Confidential

FSGS – CLINICAL TRIAL

PROTOCOL

Version 3c

06/20/2005

Includes formatting changes through 09/22/2006

1. INTRODUCTION, BACKGROUND AND RATIONALE (06/20/05)

1.1. Background

Focal segmental glomerulosclerosis (FSGS) is a clinical entity with a distinctive histopathologic appearance, which may be either idiopathic or secondary to other etiologies. The most common clinical manifestation of this disorder is proteinuria. This lesion may account for 10-20% of cases of idiopathic nephrotic syndrome in children and 35% of cases in adults. In the majority of patients, this lesion is refractory to therapeutic interventions. Progression to end stage renal disease is an expected outcome for the vast majority of patients. Overall, FSGS accounts for approximately 15% of pediatric and 5% of adult cases of end stage renal disease in North American [Seikaly 01, Agodoa 00]. The morbidity and mortality for patients with FSGS is compounded by the relative high recurrence rate for this lesion following renal transplantation. The outcomes for patients with recurrent FSGS are as poor if not worse than those for patients with primary FSGS.

Identification of the histopathologic lesions of FSGS requires identification of areas of glomerular scarring in parts of some glomeruli. By light microscopy, these focal and segmental glomerular lesions are often associated with tubular atrophy and interstitial fibrosis. In some cases, areas of segmental sclerosis will be associated with the deposition of IgM and C3, and ultrastructural evaluation may demonstrate effacement of foot processes in association with heavy proteinuria. Several variants of FSGS have been described including tip, collapsing, cellular, classical and perihilar variants [Morita 90, Fogo 95, Schwartz 95, Agarwal 93]. Although therapeutic and prognostic significance has been attributed to different histopathologic subtypes of FSGS, statistically based validation of these clinical observations does not exist. Consequently patients with all subtypes of FSGS will be enrolled in this research study. Prior to randomization, the renal biopsy of each patient will be reviewed and confirmed by a member of the Pathology Committee (see Section 5.5).

Over the past two decades there has been an increased incidence of FSGS in both urban and rural populations. Moreover, it has become clear that African Americans are more likely to be diagnosed with FSGS and their outcome is more guarded [Pontier 94, Korbet 96, Bakir 89]. The reasons for these racial differences are not known but the observation has been well documented and verified. Consequently in the present study patients will be stratified according to race prior to randomization.

In all likelihood, genetic factors play an important role in the etiology and pathogenesis of FSGS. These factors include polymorphisms in angiotensin-related genes and in genes which affect components of the glomerular filtration barrier such as nephrin, podocin, CD2AP, alpha-actinin-4 and the Wilm's tumor suppressor gene. An extensive evaluation of the potential influence of these podocyte-related factors did not provide evidence to suggest that patients with abnormalities in any of these genes should be excluded from the study or be stratified between the two therapeutic interventions [Caridi 01, Pollak 03].

Therapeutic interventions for the treatment of FSGS have been widely reported. However, evidence based treatment guidelines have not been developed because of the lack of control studies and the small number of patients included in most reports [Burgess 99]. While most studies are purportedly undertaken for the purpose of safety, the effect of therapeutic agents on proteinuria is reported and conclusions concerning efficacy are drawn despite insufficient numbers of patients enrolled in these studies to provide statistically valid outcomes. Consequently, the choices of therapeutic interventions for this clinical trial were both difficult and

controversial. Because strong biases exist in both Pediatric and Internal Medicine Nephrology communities, it was necessary to find therapeutic regimens that would be acceptable to investigators at the Participating Sites who would contribute patients to the study. Accordingly, a survey was developed by the Steering Committee and sent to the Participating Sites by the Core Coordinating Centers aligned with their respective centers. These data provided important input into the final decisions related to the protocol that has been developed. The rationale and background related to each of the drugs chosen to be a part of the FSGS-CT therapeutic interventions are outlined in this protocol.

1.2. Proposed Therapeutic Intervention

Because the definitions of complete and partial remission vary substantially between different studies and because the numbers of patients included in the available studies are small and many studies rely on uncontrolled observations, no attempt has been made to provide valid cross comparisons between the different therapies or confirm the proportion of "responding" patients for each drug. In many of the cited studies, therapy has been applied in a heterogeneous group of patients with steroid resistant nephrotic syndrome, not necessarily patients with steroid resistance FSGS. Consequently a brief overview of each of the selected medications will be given followed by the rationale for inclusion in the FSGS-CT.

1.2.1. Glucocorticoids

Standard Oral Therapy: Oral corticosteroid therapy has been the primary treatment for patients with FSGS [Burgess 99]. However, in patients who are initially resistant to a 6- to 10-week course of oral corticosteroid therapy, prolonged treatment with daily corticosteroids has not been proven to be effective in inducing remission [Cattran 99]. On the other hand, corticosteroid therapy on either a daily or alternate day basis has frequently been included with other therapeutic interventions and even in relatively low doses is thought to enhance the efficacy of Calcineurin-inhibitors and cytotoxic agents [Rose 81, Adhikari 97, Rennert 99, Tune 95, Neuhaus 92, Griswold 87]. Consequently, in the present protocol, alternate day corticosteroid therapy will be included in both arms of the clinical trial in a dose consistent with previous trials.

Pulse Steroid Therapy: The use of aggressive high dose intravenous steroids in the treatment of patients with steroid resistant FSGS has been strongly advocated but is controversial. Intravenous corticosteroid therapy has frequently been combined with alkalating agents [Rennert 99, Griswold 87, Mendoza 90, Hari 01, Mendoza 95] or calcineurin inhibitors [Waldo 92, Yorgin 01]. Therapeutic regimens, which have included pulse corticosteroid therapy, cyclophosphamide and alternate day steroids, have been impressive in uncontrolled series with small numbers of patients [Tune 95, Mendoza 90, Hari 01, Mendoza 95]. Studies of these intensive regimens have been limited by several factors: a) small numbers of patients, b) uncontrolled observations, c) inconsistent findings amongst different study groups and d) observation of diminished efficacy in African American patients [Waldo 92, Sa 96, Southwest Pediatric Nephrology Study Group 85]. Moreover, implementation of a protocol which included intravenous pulse corticosteroid therapy would likely meet with substantial reluctance from patients and participating physicians because high dose intravenous corticosteroid therapy has been associated (although not in FSGS patients) with complications including infection, decreased bone density and demineralization, induction of diabetes mellitus and poor statural growth in children in addition to the cost and inconvenience of intravenous therapy.

