and attach the participant I.D. labels provided by the DCC to the blood tubes and the urine container. Use the labels provided and place them lengthwise on the tubes. Be careful not to cover up the ID when they are wrapped around the tubes. DO NOT write the participant's name or any other personal identification information (e.g. SS#, DOB) on the tubes.

2. For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above "Exp" in the lower right corner of the BD label is equal to or later than the current month.

3. Collect the specimen in the appropriate container.

4. Follow the appropriate order of draw for blood collection in accordance with the FSGS protocol. Specifically, collect the blood specimen in the SST serum separator (gold top) tube after obtaining the blood specimens for the trial protocol (to be shipped to Spectra) and before the draw for the PST tubes.

5. After filling, invert each SST tube gently at least 5 times and the PST tube 8-10 times to mix the blood with the additives. Let the SST tubes stand in a rack at room temperature for at least 30 minutes or until the blood is separated, but not longer than 60 minutes prior to centrifuging (the PST tubes can be centrifuged immediately). Centrifuge the PST and SST tubes for at least 10 minutes at 1300 g. (Blood containing anti-coagulants such as heparin

or warfarin may take longer to clot in SSTs.) Then move the tubes to the refrigerator until the shipper is ready to go.

6. For urine collection, after the container is filled according to the laboratory procedure, tighten the cap on the container. Move the container to a refrigerator until the shipper is ready to go.

7. Double check the subject ID, and verify that ID information on the container matches that on the NIDDK Specimen Shipment Form # 295.

8. Date and identify person completing the NIDDK Biological Specimen Repository Mailing Form (Form # 295). Make a copy of each form; keep the copy and send the original with the shipment.

9. Prepare shipments for FedEx pickup on Monday through Thursday. *No Friday shipments, please.* The facility is not scheduled to be open on Saturday and Sunday when the package would be delivered. If there must be an exception, please coordinate with the Biosample Repository before close of business on Thursday.

10. Assemble the package according to the instructions for the refrigerated shipment.

11. Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number (in Section 7 - Payment) of the pre-printed FedEx Air bill, and your pickup address. FedEx will dispatch a courier to pick up the package.
12. Notify Rich Frome or Heather Higgins at the NIDDK Biosample Repository by email or fax when you have scheduled the pickup and provide them the Federal Express tracking number(s). Use the contact information in the FSGS Address Directory.

13.3.2. Assembling the FSGS Refrigerated Laboratory Shipper

1. Insert each type of Vacutainer into a separate bubble wrap pouch. Verify that the lid on the urine container is secured tightly.
2. Place the pouches and urine container, with a white absorbent strip, each inside a leak proof, zip-lock bag. Squeeze out the air and seal the bags.
3. Place a frozen ice pack in the bottom of the foam cooler. Put a piece of bubble wrap on top of the ice pack to separate it from the zip-lock bags.
4. Place the zip-lock bags containing the Vacutainers and urine specimen on top of the bubble wrap. Make sure the urine container is in an upright position. If necessary, add additional packing to prevent contents from shifting.
5. Place the lid on the foam cooler. Place the completed shipping document (Mailing Form #295) on top of the cooler.
6. Close and tape the outer cardboard box.
7. Stick the label "UN3373 DIAGNOSTIC SPECIMENS" on the top of the

box in the upper left corner.

8. Place the repository address label on the top of the box on the upper right corner.

9. Use the pre-printed Fed Ex air bill to ship the specimens to the repository. Fill in the date, your return address, and phone number in Section 1. Leave "Sender's FedEx Account Number" blank.

11. In Section 6, check the "No" block indicating no dangerous goods are contained in the shipment.

12. In Section 7, enter "1" under "Total Packages", and a total weight of 2 lbs. Follow the peel and stick instructions on the back of the air bill. Attach the airbill to the side of the box, opposite "Rush!! Perishable Shipment".

13. **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**. Give them the account number in Section 7, Payment, of the pre-printed FedEx Air bill, and your pickup address. FedEx will dispatch a courier to pick up your package.

Revision Date: 14 Dec 2004

13.4. Repository Consent Template

TITLE: Novel Therapies for Resistant Focal Segmental Glomerulosclerosis (FSGS), A Phase II Clinical Trial (FONT II)

STORED MATERIALS/NIDDK CENTRAL REPOSITORIES

INVESTIGATORS: _____

SPONSOR: National Institutes of Health- National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)

OTHER KEY PARTICIPANTS: National Institutes of Health Biosample Repository at Fisher Bioservices, National Institutes of Health Genetics Initiative at Rutgers University Cell and DNA Repository, Cleveland Clinic Foundation

NOTE: This consent form is written from the point of view of a research subject. If consent will be obtained from the parent or legal guardian or a minor, the words "you" and "your" should be read as "your child".

INTRODUCTION

You have already been asked to participate in the research study entitled, "Novel Therapies for Resistant Focal Segmental Glomerulosclerosis, A Phase II Clinical Trial.

You are now being asked to participate in a sub-study for the collection, use and storage of blood and urine samples for future research. If you choose to participate in this sub-study, blood and urine specimens will be collected and stored at NIDDK Central Repositories for future research. You do not have to agree to participate in this sub-study in order to enroll in the main research study.

Before you decide whether or not to volunteer for this study, you must understand the purpose of the research, any risks to you and what is expected of you. This process is called informed consent.

Before you give consent to be a volunteer, it is important that you read the following explanation of the proposed procedures. This consent for research describes the procedures, the drug involved, the risks and benefits, and the role you has as a participant in this research study. Please read this information carefully and do not hesitate to ask the doctor any questions about this form or about the study. You must sign this informed consent before you enter the study. Participation in this study is entirely voluntary.

You may choose not to have any sample stored for future research and still participate in the "Novel Therapy for Resistant FSGS, Phase II Clinical Trial"

PURPOSE OF THE RESEARCH STUDY

The purpose of this collection is to make samples available for use in research for the study of focal segmental glomerulosclerosis (FSGS) in an effort to advance our understanding of the pathobiology of this condition, including but not limited to its diagnosis, response to therapy, prognosis and risk of complications of therapy.

We are asking you to provide samples of blood and urine, which will be sent to the NIDDK Central Repositories, a research resource supported by the National Institutes of Health. The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. These samples may be used for genetic tests, looking for causes of FSGS or to increase our understanding of why some patients respond the therapy and others do not. However, we may also use your samples to study other unrelated diseases in the future.

EXPECTED DURATION OF PARTICIPATION

For the duration of the "Novel Therapy for Resistant FSGS" trial and for a period of two to four years following the completion of the main research trial.

DESCRIPTION OF PROCEDURES

Samples will be taken at the same time as routine tests, thus there will be no extra sticks to obtain blood. There will be no additional visits to obtain blood or urine specimens. Upon collection, urine, serum and plasma specimens will be shipped to the National Institutes of Health Biosample Repository at Fisher Bioservices in Rockville, Maryland at study weeks 0 and 26. In addition, whole blood specimens for DNA will be shipped to the National Institutes of Health Genetics Initiative at Rutgers University Cell and DNA Repository in New Jersey at study week 0. If you participate in the FSGS clinical trial and you provide a DNA sample at the time of enrollment, then this will not be repeated as part of the "Novel Therapies for Resistant FSGS" trial.

Your DNA (genes) or cells that can be used to make DNA will be stored at the repository indefinitely for research purposes. Please initial one of the following options telling us how your DNA sample may be used:

____My samples may be used for any scientific purposes involving this or any other projects. Do not contact my again for permission.

____My samples may be used for this project only. If my samples could be used for another project, contact me to ask my permission. *Please note that this option only applies during the course of the study. After the study is finished all identifying information will be destroyed.*

____My samples may be used for this project only. Do not use them for any other project. Do not contact me again for permission.

If you withdraw from the study, you may ask that your stored blood and urine specimens be removed form the bank or you may leave current specimens in the bank to be studies at a future time.

If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the study. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the study ends, you will not be able to withdraw your sample because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely.

DISCOMFORTS AND RISKS

When blood is withdrawn from the vein there may be some temporary discomfort, local bruising, infection or blockage of the vein. Precautions will be taken to minimize these risks.

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to the researchers and the organizations doing this study, but you will not receive any financial benefits.

BENEFITS

You will not receive any direct benefit or payment for participating, but your sample may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your sample. It is possible that data resulting from use of your sample may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

ALTERNATIVES

You do not have to participate in this research sub-study in order to enroll in the main study or receive standard care.

COSTS/COMPENSATIONS

The doctor's visits and laboratory tests related to this study will be provided at not cost to you. Neither your insurance company nor you will be charged for the services provided in the normal course of the conduct of this research study. You will not receive any payment for participation in this research study.

COMPENSATION FOR INJURY

If you are hurt from being in the study, you will receive medical care and treatment as needed from the North Shore-Long Island Jewish Health System. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance and/or other forms of medical coverage. No money will be given to you.

VOLUNTARY PARTICIPATION

Taking part in this study is voluntary. You have the right to choose not to take part in this sub-study. If you do not take part in this study your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled. If you choose to take part in this study, you have the right to stop at any time. You will be told of any new findings from this or other studies that may affect your health, welfare, and willingness to stay in the study.

If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the "Novel Therapy for Resistant FSGS" trial. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the "Novel Therapy for Resistant FSGS" study ends, you will not be able to withdraw your sample

because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely or be used for other research.

CONFIDENTIALITY

If you agree to participate in this study, we will collect health information that identifies you. Your blood and urine collected for this study will be identified by a code number. This code number will be able to be identified with you, but the list identifying your name and code number will be kept separate from the specimens.

We may also collect information from your medical record. We will only collect information that is needed for the research. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization.

Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside the North Shore-Long Island Jewish Health System, except as detailed below.

Investigators will share the results of your study tests and procedures with:

- NIDDK, the study sponsor and/or its agents,
- Clinical staff not involved in the study who may be involved in your treatment
- Governmental agencies in the United States and other countries where the study medicine may be considered for approval
- Collaborators at the Cleveland Clinic Foundation
- Rutgers University Cell and DNA Repository
- NIH Biosample Repository (Fisher Bioservices)

In addition, your records may be reviewed in order to meet federal or state research regulations. Reviewers may include representatives from the Food and Drug Administration, representatives from the NIDDK and the NS-LIJHS Institutional Review Board (IRB – the committee that reviews research at this institution), to make sure that the research was conducted properly. If your research record is reviewed by any of these groups, they may also need to see your entire medical record.

Please be aware that once private information is disclosed, it is subject to re-disclosure by the recipient and can no longer be considered protected.

If you change your mind about participating in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Dr. _____

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

The information that is collected for research will be analyzed for many years and it is not possible to know how long this analysis and follow-up will take. Therefore, by signing this form, you are allowing access to this information indefinitely. Data from this study may be used in medical publications or presentations. The information will be de-identified so that individual subjects cannot be recognized and the information will no longer be considered Protected Health Information (PHI).

If the study reveals public health concerns or evidence of child abuse, it will be shared with the appropriate authorities.

CONTACT FOR QUESTIONS

If you have any questions about the research, or in the event that medical assistance is required, you are instructed to call Dr. _____

SUMMATION/SIGNATURES

You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. Furthermore, you have been assured that a member of the research team will answer any future questions that may arise. You voluntarily agree to allow your child to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your or your child's legal rights. **A copy of this signed consent form will be given to you.**

_____
Subject's Printed Name

_____ __ __ /__ __ /__ __ __ __
Subject's Signature (for subjects age 18 or over) Date

_____
Parent's printed name

_____ __ __ /__ __ /__ __ __ __ __ __ : __ __
Parent's signature Date Time

_____ __ __ /__ __ /__ __ __ __ __ __ : __ __
Witness' Signature Date Time

Witness Identification: _____

PHYSICIAN'S STATEMENT

In addition to advising the above (patient/subject) of other forms of treatment and Therapy, which is appropriate, I have offered an opportunity for further explanation of the risks and discomforts, which are, or may be associated with this study and to answer any further questions relating to it

_____ __ __ /__ __ /__ __ __ __ __ __ : __ __
Physician's signature Date Time

14. FORMS COMPLETION INSTRUCTION

General Instructions

All forms should be completed in black ink. The name of the person filling out the form should be provided in space available on each form. If an error is made in completing an entry, a line should be drawn through the incorrect information, the correct data added, and the revised entry should be initialed and dated by the person completing the form. **DO NOT ERASE or OBSCURE INCORRECT ENTRIES**.

Patient identification number

The assigned ID number will have three parts; F2-123-001. The first 2 digits "F2" will be a universal prefix indicating the FONT II clinical trial. The next 6 digits will be composed of the 3 digit number assigned to each site by the DCC followed by a consecutive number for each patient enrolled at the site beginning with 001.

The patient ID number should be entered in all forms and written on all labels affixed to all subject samples.

14.1. Database and Data Entry

After completion of the Case Report Forms, they should be faxed to the Core Coordinators at University of Michigan (Ann Arbor, MI), or NYU Medical Center.

The FAX number for University of Michigan is 734-232-2353

The FAX number for NYU is 212-263-4053.

The information will be entered into the database.

Database: The database for the FONT II Study, which will reside at the Cleveland Clinic, will be in Oracle Clinical, an American National Standards Institute (ANSI) compliant relational database management system.

The server for the study's Oracle Clinical database is behind a firewall that protects it from the rest of the Internet, and behind another firewall that separates it from the rest of the Cleveland Clinic's computer network. Clinical site personnel will be provided specific study accounts and passwords to be able to get into the study's Oracle Clinical database, and these passwords will only allow sites to see their own patients' data. When personnel leave a site, their accounts and passwords are inactivated.

Data Management:

All clinical and laboratory data collected at each visit will be recorded on the case report form and entered into the Oracle Clinical database maintained by the DCC at the Cleveland Clinic Foundation. The only exception will be the Patient Reported Outcome Management Information System (PROMIS) survey which will be completed by the study subject on a secure PROMIS internet based site managed through the NIH sponsored PROMIS Assessment Center, Northwestern University, under the direction of Nan Rothrock, Northwestern University. The survey will be administered under a PROMIS specific subject identifier. This PROMIS identifier will be linked to the FONT II study ID number at the FONT II DCC. Data in the PROMIS

Assessment Center data management system will be batch transferred to the FONT II DCC using a secure data file.

15. APPENDICES

15.1. Adalimumab (Humira®) Patient Administration Log

15.2. Adalimumab (Humira®) Instruction Sheet for Administration of Medication

15.3. Summary of Sample ID Numbering System for NIDDK Biosample and Rutgers Cell & DNA Repositories

15.4. American Cancer Society (ACS) 2003 guidelines

15.5. Pediatric BP Charts

15.6. GFR Formulas for Adults and Children

15.7 Giving a Subcutaneous Injection

15.8 PROMIS Operations Manual

15.1. Participant Administration Log

Adalimumab (Humira®)

Participant Administration Log

Regimen:_____

Date	Day	Time	Dose	Site of Injection

15.2. Instruction Sheet for Administration of Adalimumab

INSTRUCTION SHEET FOR ADMINISTRATION OF ADALIMUMAB (HUMIRA®)

1. Obtain weight and height of the patient.

2. Calculate the body surface area.

3. Calculate the actual treatment dose based on therapeutic dose of 24 mg/m^2

4. Withdraw contents of drug vial (40 mg/0.8 mL) into syringe:
   a. For patients whose body surface area is ≥1.67 m^2, withdraw complete contents of vial.
   b. For patients whose body surface area is <1.67 m^2, withdraw the required treatment dose into a 1 mL syringe with 0.01 mL markings.

5. Record the lot number and vial number on the log sheet provided

6. The injection site can be pre-treated with EMLA crème or steroid inhaler spray to lessen the pain of the injection.

7. Clean the area of skin where the drug will be administered with an alcohol wipe.

8. Inject the drug subcutaneously.

9. Make a notation of the injection site so that it can be rotated over the 16-week treatment period.

10. Do NOT reuse the vial in children who receive less than the full dose.

11. Discard all open vials and used needles in a sharps container.

15.3. ID Numbering System for Repositories

ID NUMBERING SYSTEMS FOR SAMPLES COLLECTED DURING FONT STUDY FOR STORAGE IN NIDDK BIOSAMPLE AND RUTGERS CELL & DNA REPOSITORY

Patients will be entered into the FONT II trial either as completely new patients or after prior experience in the FSGS Clinical Trial with potential previous collection and shipment of DNA samples to the Rutgers Biorepository.

Methods to assign ID number:

(1) After confirmation of eligibility and signing informed consent, all participants enrolled in FONT II will be given a **new** ID number by the Data Coordinating Center (DCC).

(2) The assigned ID number will have three parts – F2-123-001

(3) The first 2 digits "F2" will be a universal prefix indicating the FONT II clinical trial.

(4) The next 6 digits will be composed of the 3 digit number assigned to each site by the DCC (see FONTII Address Directory for site assignments) followed by a consecutive number for each patient enrolled at the site beginning with 001.

(5) Rutgers, the DNA Repository, will use an extended ID number in the event of sample collection/labeling errors; the extension is the suffix FT (i.e., F2-123001-FT).

(6) When a patient who was a Treatment Failure in the FSGS-CT study is enrolled in FONT II and is assigned a new FONT II ID number, the DCC will be informed so that a linkage will be made in the FSGS-CT database between the FSGS ID number and the FONT II ID number. This will enable proper pooling of all biosamples collected in an individual participant during the course of his/her involvement in the spectrum of clinical trials in FSGS.

(7) For the Rutgers Cell & DNA Repository, the assignment of two numbers will not be a concern, because DNA will be collected only once per participant – collected either when randomized in the FSGS-CT Study or when enrolled/randomized in the FONT II Clinical Trial (having no prior involvement in the FSGS-CT Study).

15.4. ACS Guidelines

American Cancer Society (ACS) 2003 guidelines

Full publication available at *CA Cancer J Clin* 2003;53:27-43

http://caonline.amcancersoc.org/cgi/content/full/53/1/27

15.5. Pediatric BP Charts

15.5.1. Pediatric BP Chart for Boys

Table 1

BLOOD PRESSURE LEVELS FOR THE 90TH AND 95TH PERCENTILES OF BLOOD PRESSURE FOR BOYS AGE 1 TO 17 YEARS BY PERCENTILES OF HEIGHT

Age	Height Percentiles* → / BP† ↓	Systolic BP (mm Hg) 5%	10%	25%	50%	75%	90%	95%	Diastolic BP (mm Hg) 5%	10%	25%	50%	75%	90%	95%
1	90th	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	90th	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	90th	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	90th	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	116	118	119	74	74	75	76	77	78	78
8	90th	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	90th	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	90th	110	112	113	115	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	90th	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	90th	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83
13	90th	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	90th	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	90th	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	90th	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	90th	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

*Height percentile determined by standard growth curves.
†Blood pressure percentile determined by a single measurement.