Nonetheless, there is a clear consensus among the Participating Sites and the Steering Committee that the efficacy of pulse corticosteroid therapy should be evaluated in patients with

steroid resistant FSGS. Preliminary data suggests that high dose oral dexamethasone may be efficacious in patients with steroid resistant FSGS [Kopp 03]. Although not directly evaluated in children or adults with kidney disease, the pharmacokinetic profile of oral dexamethasone is comparable to that of intravenous pulse injections of the drug. In addition, there is no increase in toxicity or novel side effects associated with this route of dexamethasone administration [Toth 99, Weijtens 98]. The dose of dexamethasone that was chosen for this study is extrapolated from the dose used in the preliminary study [Kopp 03] and provides approximately 33% of the total steroid dose in the most intense therapeutic intervention. It was felt that this dose could be therapeutic, especially in combination with another agent (see Section 1.2.3.), and would be accepted by both Pediatric and Internal Medicine nephrologists. On the basis of these considerations, pulse doses of oral dexamethasone have been included in one therapeutic arm of this clinical trial.

1.2.2. Cyclosporine

Over the past decade, a number of studies have reported therapeutic efficacy for treatment with Cyclosporine-A (CSA) in patients with nephrotic syndrome including patients with steroid resistant FSGS [Tejani 88, Capodicasa 86, Brandis 88, Meyrier 86, Niaudet 87, Hino 98, Gregory 96, Walker 90, Niaudet 91, Ponticelli 93, Chishti 01, Cattran 95]. There have been two controlled trials of treatment with CSA in steroid resistant FSGS, one in children [Tejani 93] and one in adult patients [Cattran 99]. An additional controlled trial was conducted in patients with steroid resistant idiopathic nephrotic syndrome [Ponticelli 93]. Consequently, CSA is the only medication that has been documented to be efficacious in a controlled trial in both children and adults with steroid resistant FSGS. Based on these studies and a large number of published experiences, CSA has, to a certain extent, become the standard of practice among pediatric nephrologists for the treatment of patients with steroid resistant FSGS [Vehaskari 99]. Despite demonstrations of therapeutic efficacy in both children and adults, several important considerations remain unanswered with respect to the use of CSA in steroid resistant FSGS: a) the risk of nephrotoxicity associated with the prolonged use of CSA, b) the high rate of relapse of proteinuria after discontinuation of the medication, c) biochemical and cosmetic side effects associated with CSA therapy. Based on these considerations, CSA was chosen as the active control arm for this clinical trial and the dose of CSA is compatible with that used in previous trials.

1.2.3. Mycophenolate Mofetil

The experience with mycophenolate mofetil (MMF) in the treatment of patients with steroid resistant FSGS has been limited to uncontrolled trials in adult patients [Briggs 98, Choi 02] and children [Montane 99]. Although these studies are uncontrolled and consist of small numbers of patients, the combination of MMF with oral pulses of corticosteroids resulted in a significant decline in proteinuria in patients with FSGS. Because MMF is generally thought to have a steroid sparing effect [Remuzzi 99], it was felt that a combination of MMF and oral pulse dexamethasone therapy (as discussed above) would provide an effective alternate therapy to treatment with CSA and, concomitantly, allow an evaluation of intermittent pulse doses of corticosteroids (albeit at doses lower than the most intense therapies reported). Consequently, MMF and oral pulse dexamethasone therapy have been combined in one therapeutic arm of this clinical trial. The dose of MMF is consistent with use in renal transplant patients and previous trials.

1.2.4. Inhibition of Angiotensin Converting Enzyme

Multiple studies have demonstrated the beneficial effect of angiotensin converting enzyme inhibitors (ACEi) on proteinuria and preservation of renal function [Milliner 91, Proesmans 96, Gansevoort 95, Navis 97, van Essen 97, McLaughlin 99, Hebert 01, Jafar 01]. Although a retrospective study failed to demonstrate an antiproteinuric effect of ACEi in patients with FSGS [Stiles 01], these drugs have been shown to reduce proteinuria in patients with other glomerulopathies [Stiles 01, Woo 00, Russo 01, Cohen 96, Erley 96, Lama 00]. Because ACEi have been shown to decrease proteinuria independent of their effects on hypertension, it was felt that all patients should be placed on a maximal dose of angiotensin converting enzyme inhibitor. Consequently, both therapeutic arms of this clinical trial will include treatment with ACEi and if patients are intolerant of the ACEi, angiotensin receptor blocker will be substituted.

1.3. Justification for Therapeutic Interventions

In evaluating the therapeutic interventions that have been chosen for this clinical trial, one must take into consideration several important factors. Simply stated, there is no evidence-based medicine to suggest that any specific therapeutic intervention for the treatment of steroid resistant FSGS will provide a significant reduction in proteinuria or preservation of renal function in a substantially large proportion of patients. The lack of uniformity in the definition of therapeutic response (complete or partial reduction in proteinuria) and the paucity of well-controlled clinical trials makes the comparison of various putative therapeutic regimens complex and lacking in scientific rigor. Nonetheless, there are at least four prevailing factors which significantly influenced the design of this clinical trial: a) an established role for CSA in the treatment of FSGS, b) the potential but unproven benefit of intermittent high dose corticosteroid therapy in combination with another immunosuppressive agent, c) the efficacy of either therapeutic intervention to induce sustained reduction in proteinuria after withdrawal of a therapeutic agent and d) the side effects and consequence of any long-term therapeutic intervention, if withdrawal of medication is unsuccessful.

Moreover, to accrue sufficient numbers of participants for statistical validity, over 200 Participating Sites were solicited to enroll participants. The physicians at these sites include both Pediatric and Internal Medicine Nephrologist because the age range of participants to be enrolled in this clinical trial is from 2-40 years of age. There are clear differences between Pediatric and Internal Medicine Nephrologists with respect to the therapeutic interventions commonly employed for the treatment of patients with steroid resistant FSGS and most other glomerulopathies. Consequently the protocol for this clinical trial evolved as a compromise, particularly related to the dose and duration of alternate day and pulse corticosteroids.

The decision to include alternate day corticosteroid therapy and inhibition of the renin angiotensin system as background therapy for both therapeutic arms of this clinical trial reflects current standards of practice, to a large extent. Most therapeutic interventions of patients with steroid resistant FSGS included these two elements irrespective of the primary therapeutic intervention. The ultimate effectiveness of therapeutic intervention could be appreciated, best, if it were possible to sustain an antiproteinuric effect when the medication is withdrawn. For the medications being considered for this clinical trial this is a particularly important outcome because long-term therapy of either CSA or MMF may be associated with significant and serious side effects including nephrotoxicity and malignancy.

In the final analysis, the recommended therapeutic protocol is a blending of scientific data, conventional wisdom, practicality and pragmatism. Moreover, if either therapeutic intervention is found to be superior, it is quite feasible for that therapy to be adopted widely resulting in improved outcomes for the greatest number of patients.

1.4. Study Calendar Timeline

The Study Calendar Timeline is as follows:

Month 1	Sept 2002	Funding begins
Month 2	Oct 2002	Steering Committee Meetings begin
Month 9	May 13, 2003	Preliminary protocol submitted to Data Safety and Monitoring Board (DSMB)
Month 9	May 27, 2003	DSMB meeting
Month 12	Aug 2003	Core Laboratory and Core Pharmacy selected
Month 27	Nov 9, 2004	Participant enrollment begins
Month 67	Mar 1, 2008	Participant enrollment ends
Month 86	Oct 1, 2009	Final follow up data collection on last participants enrolled
Month 89	Jan 1, 2010	Completion of Study Close Out and primary analysis

1.5. Brief Summary Participant Timeline

Participants will be enrolled at the participating sites and all visits will be held at the participating site where the participant is enrolled. Participant data will be key entered at the participating site or at the site's affiliated Core Coordinating Center. Participants will be followed with regular visits at weeks:
–2 (screening), 0 (randomization), 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, 52, 65, and 78, after which more limited follow-up will continue until the end of the trial with visits at 6 month intervals. See Section 10.2 for further details.

1.6. Documentation: Protocol, Manual and Forms

1.6.1. Purpose of the Protocol

The protocol describes the study, explains which procedures will be done, why they will be done and how the results will be utilized and interpreted.

1.6.2. Manual of Operations

The Manual of Operations includes the detailed instructions for performing the procedures required by the protocol. Sections of the Manual of Operations will be aimed toward the Core Coordinating Center Study Coordinator, the Core Coordinating Center Data Entry Specialist, and the Participating Center Study Coordinator.

1.6.3. Forms and Reports Manual

The Forms and Reports Manual includes forms to be used for study data collection with instructions for their use, and drafts of reports pertaining to enrolled participants.

1.7. Training and Certification Plans

Quality data collection and appropriate conduct of the study will require careful attention to the training of personnel at the Core Coordinating Centers and participating sites.

Training and certification sessions for Core Coordinating Center Study Coordinators and key entry personnel will be held prior to the initiation of participant recruitment. The protocol, forms and other materials will be distributed to the appropriate personnel prior to the training session. Each center's personnel will be trained centrally in the study requirements, standardized measurement of height, weight, and blood pressure, requirements for laboratory specimen collection including morning urine samples, counseling for adherence and the eliciting of information from study participants in a uniform reproducible manner.

During the training session, presentations will be made by staff members of the Data Coordinating Center, Genetics Repository, Core Lab and Drug Distribution Center. This training session will cover participant recruitment and participant eligibility and exclusion criteria. The study personnel will be shown how to enroll participants as uniformly as possible over time and ways to reach the recruitment goals in the allotted time period. The data to be collected and the procedures to be conducted at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item by item basis. Coordinators will learn how to code medications using the WHODrug software and how to code symptoms using the MedDRA software. Entering data forms, responding to data discrepancy queries and general information about obtaining research quality data will also be covered during the training session.

2. OBJECTIVES AND DESIGN (03/03/04)

2.1. Objectives

The primary objective is to conduct a multi-center, prospective, randomized trial to compare the effectiveness of a treatment regimen including CSA to a regimen including MMF and oral pulse steroids in inducing remission of proteinuria in participants with steroid resistant FSGS. Both of the regimens will also include an ACE inhibitor and alternate day low dose prednisone. On a therapeutic background of alternate day steroids and inhibition of renin angiotensin system, the main research hypotheses are that participants with steroid resistant FSGS who are treated with MMF/oral pulse dexamethasone will have significantly greater proportion with a) remission of proteinuria after 52 weeks on therapy and/or b) remission of proteinuria 26 weeks after withdrawal of therapy when compared to similar participants receiving CSA. Additional research hypotheses are that one or more of the following will differ between the two therapeutic groups:

a) Improved quality of life
b) Decreased numbers of adverse events and extrarenal complications
c) Preservation of renal function.

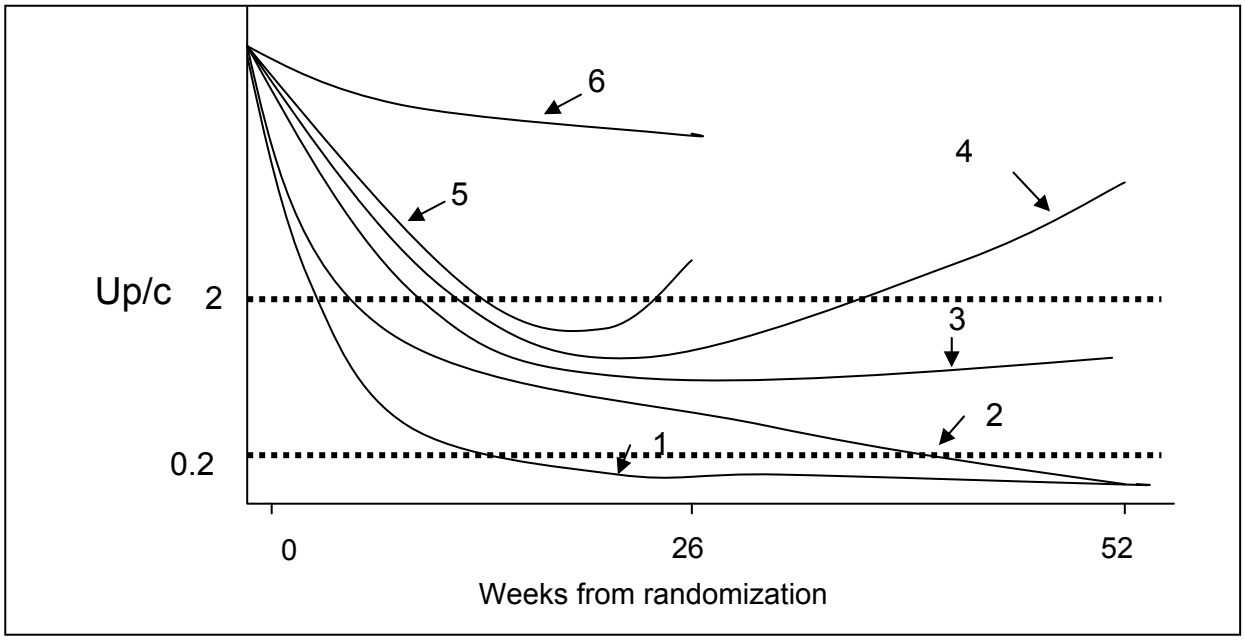
2.2. Design and Primary Outcome

The experimental design is a multi-center, prospective, controlled, open label randomized trial comparing two treatment regimens, CSA and MMF/Pulse steroids. The treatment regimens in both arms also include ACE inhibitor therapy and alternate day low dose prednisone. The CSA and MMF/Pulse steroid treatment regimens will be implemented over the first 52 weeks after randomization, with the ACE inhibitor component continuing for an additional 26 weeks.