15.5.2. Pediatric BP Chart for Girls

BLOOD PRESSURE LEVELS FOR THE 90TH AND 95TH PERCENTILES OF BLOOD PRESSURE FOR GIRLS AGE 1 TO 17 YEARS BY PERCENTILES OF HEIGHT

Age	Height Percentiles* → / BP† ↓	Systolic BP (mm Hg) 5%	10%	25%	50%	75%	90%	95%	Diastolic BP (mm Hg) 5%	10%	25%	50%	75%	90%	95%
1	90th	97	98	99	100	102	103	104	53	53	53	54	55	56	56
	95th	101	102	103	104	105	107	107	57	57	57	58	59	60	60
2	90th	99	99	100	102	103	104	105	57	57	58	58	59	60	61
	95th	102	103	104	105	107	108	109	61	61	62	62	63	64	65
3	90th	100	100	102	103	104	105	106	61	61	61	62	63	63	64
	95th	104	104	105	107	108	109	110	65	65	65	66	67	67	68
4	90th	101	102	103	104	106	107	108	63	63	64	65	65	66	67
	95th	105	106	107	108	109	111	111	67	67	68	69	69	70	71
5	90th	103	103	104	106	107	108	109	65	66	66	67	68	68	69
	95th	107	107	108	110	111	112	113	69	70	70	71	72	72	73
6	90th	104	105	106	107	109	110	111	67	67	68	69	69	70	71
	95th	108	109	110	111	112	114	114	71	71	72	73	73	74	75
7	90th	106	107	108	109	110	112	112	69	69	69	70	71	72	72
	95th	110	110	112	113	114	115	116	73	73	73	74	75	76	76
8	90th	108	109	110	111	112	113	114	70	70	71	71	72	73	74
	95th	112	112	113	115	116	117	118	74	74	75	75	76	77	78
9	90th	110	110	112	113	114	115	116	71	72	72	73	74	74	75
	95th	114	114	115	117	118	119	120	75	76	76	77	78	78	79
10	90th	112	112	114	115	116	117	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	90th	114	114	116	117	118	119	120	74	74	75	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	79	79	80	81	81
12	90th	116	116	118	119	120	121	122	75	75	76	76	77	78	78
	95th	120	120	121	123	124	125	126	79	79	80	80	81	82	82
13	90th	118	118	119	121	122	123	124	76	76	77	78	78	79	80
	95th	121	122	123	125	126	127	128	80	80	81	82	82	83	84
14	90th	119	120	121	122	124	125	126	77	77	78	79	79	80	81
	95th	123	124	125	126	128	129	130	81	81	82	83	83	84	85
15	90th	121	121	122	124	125	126	127	78	78	79	79	80	81	82
	95th	124	125	126	128	129	130	131	82	82	83	83	84	85	86
16	90th	122	122	123	125	126	127	128	79	79	79	80	81	82	82
	95th	125	126	127	128	130	131	132	83	83	83	84	85	86	86
17	90th	122	123	124	125	126	128	128	79	79	79	80	81	82	82
	95th	126	126	127	129	130	131	132	83	83	83	84	85	86	86

*Height percentile determined by standard growth curves.
†Blood pressure percentile determined by a single measurement.

15.6. GFR Formulas for Adults and Children

GFR for adults
Cockroft-Gault Formula

This formula is used for participants of age > 18 yrs.

For men: CrCL ={ [(140-age) X W]/ (72 X SCR) }* 1.73/BSA

For women: CrCL = {0.85 X [(140-age) X W]/ (72 X SCR) }* 1.73/BSA

Where CrCL = GFR in ml/min/1.73m^2
W = body weight in kg – based on F46, Q5b
SCR = serum creatinine in mg/dL – based on R85
Age based on F10, Q3 and date of R85

The formula for BSA is:

BSA = [$W^{0.425}$ x $H^{0.725}$ X 71.84]/10,000

Where BSA = body surface are in m^2
W = weight in kg – based on F46, Q5b
H = height in cm – based on F46, Q5a

The reference is:
Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976. 16:31-41.

GFR for kids
Schwartz formula

Schwartz = (k X height in cm) / serum creatinine in mg/dL

Where k = 0.55 for children (2 – < 13) and adolescent girls (age 13 – 18)
k = 0.70 for adolescent boys (age 13-18)
Height is based on F46, Q5a
Serum Creatinine is based on R85
Age based on F10, Q3 and date of R85

The references are:
Schwartz GJ, Brion LP, Spitzer A: The use of plama creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents.
Pediatric Clinics of North America. 34(3): 571-590, 1987.

http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm

15.7. Giving a Subcutaneous Injection

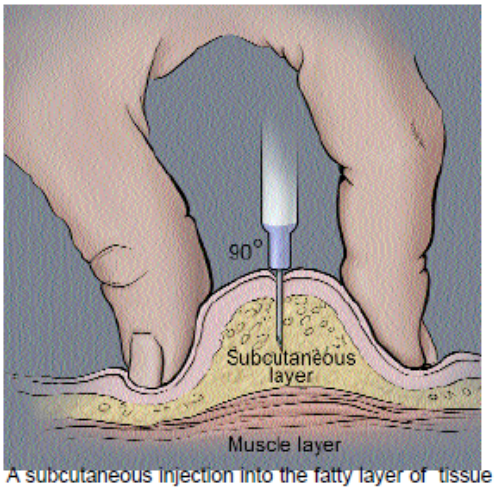
Patient Education

Clinical Center
NATIONAL INSTITUTES OF HEALTH

Giving a subcutaneous injection

What is a subcutaneous injection?

A subcutaneous injection is given in the fatty layer of tissue just under the skin.



A subcutaneous injection into the fatty layer of tissue (pinched up to give the injection) under the skin.

Why are subcutaneous injections given?

These injections are given because there is little blood flow to fatty tissue, and the injected medication is generally absorbed more slowly, sometimes over 24 hours. Some medications that can be injected subcutaneously are growth hormone, insulin, epinephrine, and other substances.

Preparing to give medication

Subcutaneous injections are not given if the skin is burned, hardened,inflamed, swollen, or damaged by a previous injection.

1. Wash your hands thoroughly. This is the best way to prevent infection.
2. Assemble your equipment:

medication

- May be a multidose vial of liquid or may be a vial with powder that requires "reconstitution." Follow the manufacturer's instructions as to what and how much diluent to use. The diluent is usually saline (a mixture of salt water) or sterile water.

syringe and needle:

Depending on the amount of medication to be given and the size of the child or adult:

- 0.5 cc,1.0 cc, or 2 cc with 27-gauge needle (5/8 of an inch long)
- 3 cc luer lock syringe—used when solution is more than 1 cc
- 25-gauge needle (5/8 of an inch long or 27-gauge needle (5/8 of an inch long)
- 0.3 mL insulin syringes with 28-gauge needles (1/2 inch long) are available for those who are visually impaired or for those who need very small doses of medication.
- medication log
- container for syringe disposal
- sterile 2 x 2 -inch gauze pad
- alcohol pads

Drawing up medication

1. Check the label for correct medication.
2. Remove the soft metal or plastic cap protecting the rubber stopper of the vial.

3. If the medication vial can be used for more than one dose, record the date and time on the label.

4. Clean the exposed rubber stopper using an alcohol swab.

5. Remove the syringe from the plastic or paper cover. If necessary, attach the needle securely.

6. Pull back and forth on the plunger by grasping the plunger handle. Grasping the handle end will pre-vent contamination of the plunger shaft (which is sterile) and help check for easy movement.

7. With the needle capped, pull back the plunger, filling the syringe with air equal to the amount of medication to be administered.

8. Remove the cap covering the needle and set it on its side to prevent contamination. Be careful not to touch the needle. The inside of the cap and needle is sterile, and the needle will be covered again with this cap.

9. With the vial in an up-right position, push the needle through the cleansed rubber stopper on the vial. Push the needle in at a 90 degree angle, being careful not to bend the needle.

10. Inject the air in the syringe into the vial. Air is injected into a multi-dose vial to prevent a vacuum from forming. If too little or no air is injected, withdrawing the medication may be difficult. If too much air is injected, the plunger may be forced out of the barrel causing the medication to spill.

11. Turn the vial upside down, with the needle remaining in the vial. The needle will be pointing upward.

12. Make sure that the tip of the needle is completely covered by the medication. This will make it easier to withdraw the solution (and not air).

13. Pull back on the plunger to fill the syringe with the correct dose of medication.

14. Keep the vial upside down, with the needle in the vial pointed upward. Tap the syringe, or "flick" it with your fingertips. This helps move bubbles to the top of the syringe.

15. Once the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.

    Or, you may push all the medication solution back into the vial, withdraw again slowly, and repeat steps 14 and 15.

    Note: It is important to eliminate large air bubbles because they take up space needed for the medication, and they may cause pain or discomfort when injected.

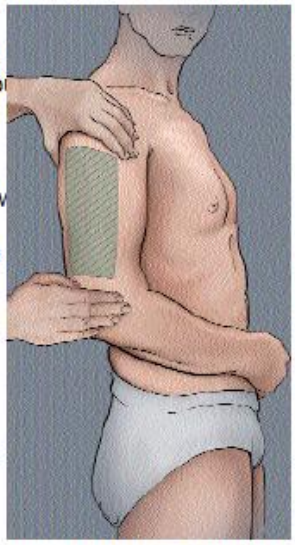
16. After removing the bubbles, check the dose of medication in the syringe to be sure you have drawn up the correct amount.

17. After the medication is correctly drawn up, carefully replace the needle cap to prevent contamination.

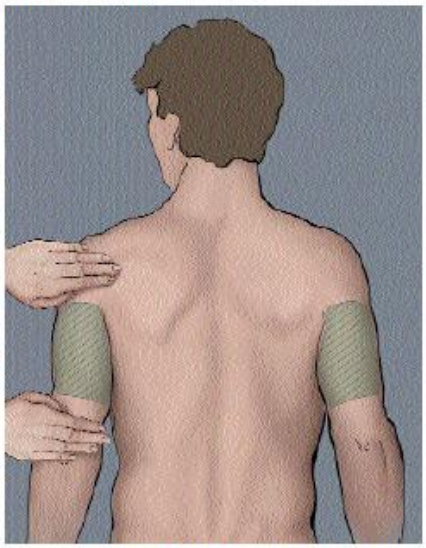
Locating injection sites

Subcutaneous injections can be given in the arms, legs, or abdomen. Your nurse or doctor will help you select the best sites to administer your medication.

1. To locate injection sites on the arms, fold one arm across the chest. Place yo hand on the shoulder and draw an imaginary line below your hand. Place another hand on the elbow Draw an imaginary line down the outer side of the arm and down the center front of the arm, starting at the elbow. The area inside these imaginary lines is where injections are given. (If you are injecting yourself, imagine the hand placement.)

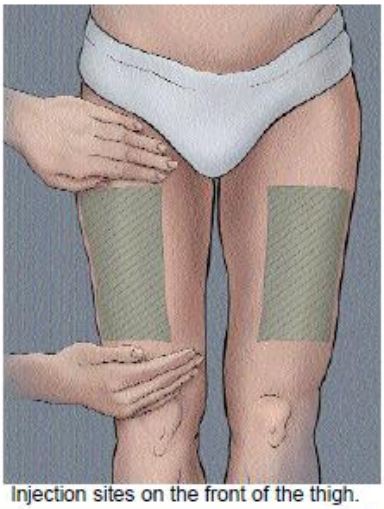


Injection sites on the side of the arm.



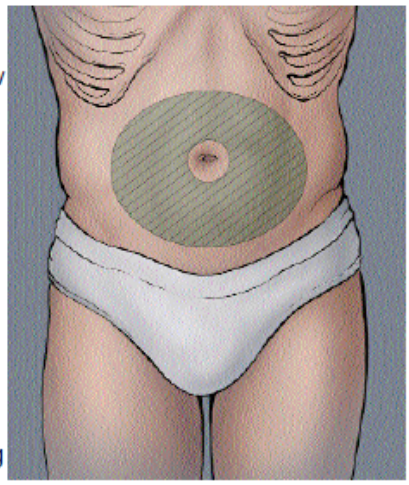
Injection sites on the back of the arm.

2. To locate injection sites on the thighs, sit down, place your hand above the knee, and draw an imaginary line above it. Place your hand at the uppermost part of the thigh and draw an imaginary line below your hand. Draw an imaginary line down the outer side of the leg and down the center front of the leg. The area within these imaginary lines is where injections may be given.



Injection sites on the front of the thigh.

3. To locate injection sites on the abdomen, place your hands on the lower ribs and draw an imaginary line below them. Use this area below your hands for injections, as far around as you can pinch up fatty tissue. Do not use a 1-inch area around the navel.



Injection sites on the abdomen

Rotating injection sites

It is extremely important to rotate sites to keep the skin healthy. Repeated injections in the same spot can cause scarring and hardening of fatty tissue that will interfere with absorption of medication. Each injection should be about 1 inch apart. Each injection site can be measured with a small dot Band-Aid, providing the patient is not sensitive to the adhesive. Start injections at the highest point of the area and continue down toward the point farthest away from the body (for example, upper arm down toward elbow). It is preferable to use all sites available on one body part (arm or leg) before moving on to another. However, some parents find that children are more accepting of injections if they are rotated from one body part to another (arm, leg, arm, leg). Avoid giving injections in areas that are burned, reddened, inflamed, swollen, or damaged by prior injections.

Preparing the skin

Since the skin is the body's first defense against infection, it must be cleansed thoroughly before a needle is inserted.

Cleanse the skin in a circular motion using an alcohol swab. Begin at the center of the site and progress outward. This motion moves bacteria away from the injection site. Allow the alcohol to dry completely either by air or by using sterile 2x2 gauze.

Giving the injection

1. Take the cover off the needle. Be careful not to contaminate the needle. Place the cover on its side.
2. Hold the syringe in one hand like pencil or a dart.
3. Grasp the skin between the thumb and index finger.
4. Quickly thrust the needle all the way into the skin. Do not "push" the needle into the skin slowly or thrust the needle into the skin with great force. Do not

press down on the top of the plunger while piercing the skin.

5. Insert the needle at a 90-degree (right) angle. This angle is important to ensure that the medications will be injected into the fatty tissue. However, for small children, and persons with little subcutaneous fat on thin skin, you may be taught to use a 45-degree angle.
6. After the needle is completely inserted into the skin, release the skin that you are grasping.
7. With your free hand, grasp the syringe near its base to stabilize it.
8. Gently pull back on the plunger and check for the appearance of blood in the syringe.

   Note: Not all injections require you to check for blood. Before you are discharged, your nurse will let you know if you need to do this. If you do not, then skip down to step 10.
9. If blood appears, remove the needle, discard it, and start over. Blood in the syringe means that you may be in a blood vessel, so discard the syringe with medication.

   Do not inject medication into a blood vessel: the medication is absorbed too rapidly if it is injected there.
10. If no blood appears, inject the medication at a slow, steady rate. Medication should be injected within 5 seconds.
11. As the needle is pulled out of the skin, gently press a 2x2 gauze onto the needle insertion site. Pressure over the site whileremoving the needle prevents skin from pulling back, which may be uncomfortable. The gauze also helps seal the punctured tissue and prevents leakage.
12. If instructed to do so, press or rub the site for a few seconds.
13. It is not serious if you notice blood at the site after the needle is removed. You may have nicked a surface blood vessel when you injected, and blood is following the needle track out to the surface. Simply press the site with a 2 x 2 gauze pad. Also, a small amount of clear fluid may appear at the site. This may be medication that isfollowing the needle track to the surface. Again, apply pressure using a 2 x 2 gauze pad.

Safe needle disposal

Please refer to the Clinical Center pamphlet "Handling Sharp Objects Safely at Home."

Medication
Dose
Schedule
Primary Nurse Phone
Physician Phone

National Institutes of Health Clinical Center
Bethesda, MD 20892
Questions about the Clinical Center?
http://www.cc.nih.gov/comments.shtml
2002

PROMIS Validation in FONT II Clinical Trial

OPERATIONS MANUAL

Principal Investigator:
Debbie Gipson, MD

June 21, 2010
Version 4

PURPOSE

This protocol describes procedures designed to meet the following objectives: to evaluate the change in patient-reported outcome domains for each arm of a randomized clinical trial of treatments for focal segmental glomerulosclerosis (FONT II study) and compare the change in PROMIS domain scores to changes in legacy instrument scores (PedsQL and SF-36) across arms of the randomized clinical trial. Data collection will take place up to 20 participating sites in the US and Canada. In total, PROMIS items will be tested in a sample of approximately 126 individuals. These PROMIS items will be administered in addition to any paper-based FONT II forms. Please note that this document covers only the PROMIS validation aspect of the FONT II study; information regarding the entire study protocol can be found in the relevant protocol manual.

DEFINITIONS

The following definitions of terms used in this document are provided to aid in the understanding of this testing protocol.

A. *Domain*: A domain is a defined aspect of health status or well-being; in this study, there are five generic domains: Physical Function, Fatigue, Pain, Emotional Distress, and Social Health.
B. *Item bank*: An item bank is a compilation of carefully calibrated questions that develop, define and quantify a common theme. The objective of this study is to test the following six item banks: Physical Function-mobility, Depressive Symptoms, Anxiety, Fatigue, Pain Interference and Peer Relationships.
C. *Legacy item*: Legacy items are those measures that are deemed by content experts in the PROMIS domains to be the most widely used, accepted, and established items with respect to content and psychometric properties within a specified domain thereby representing "gold standard" instruments.
D. *Short forms*: Participants will be administered a subset of items in a given item bank. These subsets are known as "short forms".
E. *Researcher*: The terms "researcher", "research assistant", "RA", and "clinical research nurse" will be used interchangeably throughout this document to represent any person enrolling and assessing pediatric participants.

BACKGROUND

The purpose of utilizing PROMIS items in the FONT II Clinical Trial is two-fold: to evaluate the change in patient-reported outcome domains for each arm of a randomized clinical trial of treatments for focal segmental glomerulosclerosis (FONT II study) and compare the change in PROMIS domain scores to changes in legacy instrument scores (PedsQL and SF-36) across arms of the randomized clinical trial.

PRINCIPAL INVESTIGATOR

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ASSESSMENT CENTER CONTACT

Heather Gross (T) 919-966-0894
hgross@schsr.unc.edu

(C) 412-680-5492

* Any major changes of procedure will need to be approved by the Clinic Manager. **Please work through Heather with general questions or concerns about Assessment Center only. For other study-related questions, please contact Emily Herreshoff or Suzanne Vento.**

ESSENTIAL MATERIALS FOR FIELD RESEARCHERS

In order to access Assessment Center, research assistants should ascertain that all materials and equipment are gathered and functioning prior to the start of the day's data collection.

- 1 copy of this Operations Manual (including IRB Approval Documentation)
- Laptop(s), Carrying cases, Mouse, Mouse pad, Power cord
- Extension Cord(s) and Power Strip(s)
- Internet Access (wireless or otherwise)

SURVEY EXECUTION & DATA COLLECTION

*** Do not begin the study until both an assent and consent have been signed and dated by the participant(s) and the RA. Data collected without a proper consent and assent must be deleted.**

Note: In order for survey administration to be successful, there must be consistent, uninterrupted access to the Internet.