The primary outcome is defined as described below based on the achievement of remission from proteinuria during the first 52 weeks after randomization. At each protocol assessment of proteinuria, a partial remission is defined as a 50% or greater decline in the first morning urine protein/creatinine ratio (Up/c) from the mean of two baseline measurements to a level between 0.2 and 2.0. A complete remission is defined as a decline in the Up/c ratio to a level no greater than 0.2. For participants who achieve a partial or complete remission, a sustained relapse is defined as relapse of proteinuria (see page 27) for two successive central Up/c measurements obtained at least four weeks apart.

The primary outcome variable is a 6-level ordinal classification. Sample patterns of change in Up/c corresponding to the 6 levels of the primary outcome are illustrated in the figure at the top of the following page. Note that the two sample patterns assigned to levels 5 and 6 are assigned to participants who fail to achieve either a partial or complete remission at the 26 week assessment, while the remaining four patterns, assigned to levels 1 through 4, represent different outcomes after the week-26 assessment among those participants who achieve at least partial remission at week 26.

Sample Patterns for 6 Possible Levels of the Primary Outcome



The least favorable outcome, designated as level 6, is assigned if the participant fails to achieve either a partial or a complete remission at any of the protocol assessments of proteinuria (see Section 10.2) from weeks 2 through 26, inclusive). The next least favorable level (level 5) is designated if the participant achieves at least one partial or complete remission between weeks 2 and 20, but does not achieve either a partial or complete remission at week 26. By this definition the primary outcome is not affected by level of proteinuria after 26 weeks for those participants who fail to achieve a partial or complete remission at 26 weeks. This allows those participants who do not achieve a partial or complete remission at 26 weeks to switch to salvage therapy with no effect on the primary outcome.

For participants who do achieve a partial or complete remission at the week 26 assessment, the primary outcome is assigned a score between 1 and 4 depending on remission status between week 26 and week 52 as described in the Table below. Level 4 is assigned if the participant fails to achieve either a partial or complete remission at week 52 or has a sustained relapse between weeks 26 and 52. Level 3 is assigned if the participant achieves a partial remission at week 52. Level 2 is assigned if the participant achieves a complete remission at week 52 but has had at least one Up/c > 0.2 after week 26 but before week 52. Level 1 is assigned if the participant achieves a complete remission at week 52 and has had Up/c $\leq$ 0.2 since the week 26 visit.

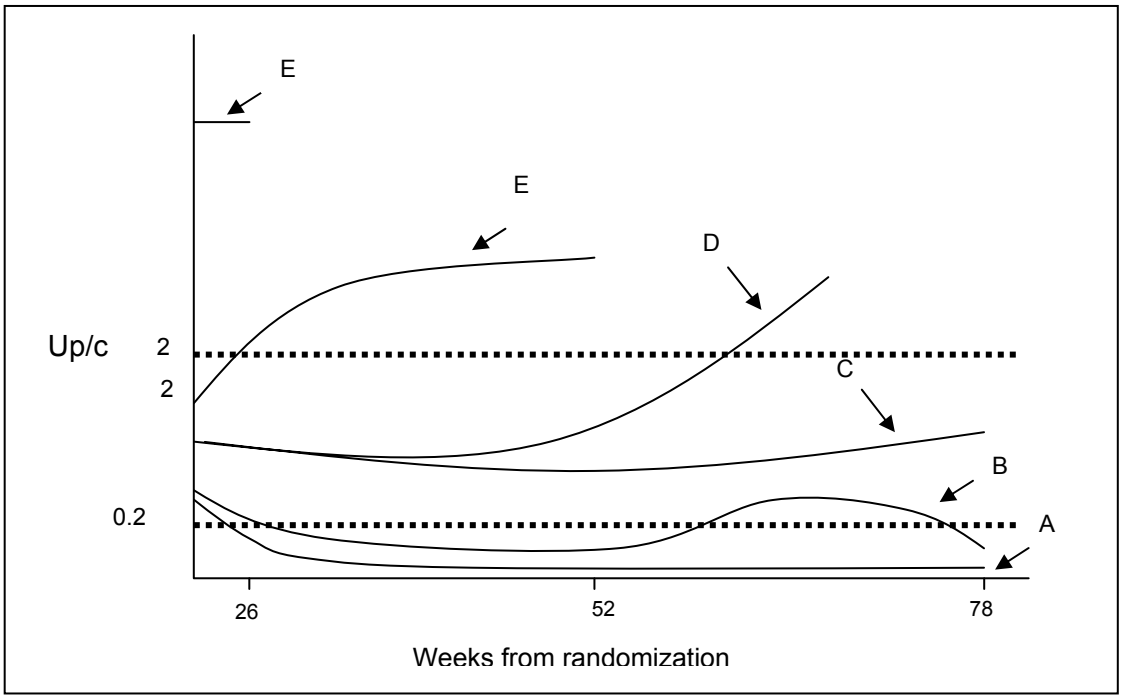
Definition of Primary Outcome at 52 Weeks for Participants Achieving a Partial or Complete Remission at 26 Weeks

Remission Category	Sustained complete remission	Limited complete remission	Partial remission	No remission
Level	1	2	3	4
Definition	Complete remission throughout weeks 26-52	Complete remission at week 52 but Up/c > 0.2 between weeks 26 and 52	Partial remission at week 52	No remission at week 52

2.3. Main Secondary Outcome

To evaluate whether reductions in proteinuria will persist after immunosuppressive agents are withdrawn, the main secondary outcome is a 5-level ordinal categorical outcome based on the participant's level of proteinuria during the period from week 52 through week 78 following withdrawal of CSA or MMF/Pulse steroids (participants will remain on ACEi). The levels of the main secondary outcome are labeled with letters from A (the best outcome) to E (the poorest outcome) to avoid confusion with the numerical labels that define the levels of the primary outcome. The main secondary outcome evaluates whether either therapeutic regimen will induce a sustained complete or partial remission following termination of the therapy. Sample patterns of change in Up/c corresponding to the 5 possible levels of the main secondary outcome are illustrated below.

Sample Patterns for 5 Possible Levels of Main Secondary Outcome



Participants who are assigned to levels 4, 5, or 6 for the primary outcome at the 26 and/or 52 week assessment will be assigned to level E for the main secondary outcome. Thus, these participants may subsequently receive salvage/alternate therapy without affecting the main secondary outcome.

Among participants with a primary outcome level of 3 or better at week 52, the main secondary outcome is assigned to levels A, B, C, or D as described in the table at the top of the following page. Level D is assigned if the participant fails to maintain at least a partial remission from week 52 through week 78. Participants who do maintain at least a partial remission from week 52 through week 78 are assigned to level C if they have a partial remission at week 78, to level B if they have a complete remission at week 78 but had at least one Up/c between 0.2 and 2.0 between weeks 52 and 78, and to level A if they maintained a complete remission from week 52 through week 78.

Definition of Main Secondary Outcome at Week 78 for Participants with a Primary Outcome Level of at least 3

Remission Category	Full persistence of complete remission	Limited persistence of complete remission	Partial remission	No remission
Level	A	B	C	D
Definition	Complete remission throughout weeks 52-78	Complete remission at week 78, but Up/c between 0.2 and 2.0 between weeks 52 and 78	Partial remission at week 78, and partial or complete remission between weeks 52 and 78	Failure to maintain at least a partial remission after week 52

Note that similarly to the primary outcome, the main secondary outcome is defined in all randomized participants to allow analysis according to the intent-to-treat principle.

2.4. Rationale for Using the Urine Protein/Creatinine (Up/c) Ratio as the Primary Outcome Measure.

While proteinuria is considered a surrogate end point for progression of renal disease, proteinuria is the hallmark of idiopathic glomerulopathies, such as FSGS, and reductions in proteinuria are a primary outcome for most therapeutic interventions in these disorders. Moreover, the risk of progression and the ultimate outcome for both children and adults with FSGS has been linked with the level of renal function at onset and the degree of sustained proteinuria over time (1-5). Since progression to ESRD occurs over 5-10 years (on average), for patients with FSGS, alterations in proteinuria are much more likely to be identified in a study with a 78 week observation interval.

The measurement of 24-hour urine protein excretion in either children or adults is a difficult and frequently inaccurate determination. Spot Up/c ratio has been extensively evaluated and is a sensitive test for the detection of proteinuria. After extensive evaluation of the cumulative data related to Up/c ratio to monitor proteinuria, the kidney disease outcome quality initiative (K-DOQI) has recommended the first morning urine to monitor proteinuria [Agarwal 93]. Consequently, on the basis of these findings the proposed primary outcome for this study will be the use of a urine protein/creatinine ratio.

2.5. Sample Size

The sample size will be 500 participants, with a target of 100 participants to be accrued over 26 months by each of the five core clinical coordinating centers. Details on sample size and power are included in the Analysis Plan, Section 12.

3. PARTICIPANT SELECTION/ELIGIBILITY AND EXCLUSION CRITERIA (06/20/05)

The following inclusion and exclusion criteria will be used to determine eligibility of subjects for the FSGS-CT.

3.1. Inclusion Criteria

1) Age 2-40 years at onset of signs or symptoms of FSGS
2) Age ≤ 40 years at time of randomization (randomization date before 41th birthday)
3) Estimated GFR ≥ 40 ml/min/1.73 m^2 at most recent measure prior to randomization[1]
    a) For participants < age 18 years: Schwartz formula
    b) For participants ≥ age 18 years: Cockroft-Gault formula
4) Up/c > 1.0 g protein/g creatinine on first am void at time of randomization[1]
5) Biopsy confirmed as primary FSGS (including all subtypes) by study pathologist (see Section 5.5). A minimum of 1 glomerulus demonstrating segmental sclerosison light microscopy will be required to confirm the diagnosis.
6) Steroid resistance: The participant must have demonstrated steroid resistance (defined as a failure to achieve a sustained Up/c ≤ 1.0) based on at least one treatment course with high dose steroids prior to randomization which satisfies *both* of the following conditions:
    a) minimal treatment duration of 4 weeks
    b) minimum cumulative dose of 56 mg/kg or 1680 mg of prednisone or its equivalent

    In addition, the participant must *not* have had a complete remission of proteinuria (Up/c < 0.2 or dipstick urine protein 0/trace) subsequent to the latest qualifying 4-week course demonstrating steroid resistance.
7) Willingness to follow the clinical trial protocol, including medications, and baseline and follow-up visits and procedures.

Participants may be taking ACEi, ARB, Vitamin E, or lipid-lowering therapy.

3.2. Exclusion Criteria

1) Secondary FSGS
2) Prior therapy with sirolimus, CSA, tacrolimus, MMF, or azathioprin (Imuran)
3) Treated with cytoxan, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 30 days
4) Lactation, pregnancy, or refusal of birth control in women of child-bearing potential[1]
5) Participation in another therapeutic trial concurrently or 30 days prior to randomization[1]
6) Active/serious infection (including, but not limited to Hepatitis B or C, HIV)[1]
7) Malignancy
8) Blood pressure > 140/95 or > 95th percentile for age/height.[1]
9) Participant is receiving 4 or more antihypertensive agents for the primary purpose of controlling blood pressure.[1]
10) Participants with previously diagnosed diabetes mellitus Type I or II: the diagnosis of DM I or II will be based on local criteria for participants with an

established diagnosis. If hyperglycemia is detected during the screening period, the WHO criteria for the diagnosis of DM I and II will be used.

11) Clinical evidence of cirrhosis or chronic active liver disease
12) Abnormal laboratory values at the time of study entry:
    a) Absolute neutrophil count (ANC) < 2000/mm^3, or
    b) Hematocrit (HCT) < 28%
13) History of significant gastrointestinal disorder, e.g, severe chronic diarrhea (> 5 watery stools per day) or active peptic ulcer disease.
14) Organ transplantation
15) Obesity (based on estimated dry weight at onset of disease prior to steroid therapy) defined as
    a) BMI > 97th percentile for age if age 2-20 years
    b) BMI > 40 kg/m^2 for age ≥21 years
16) Allergy to study medications
17) Inability to consent/assent

[1]Participants with conditions meeting exclusion criteria at a particular evaluation for eligibility may be re-evaluated at a later time to determine if the conditions have changed so that all entry criteria are met. In particular, if blood pressure > 140/95 or > 95^{th} percentile for age/height while the participant is on less than three antihypertensive agents, the participant may be re-evaluated for eligibility after adding other antihypertensive agents so long as the total number of agents does not exceed three.

3.3. Study Population Proportions

No more than 200 participants will be randomized in each of the following age groups: Age 2 to 12 years, Age 13 to 24 years, and Age 25 to 40 years.

4. INFORMED CONSENT (03/03/04)

4.1. General Principles of Consent

To be eligible for the study, each participant must meet preliminary eligibility criteria and the participant or guardian must be willing to sign a statement of informed consent. This will document the agreement of the participant to participate in the study activities. Separate informed consent will be obtained for participation in the clinical trial and for obtaining and storing of biological samples. Assent will also be obtained from all children age 7-17, if required by the Participating Site's IRB.

4.2. Participation in Other Studies

Participants will be asked by study personnel not to participate in any other therapeutic research studies during the participant's follow-up period from baseline to the 18-month visit unless it is an ancillary study of the FSGS-CT, reviewed by the Ancillary Studies Subcommittee and approved by the Executive Committee.

4.3. Sequence of Consent Procedures

It is recognized that Core Coordinating Center and participating site Institutional Review Boards (IRBs) have official responsibility for determining informed consent procedures. Prototype informed consent forms have been developed for the study. The FDA-approved IND number for the trial is 68,498.