Prior to beginning the computer assessment, the RA should (in plain view of parent and child) use an anti-bacterial wipe to sanitize the keyboard, screen, mouse and desk

area surrounding each laptop computer. Please be sure to sanitize the data collection instruments and area before each and every participant.

Overview:

The RA will follow the instructions in the FONT II protocol manual to determine if the participant is eligible to participate in the study. If eligibility criteria are met, the RA will enroll the participant following the procedure outlined in the FONT II protocol manual. Participants will then be administered the paper-based FONT II items. Once the participant has finished the paper-based items, the RA will instruct the participant to complete the computer-based PROMIS items. Based on the participant's age, the RA will guide the participant to the appropriate computer-based survey (pediatric or adult survey). The RA should reassure participants that they can stop the survey **at any time** without losing any information and can pick up where they left off following his/her appointment if needed.

If the participant is age 8-17 at the first PROMIS assessment, he/she will complete the specified PROMIS pediatric items for this assessment and all follow-up visits.

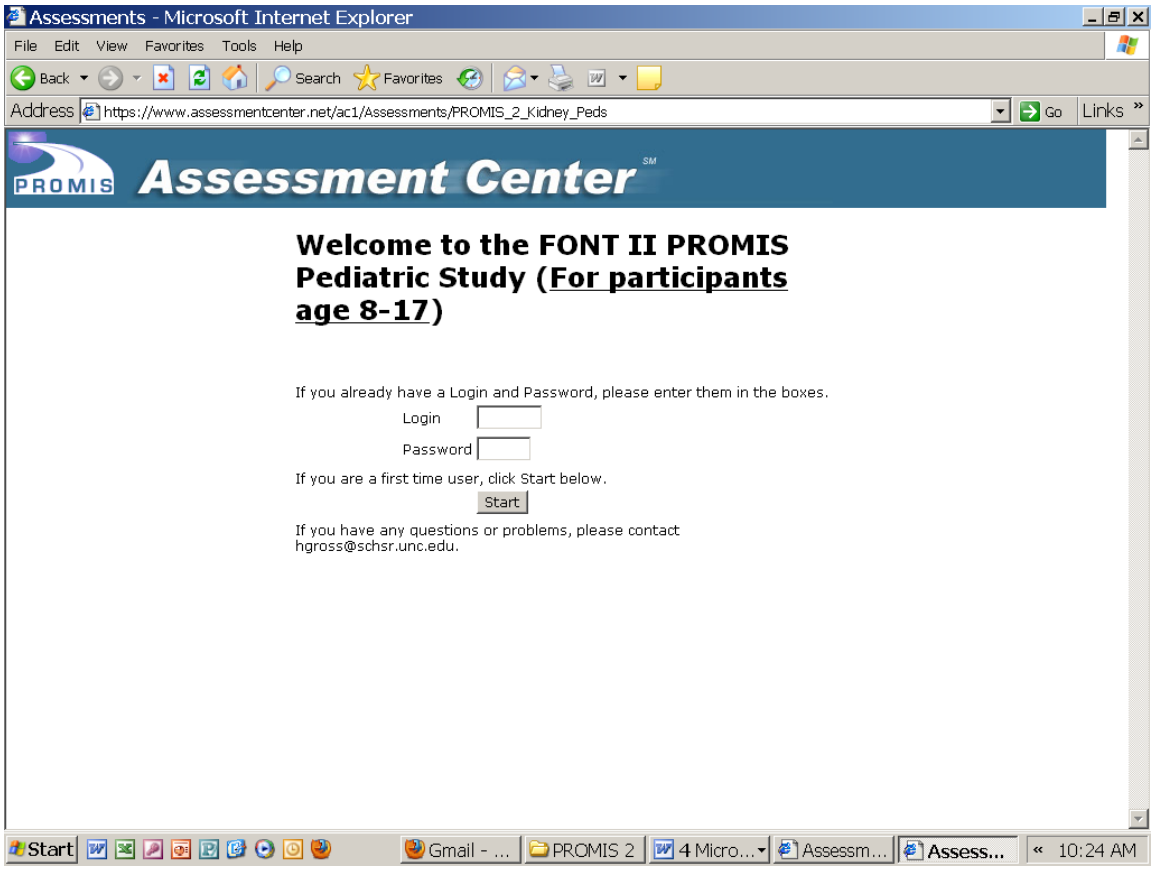
If the participant is age 18 and above, he/she will complete the specified PROMIS adult items.

The following are stepwise instructions for administering the survey:

1. **Access the appropriate study website using Internet Explorer.**
   This study utilizes two websites: one for participants age 8-17 (pediatric participants) and one for participants age 18 and above (adult participants). These websites will be used each time the RA administers a survey so it is recommended that shortcuts be placed on each laptop's desktop to facilitate navigation. All sites should be using Internet Explorer (vs. Netscape, Firefox, or other web browsers) to access the platform.

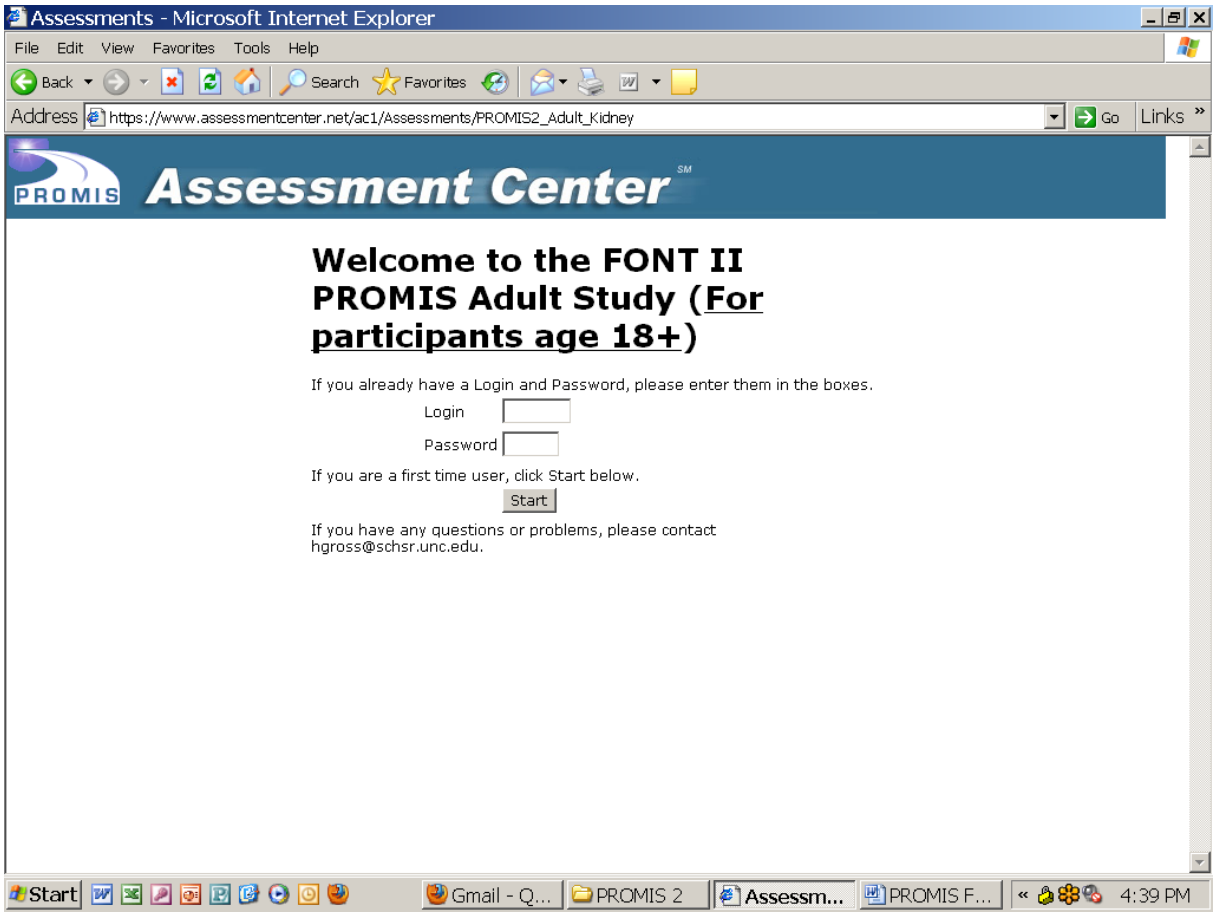
Pediatric participants (participants age 8-17):