4.4. Privacy

At the beginning of the study, each participant is assigned an identification number and a study code. In any individual tabulations participants will be identified only by number. The medical records of participants in the FSGS-CT will be confidential. Specific study related information might be made available to the Food and Drug Administration and the National Institutes of Health. All procedures will be in compliance with HIPAA regulations.

5. SCREENING PERIOD EVALUATION (06/20/05)

5.1. General Principles of Screening

The screening phase allows confirmation of subject eligibility for this trial based on the inclusion and exclusion criteria detailed in Section 3. The local kidney biopsy specimen will be reviewed by a study pathologist during the screening period to confirm the tissue diagnosis of idiopathic FSGS. Informed consent/assent will be obtained prior to submission of study forms or biopsy specimens to the Core Coordinating Center or Data Coordinating Center.

5.2. Recruitment Strategy

Potential subjects will be approached by the primary nephrologist or his/her designee at participating sites. When the participant/family expresses an interest in the study, a study investigator or his/her designee will review the protocol and eligibility criteria with the participant either in person or by telephone. If the potential participant remains interested, a screening visit will be conducted and informed consent and assent will be obtained for eligible subjects.

5.3. Screening Period Eligibility

In accordance with the inclusion and exclusion criteria outlined in Section 3, subjects with biopsy proven, idiopathic FSGS, documented steroid resistance after a minimum corticosteroid exposure of 4 weeks, an estimated GFR of 40 ml/min/1.73 m^2 or greater, and first morning urine protein/creatinine ratio 1.0 or greater are eligible for screening. Screening Form 10 will be used to document eligibility.

5.4. Screening Procedures

1) Detailed review of medical history to confirm eligibility (Form 10)
2) Obtain informed consent/assent
3) Measurement of blood pressure and anthropometrics (height and weight)
4) Obtain first morning urine on 2 occasions, at least 24 hours apart, for protein and creatinine measurement. Submit to Core Lab.
5) Obtain blood at for serum chemistries, blood count, and viral studies as described in Sections 6 and 7. Submit to Core Lab.
6) Urine pregnancy test for post-menarchal females. Should be assessed centrally at the Core Lab.
7) Place PPD, if not done within the previous 3 months of entry, and document results.
8) Submit kidney biopsy specimen to Core Coordinating Center Study Pathologist.

5.5. Protocol for Confirmation of Histology of FSGS

The following protocol will be used to confirm a histology of FSGS prior to randomization:

A. Criteria: The pathologist at each Core Coordinating Center (CCC) will confirm the standardization for evaluation of biopsy specimens. A minimum of 1 glomerulus demonstrating segmental sclerosis on light microscopy will be required to confirm the diagnosis. Subtype classification will not be required prior to randomization.
B. Materials for Review: To exclude secondary patterns of sclerosing glomerulopathy, a systematic integration of light, immunofluorescence and electron microscopy will be used. Participating Sites will provide the following materials to the renal pathologist at the CCC:

1) At least one slide showing the FSGS lesion, and, if available, a full set of slides including H & E, special stains, and an unstained slide
2) Print of electron microscopy including glomeruli is mandatory

C. These materials will be retained by the CCC pathologist.

D. Turn around time: Confirmation of biopsy diagnosis should be available within two business days after materials are received by the CCC pathologist. Each CCC pathologist will have a designated back up who will participate in the standardization of criteria for diagnosis.

6. CLINICAL CENTER MEASUREMENTS AND PROCEDURES DURING SCREENING, BASELINE AND FOLLOW-UP (03/03/04)

6.1. General Procedures

The purpose of this section is to describe the procedures that are to be used for measurements that will be taken during the screening, pre-randomization baseline and follow-up periods. These assessments are critical to the goals of this study and, therefore, must be carefully standardized across all of the participating centers and include: confirmation of pathology, measurement of blood pressure, and laboratory studies including the Up/c.

6.2. First Morning Urine Samples

First morning urine samples will be obtained at each protocol visit as indicated in Section 10.2. In addition, increases in proteinuria will be documented by Up/c in the Core Lab prior to initiation of relapse therapy, salvage therapy or a medication stop point (withdrawal of the participant from the protocol's treatment regimen).

Drugs that interfere with creatinine excretion [e.g., pyridium, most cephalosporins (except cephalexin), bactrim/septra, H-2 blockers (specifically Tagamet – cimetidine), and NSAIDS will be withheld for 48 hours prior to Up/c determination. Details concerning the standardization for collection of first morning urine samples are given in Section 7.3 and instructions for shipping specimens to the Core Lab are specified in the Manual of Operations.

6.3. Arterial Blood Pressure Determinations

Blood pressure will be measured by trained personnel at each visit using the techniques and procedures listed in the Manual of Operations. A standing and sitting blood pressure will be recorded at each visit.

6.4. Tests

Blood and urine assays will be conducted in the Core Lab (see RFP). The following tests have been included in the study: SMA (or equivalent), CBC with platelet count and Up/c at each protocol visit; Cyclosporine level at 7 visits and a fasting lipid profile at 5 visits. See Section 10.2 for details.

Urine pregnancy test, Human Chorionic Gonadotropin (HCG), will be assessed locally at the participating sites at baseline in women of childbearing potential (post pubertal, pre-menopausal, not surgically sterilized).

6.4.1. Samples for Biorepositories

Additional biological samples will be obtained to be stored for use in future studies of the pathobiology of FSGS. A materials consent will be obtained to specifically address the collection of these specimens. Among those participants who consent for storage of biological specimens, urine, serum and plasma specimens will be shipped to the National Institutes of Health Biosample Repository at McKesson BioServices at study weeks 0, 26, 52, and 78. 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 at study week 0. During the course of the trial, all studies using the biorepository samples must receive the approval of the

FSGS Ancillary Studies Committee and follow the study policies of the trial regarding ancillary studies (see Section 14).

6.5. Estimation of Glomerular Filtration Rate

The purposes for estimating glomerular filtration rate (GFR) are to:

a) determine eligibility for the study and
b) 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.

As indicated in inclusion criteria (Section 3) GFR will be estimated by the Schwartz formula if the participant's age is < 18 years and by the Cockroft-Gault formula if participant's age is ≥18 years. The average of serum creatinine values at the baseline and randomization visits (visit numbers B1 and W0; see Section 10.2) will be used for the calculation of the estimated GFR baseline.

6.6. Questionnaires

The questionnaires to be used include a patient symptom checklist, family history, and a quality of life instrument.

The SF-36 - a 36 item quality of life questionnaire for adults age 19 and above. This is a self-administered questionnaire to be completed at baseline, study weeks 26, 52 and 78.

The PedsQL - a 23 item quality of life questionnaire self-reported for children ages 5 –18 and parent proxy-reported for ages 2-5. It will be administered at baseline, study weeks 26, 52 and 78. Validated translations of the SF-36 and the PedsQL will be provided in English, Spanish, and French.