https://www.assessmentcenter.net/ac1/Assessments/PROMIS2_Pediatric_Kidney

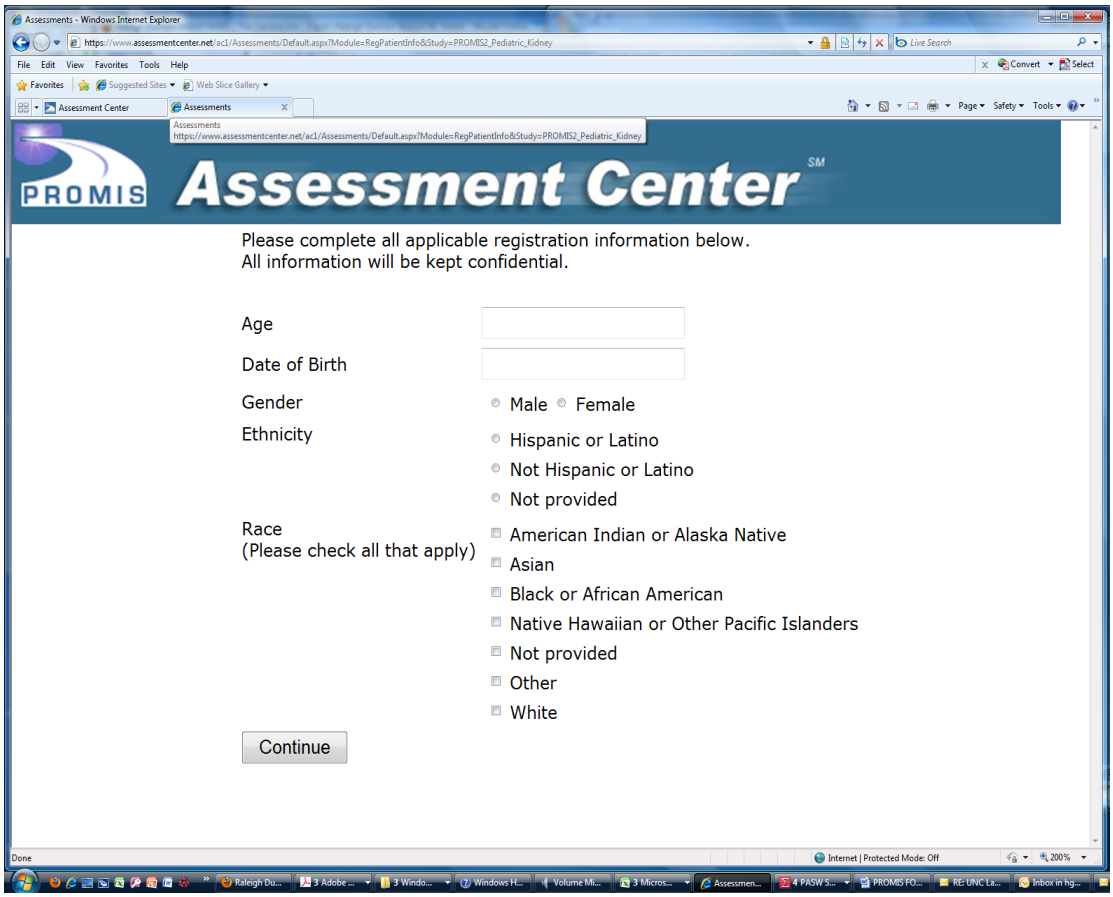


Adult participants (participants age 18 and above):

https://www.assessmentcenter.net/ac1/Assessments/PROMIS2_Adult_Kidney

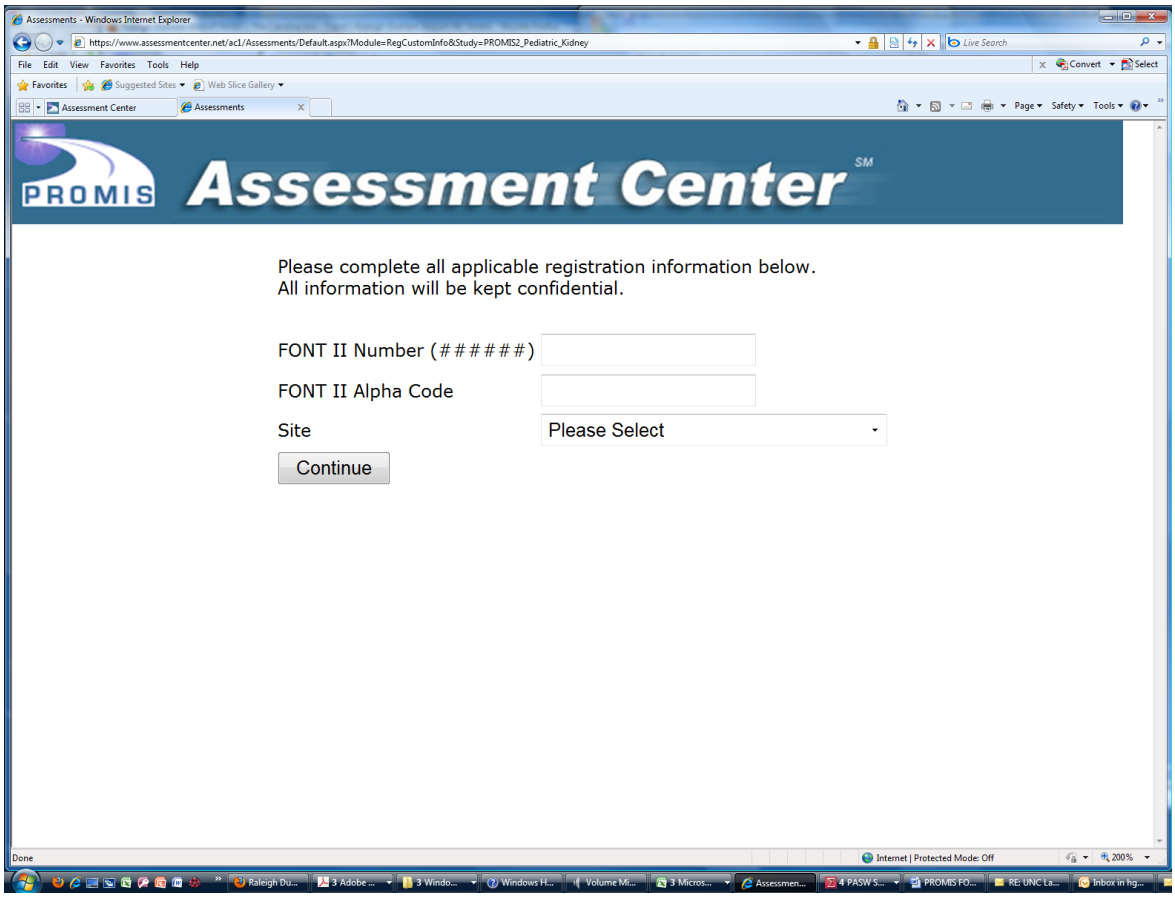


2. **Initiate the RA registration process.**
   Click on the "Start" button to begin the registration process. Here the RA will need to complete all items.
   a. Enter the participant's age
   b. Enter the participant's date of birth
   c. Select the participant's gender
   d. Select the participant's ethnicity
   e. Check the appropriate boxes for the participant's race (select as many boxes as appropriate)
   f. Click "Continue"

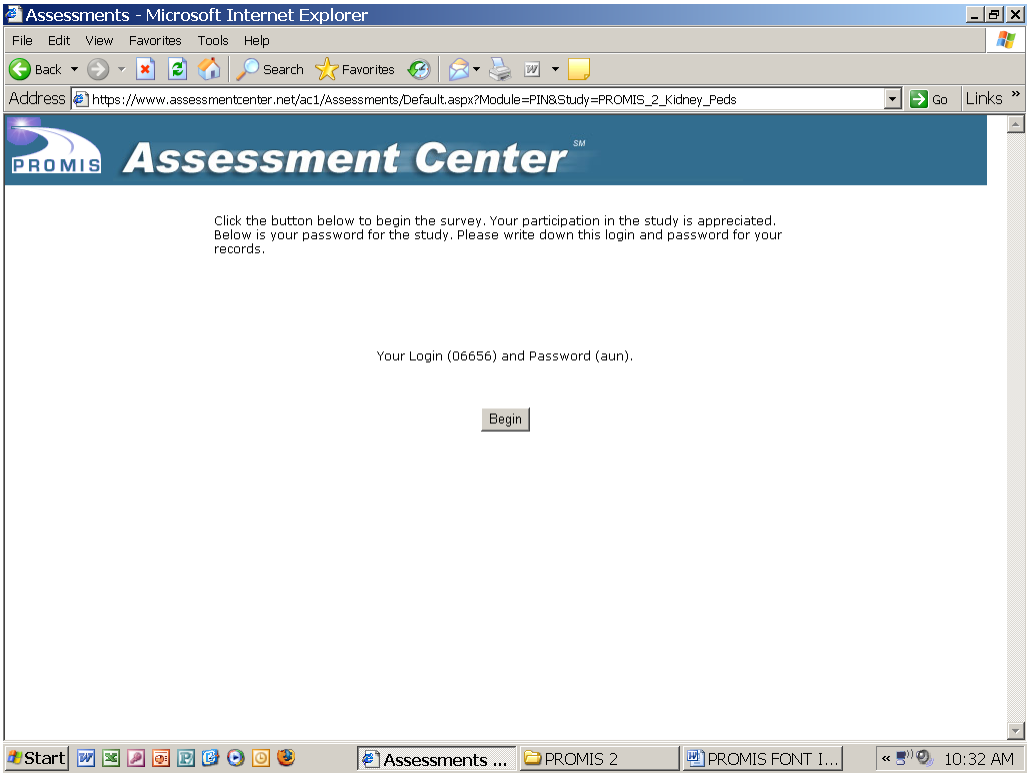


3. **Enter participant's FONT II ID Number & Alpha code and Site.**
   The next screen asks the RA to enter the participant's FONT II ID number & alpha code and the data collection site. It is important to ensure that the ID number and alpha code are entered correctly as they are the only link between the PROMIS items and the FONT II paper-based forms. To ensure accuracy, the RA (not the participant) should enter this information.