6.7. Monitoring of hospitalizations

If a participant is hospitalized after consenting for the study, the following information about the hospitalization will be recorded at the first visit after discharge: reason for admission, duration of hospitalization, date of admission, date of discharge, changes in study medication, and patient status at the time of discharge. If the hospitalization occurred after randomization, then the DCC and the Clinical Coordinating Center must be informed immediately because this represents a Serious Adverse Event (SAE). Reporting of hospitalizations will use the Hospitalization Form 62 and SAE Form 61.

6.8. Medications

All medications will be recorded at baseline and scheduled study visits during follow-up.

7. BASELINE PERIOD EVALUATION (03/03/04)

7.1. General Principles

The Screening and Baseline periods are expected to last at most two weeks. Before entering Baseline, participants will be screened to ensure that they meet the inclusion criteria and that none of the exclusion criteria are present. A preliminary screening form will be completed (see Form 10). Some eligibility criteria will require confirmation by laboratory tests at visit B1 (see Section 10.2).

7.2. Laboratory Tests from Screening through Randomization

Laboratory tests will include both blood and urine studies. Analyses will be done locally for HCG and by the Core Lab for CBC, serum chemistries, lipid profile and early morning Up/c. GFR will be estimated as indicated in Section 6.5. HCG will be determined as indicated in Section 6.4. During the screening phase, blood samples for HIV and active Hepatitis B and Hepatitis C will be analyzed by the Core Lab.

7.3. Details Regarding Baseline First Morning Urine Specimen

A urine sample will be collected as soon as the participant awakes in the morning prior to engaging in any activity. A specimen will be collected on two mornings prior to the Baseline visit and participants will bring these specimens in to their visit. Participants will be asked if they have/had an intercurrent illness or is/were taking a medication that interferes with creatinine excretion (see Section 6.2). If either of these occurred, the samples will be discarded without being sent to Core Lab and repeat samples will be obtained. Subsequently, baseline samples will be obtained. The baseline Up/c ratio will be calculated as the average of the values measured in the two early morning urine samples.

7.4. Details Regarding Baseline Tests

Blood will be collected at any time of the day, except for lipid profiles, which will be determined in samples drawn after the participant has been fasting for at least 12 hours with a 10 hour minimum for children under age 10. Indication of fasting status and duration prior to blood draw will be documented on the appropriate form. Serum chemistries and CBC will be analyzed by the Core Lab. Instructions for mailing samples to Core Lab are in the Manual of Operations.

Baseline assessments include:

HIV, hepatitis B and C.
SMA18 or equivalent
CBC including differential, ANC and platelet count.
HCG (see Section 6.4)

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 three 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 will be an acceptable alternative.

7.5. Screening Medication Status

During the screening visits, the participating site will:

1) review the indications for all prescribed medication
2) ensure that the participants are not receiving a medication that would result in an exclusion
3) screen for any condition that precludes the participant from being randomized to either of the study regimens

Any medication that does not result in the exclusion of the participant may be continued as necessary during the study.

7.6. History and Physical Examination

A history and physical examination will be performed during the baseline using the Health and Physical Exam form (see Form 46).

7.7. Blood Pressure Measurement

Blood pressure will be measured by trained personnel at each visit using the techniques and procedures listed in the Manual of Operations. A sitting and standing blood pressure will be recorded at each visit.

7.8. Participant Questionnaires

Participant questionnaires administered at baseline include the Disease Information and Detailed Participant Information forms with information on medications, medical conditions, and family history of related disease. A questionnaire concerning socio-economic variables will be optional.

7.9. Assessment of Eligibility and Randomization

Participants will be considered eligible for randomization if they provide all of the required baseline data and no additional exclusion criteria come up during baseline.

8. RANDOMIZATION PROCEDURE (5/1/03)

Treatment assignments for this study will be made using separate randomization schedules for each of the five Core Coordinating Centers.

The randomization schedules will be prepared by the Data Coordinating Center prior to the start of recruitment. Allocation to the treatment groups will be equal and stratified by Core Coordinating Center, baseline estimated GFR (GFR < 90 ml/min/1.73 m^2 vs. GFR $\geq$ 90 ml/min/1.73 m^2), and participant's self-reported race (black vs. non-black). Randomly permuted blocks of random sizes will be used to help balance numbers of participants assigned to both treatment regimens. This method guarantees that at no time during randomization will the participants in the individual groups be grossly unequal.

The randomization process will be centrally administered. All randomization schedules will remain confidential and known only by members of the Data Coordinating Center staff.

Once all baseline period studies have been completed and the forms corresponding to these studies have been received by the Data Coordinating Center, and the forms have been checked to be sure the participant meets eligibility requirements, the Principal Investigator or the study coordinator shall access the interactive randomization program. The program will verify through a defined set of questions that the participant is ready to be randomized and provide a randomized treatment assignment for that participant based upon his or her stratum. The randomization assignment will be displayed on the screen and emailed to the Core Coordinating Center and the Central pharmacy.

Randomization marks the participant's official and irrevocable entry into the Follow-up Period. Once a participant has been randomized, efforts will be made to conduct all evaluations irrespective of whether the participant starts the study treatment regimen, how long the participant continues on the study treatment regimen or not, and how well the participant complies to the study treatment regimen. These efforts should continue until termination of the Follow-up Period. Data collections will continue even if medication must be stopped.

9. THERAPEUTIC INTERVENTIONS (09/14/05)

9.1. General Considerations for Both Treatment Arms

The duration of immunosuppressive therapy will be 12 months. All study medications will be administered orally. In both treatment groups, efficacy will initially be assessed after 6 months and those participants who have not achieved a complete or partial remission will be considered treatment failures and the participants need no longer follow the study treatment regimen. After 52 weeks, immunosuppressive medications will be withdrawn, and participants will remain on ACEi only for an additional 26 weeks.

9.2. Treatment Arm A: Cyclosporine (CSA)

Drug dosage: Participants assigned to this group will initiate treatment with CSA, 5-6 mg/kg per day with a 250 mg/day maximum starting dose, divided into two daily doses. The CSA dose will be adjusted based on drug levels determined at specified study visits in order to achieve a 12-hour trough concentration in the therapeutic range of 100-250 ng/ml.

Dosage Modification to Maintain 12 Hr Trough Level: The CSA trough level will be measured 7 times over the course of the study – after 2, 4, 6, 14, 26, 38 and 52 weeks of therapy. If the level is below the therapeutic range, then the dose will be increased in 1 mg/kg/day increments until a level within the therapeutic range is achieved. If the level is above the therapeutic range, but less than 400 ng/ml, then the dose will be lowered in 1 mg/kg/day decrements (rounded to the nearest 25 mg dose) until a level within the therapeutic range is achieved. If the level is above the therapeutic range and equal to or greater than 400 ng/ml, then the dose will be lowered according to the dose modification algorithm described below. The trough CSA level will be checked within 2 weeks of any dose modification made in response to a trough CSA measurement.