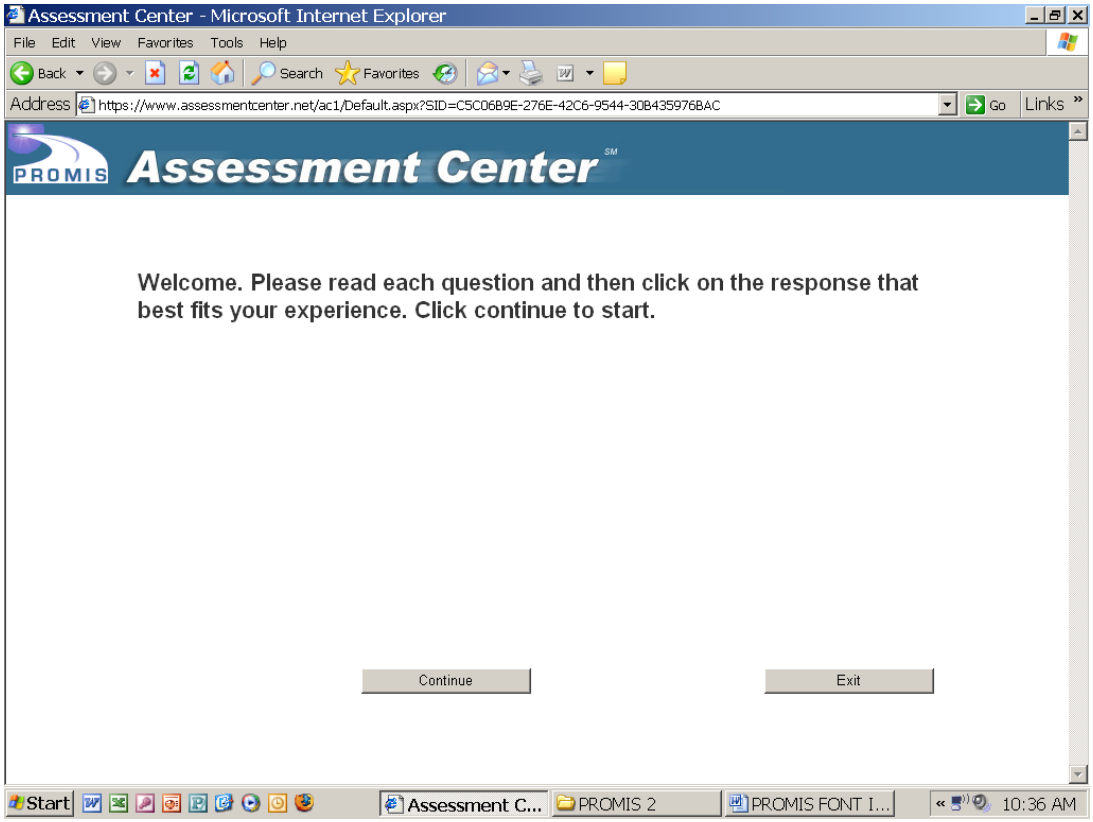
   Please select the site from the drop down list. If your site is not listed, select the Other option and contact Heather Gross (hgross@schsr.unc.edu) so that your site can be added to the list.



4. **Complete the registration process.**
   The next screen will provide the participant's unique Assessment Center 5-digit PIN and 3-character password. The RA should pause here and ***carefully*** write the PIN and password down on the tab of the participant's folder and enter the information in the FONT II enrollment log. Without the appropriate PIN and password combination there is no way to re-enter or return to an assessment. Click "Begin".

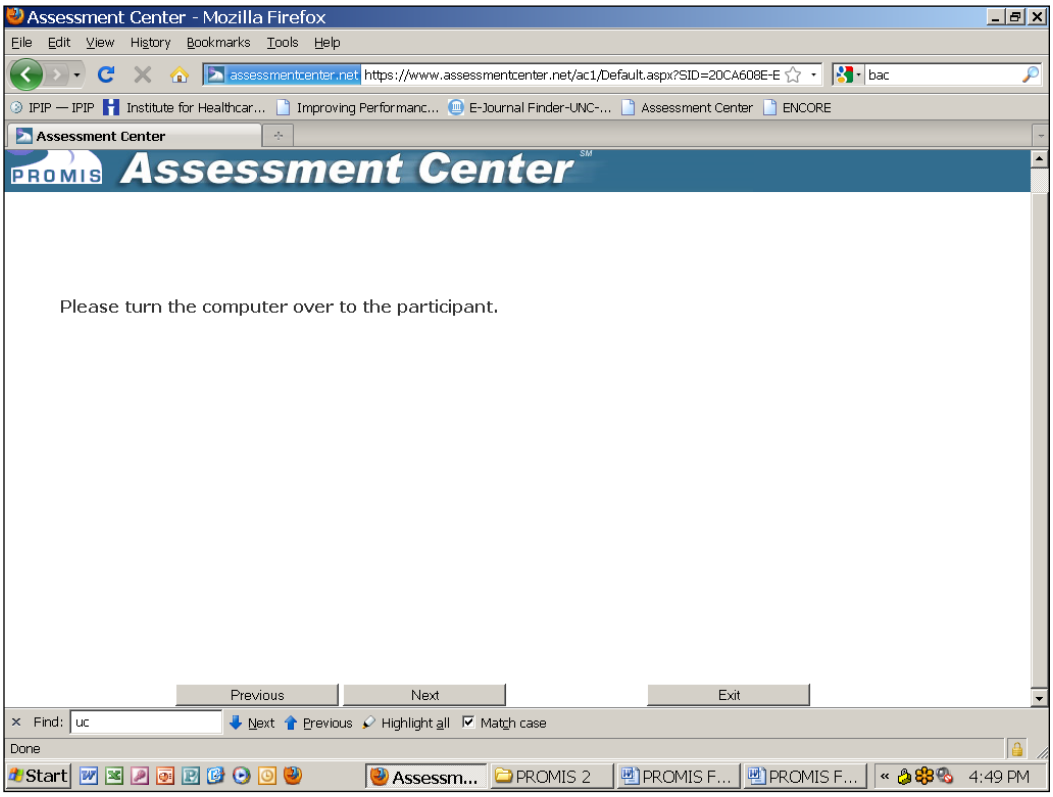


The next welcome screen indicates that the participant has been appropriately registered for the survey. Before turning the computer over to the participant, click “Continue”.

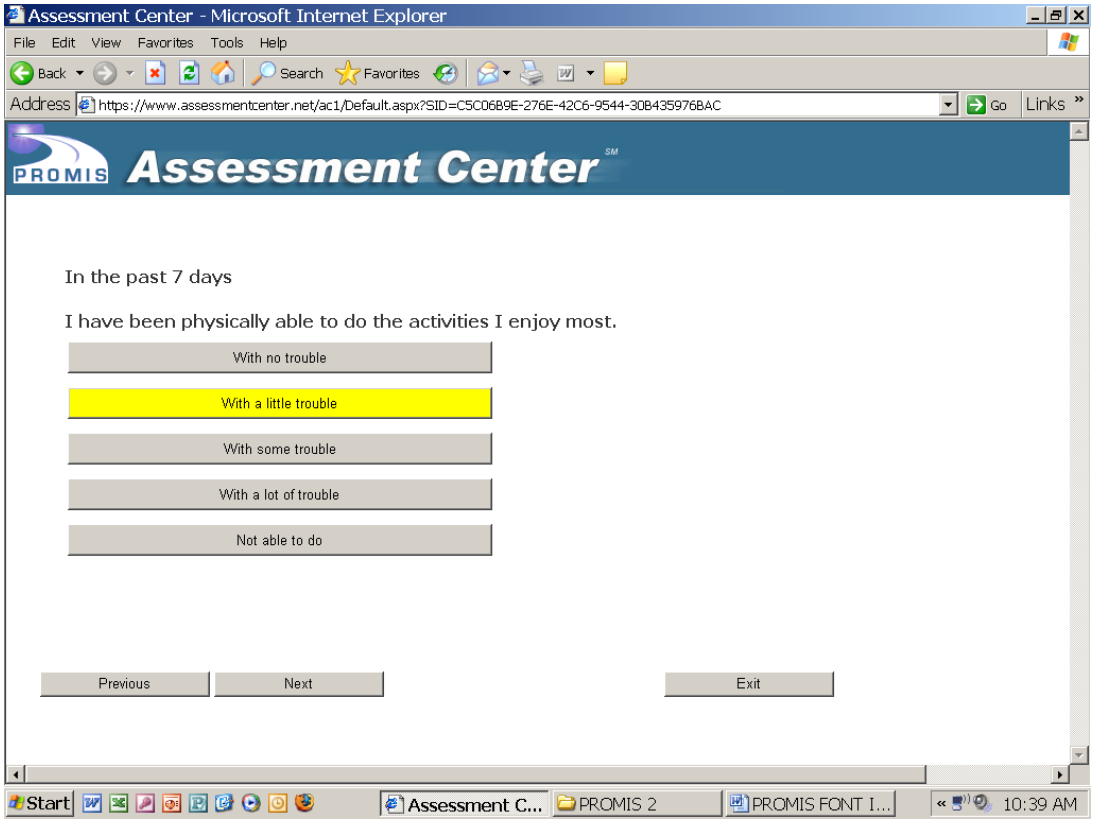


5. **Inform participants about the survey.**
   Instruct the participants that "Each question should be answered by selecting the best response from the options given; and there are no right or wrong answers". For pediatric participants, the RA should emphasize that this survey is to be taken individually **with no assistance** from the parent to the child.

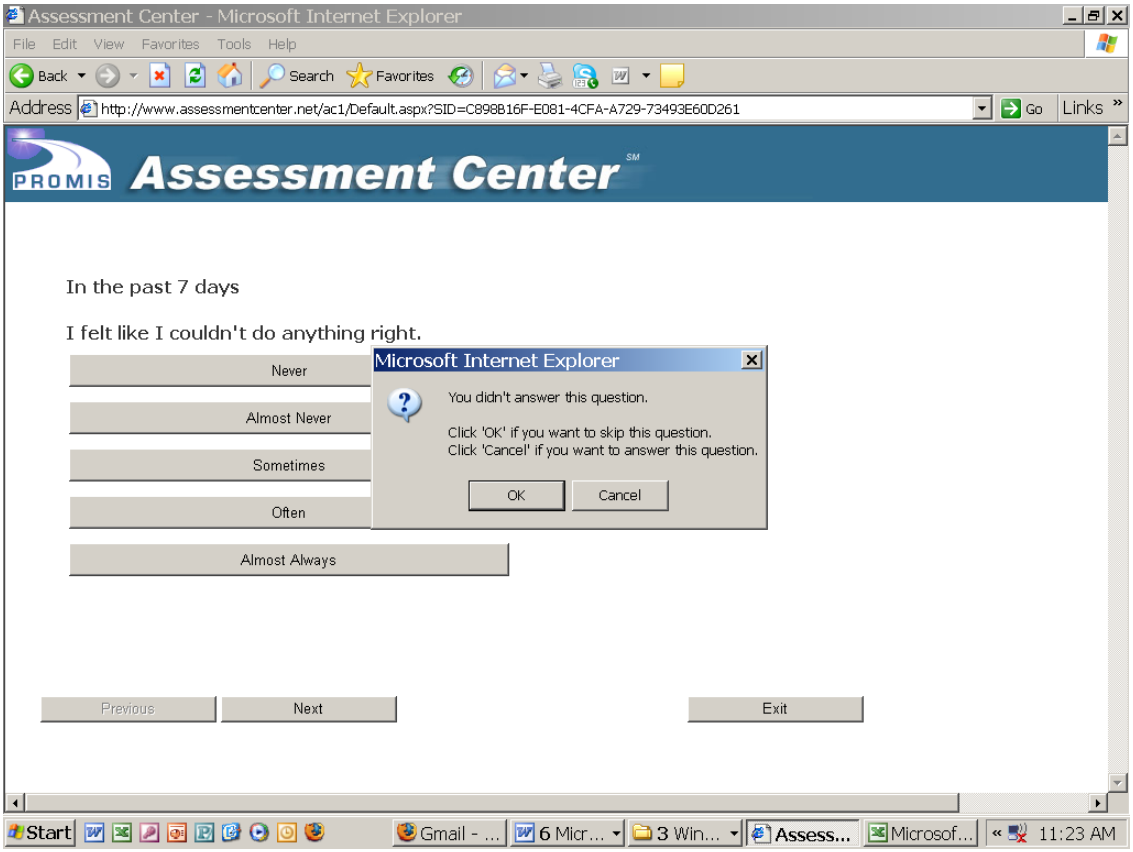
6. **Turn the laptop over to the participant.**
   At this point, the assessment may be started by the participant.



There will be welcome and instructions screens, followed by questions about the participant's health status. Response options have radial buttons and respondents can click on the words themselves. Responses will turn yellow when selected. Each screen calls for clicking on a response, then clicking "Next."



During the computer-based survey, participants are permitted to skip any question they do not feel comfortable answering. Before permitting them to advance to the next screen however, the following pop up box must be responded to. Participants are encouraged to discuss their answers with the RA if they are unsure about responses to the questions.



7. **Wait for the participant to complete the computer-based assessment.**
   Pediatric participants will be administered approximately 50 items; adult participants will be administered 43 items. This takes most participants about 20 minutes. The process can be stopped and re-started at any point (within a 7 day period) as often as is needed. Response options for the participants are almost always limited to five choices. Once selected, a participant's response will turn yellow. Since the item blocks are randomized, it is possible that two surveys will not look the same.

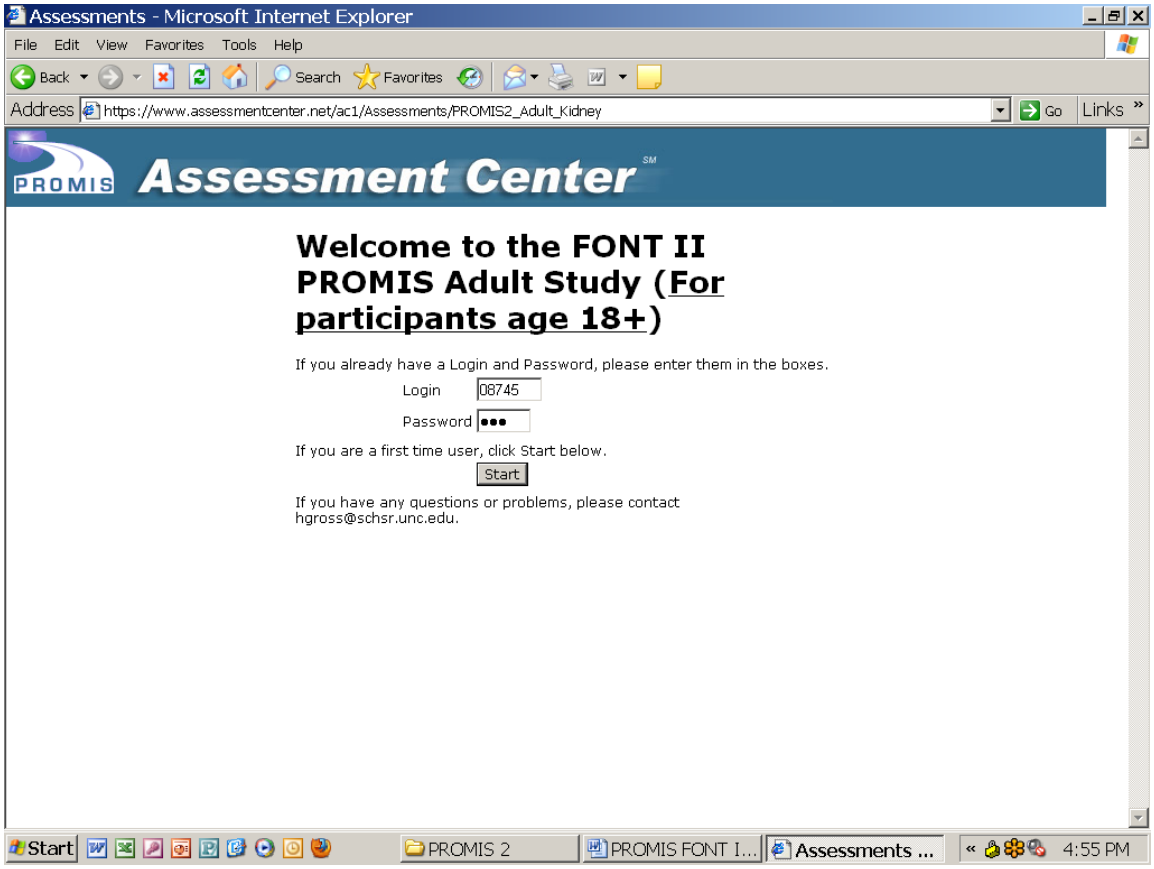
8. **Complete the survey.**
   Once the survey is complete, the RA should click "Next" on the "Thank You" screen and then close all the way out of Internet Explorer and re-navigate to the survey link for the next participant.

   If the participant needs to leave and come back later, or in the event of a significant interruption to the server, the participant can access their survey again that day (provided there is an RA in clinic to administer). Note, however, that that particular survey is only accessible for 7 days from the point of first log-in.

Participants should be able to follow all online instructions and independently complete the survey. However, if the participants have any questions, the RA should address them, as long as they do not concern the content of the surveys themselves. Any technical difficulties experienced by the participants should be resolved by the RA and/or reported to Heather Gross at hgross@schsr.unc.edu or (919) 966-0894.

9. **Remind participant about follow-up visits**
   The RA will explain to the participant and guardians (if applicable) that participants will be asked to complete the PROMIS items during follow-up visits. Follow-up visits will occur approximately 26 and 52 weeks after the initial visit.

10. **Help participant login to complete follow-up assessments.**
    When the participant returns for follow-up visits approximately 26 and 52 weeks after the initial visit, look up the participant's Assessment Center PIN and password. Direct the participant to the appropriate study page (pediatric or adult), being sure that it is the same survey they completed during the initial visit. If the child has turned 18 since the last visit, continue to administer the pediatric study. Enter the participant's PIN and password on the log-in screen. ***There is no need to create a new PIN for a follow-up assessment.*** Please enter the participant's original PIN and password. Click "Start". Then, turn the computer over to the participant so that they can complete the follow-up assessment.



DATA COLLECTION ISSUES

Non-English Speaking Participant. Participants must be able to speak and read English to participate in the study. Parent-child dyads where one dyad member does not speak and read English should **not** be recruited to participate in the study. IRB requires that both parent and child fully understand consent and assent forms prior to signing. The survey is only administered in English at this time.

Tiring or Struggling Pediatric Participants. Participants should be reminded that it is ok to stop the survey if they want to. The RA will remind the patient that there are no "right" or "wrong" answers to these questions and that we have children who provide us with every possible response.

Reading Issues. The PROMIS pediatric assessments are meant to be self-administered. Children on the younger end of the study sample (8 and 9 year olds) will occasionally struggle with the items (depending on his/her reading abilities.) The research assistant can answer any question the child may ask; however, researchers are encouraged to guide the child through trouble spots and questions with re-directs such as "What do *you* think that means?" or "What does that word or

question mean to *you*?" Parents should be discouraged from "helping" their child. This includes watching over their child's shoulder as they complete the assessment.

Survey or Internet Error Messages. Assessment Center will periodically present you with an error message and ask to be re-launched. It is recommended that the RA not only close out of the Assessment Center but also close out of the browser (i.e., Internet Explorer). The RA should open the browser and re-launch Assessment Center at which point the RA should be brought back to the question that was on the screen when the error message appeared. Please report all error messages and other issues to Heather Gross at hgross@schsr.unc.edu