Toxicity Related Indications for CSA Dose Modification: If the CSA level is in the therapeutic range, the CSA dose will only be modified if a change in GFR or an elevated serum potassium level persists after reduction in the ACEi dose (see below):

a) GFR: A decline in GFR of 30% or more below the baseline GFR to GFR ≤ 100 ml/min/1.73m^2 which is repeated and confirmed in a well hydrated participant requires modification

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 or serum potassium is greater than 6 mmol/L, dosage modification should be instituted.

c) Toxic blood levels (greater than 400 ng/ml): See drug levels and dosage modification above.

d) Significant side effects: If thought to be related to CSA, an adverse event form should be completed and the Core Coordinating Center should be contacted.

Dosage Modification for CSA Toxicity: If a, b, c or d above pertain, the dose of CSA should be reduced to 0.67 of the original dose for 2 weeks. If the indication for dosage modification persists, the dose should be reduced to 0.33 of the original dose for 2 weeks. If the abnormality

persists, the medication should be discontinued and the Core Center notified. In participants who take pills rather than liquid formulations, doses will be rounded to the nearest 25 mg.
Subsequent Dosing: The dose of CSA at which a, b or c above is corrected should be maintained for the remainder of the study. If significant side effects (d above) remit with modification of the CSA dose or with discontinuation of CSA, an attempt should be made to return to the original dose in the reverse order of the changes described above.

9.3. MMF and Dexamethasone Pulses Treatment Arm

Drug dosage: Participants assigned to this group will be treated with:

MMF, 25-36 mg/kg per day with a maximum dose of 2 g/day divided into two daily doses. The dose range reflects the use of fixed size (250 mg) capsules and application of defined daily doses to specific weight ranges (see Table below). In younger children or those participants who are unable to swallow capsules, a liquid formulation will be used to provide 36 mg/kg per day to a maximum of 2 g per day. The starting MMF dose will be 0.5-0.67 of the full dose for 2 weeks before advancing to the full dose for the duration of the 12-month treatment period.

The following dosage schedule by subject weight will be used in participants over 12 years of age:

Weight (Kg)	Initial Dose (mg)	Full Dose (mg)	Full Dose in
	AM PM	AM PM	mg/Kg/day
25 - 30	250, 250	500, 250	25 - 30
30 - 40	250, 250	500, 500	25 - 33
40 - 45	500, 250	750, 500	28 - 31
45 - 50	500, 500	750, 750	30 - 33
50 - 55	500, 500	1000, 750	32 - 35
≥ 55	500, 500	1000, 1000	≤ 36

Dexamethasone, 0.9 mg/kg per dose, with a maximum dose of 40 mg, given as a single dose on two consecutive days at the start of weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 34, 38, 42, 46 and 50 for a total of 46 doses.

Toxicity Related Indications for MMF Modifications:

a) G.I. Toxicity: Diarrhea will be treated as follows: infectious causes (C. difficile and enteropathogens) should be ruled out and treated, if necessary. Once excluded, agents such as Lomotil or tincture of opium may be used to decrease diarrhea so that MMF dosing can be maintained. Finally, if diarrhea persists, the MMF dose should be adjusted.

b) Leukopenia: ANC < 1,000 – Discontinue MMF
ANC 1,000-1,500 – Modify dose

c) Anemia: If HCT < 25%, MMF dose should be modified

Dosage Modification for MMF: If a, b, or c above pertain, the dosage of MMF should be reduced accordingly to Step 1 in the table below for 2 weeks. If the indication for dosage modification persists, the dose should be further reduced to Step 2 in the table below for 2 weeks. If the abnormality persists, the medication should be discontinued and the Core Center notified.

Recommended Daily Dose Reduction Guidelines

Maintenance Dose (mg/day)	Dose Reduction (Step 1)	Dose Reduction (Step 2)
Participants Taking Capsules	mg/day	mg/day
2000	1250	750
1750	1250	750
1500	1000	500
1250	750	500
1000	500	250
750	500	250
Participants Taking Liquid		
36 mg/kg/day	24 mg/kg/day	12 mg/kg/day

Reinstituting MMF: After a dose reduction or interruption, every effort should be made within 14-21 days, unless medically contra-indicated, to reinstate MMF in increments until the protocol recommended MMF dose is achieved. Under such circumstances, the dose should be increased in reverse order to that given in the Table above (i.e. Step 2 dose, then Step 1 dose, then Maintenance dose).

Toxicity Related Indications for Dexamethasone Dose Modifications:

a. Hyperglycemia: Serum glucose above the normal range should be initially treated with dietary changes to limit sugar content in foods. If the fasting serum glucose cannot be maintained less than 140 mg/dl or random glucose less than 200 mg/dl during study weeks 1 to 26, the alternate day prednisone dose should be modified as outlined Section 9.4 (Common Therapy). If the fasting serum glucose remains above 140 mg/dl or random glucose above 200 mg/dl after following the modifications to Common Therapy outlined in Section 9.4, the dexamethasone dose modification should be instituted.

b. Neuropsychiatric: The dexamethasone dose modification should be instituted for any of the following toxicities

1. Major depression documented by a psychiatric evaluation
2. Psychotic behavior documented on a psychiatric evaluation
3. Pseudotumor cerebri confirmed by a neurological / ophthalmologic evaluation and imaging study

c. Miscellaneous: The dexamethasone dose modification should be instituted for severe muscle weakness

Dosage Modification for Dexamethasone Toxicity: If any of the toxicities defined as a, b, or c above occurs, the dose of dexamethasone should be reduced to 0.67 of the original dose (Step 1) for both treatment days for the next scheduled dosing week. If the indication for the dosage modification persists for the subsequent 2 weeks, the dose should be reduced to 0.33 of the original dose (Step 2) for both treatment days for the subsequent scheduled dosing week. If the abnormality persists 2 weeks after the Step 2 dexamethasone dose adjustment, the medication should be discontinued and the Core Coordinating Center notified.

Subsequent Dosing: If the dexamethasone dose is modified during the initial 8 weeks of the study, the dose of dexamethasone at which the toxicity is corrected should be maintained for the remainder of the weekly study doses (i.e. study weeks 1-8). When the participant progresses to the study weeks 10 through 50, attempts should be made to increase the dexamethasone dose (or reintroduce dexamethasone following discontinuation of dexamethasone) in a stepwise fashion, i.e. Step 2 to Step 1 etc., to return to the full dose where possible.

9.4. Common Therapy in Both Treatment Arms

Drug Doses: Participants assigned to either study group will be treated with:

Prednisone (prednisolone for children taking the liquid preparation): 0.3 mg/kg per dose to a maximum dose of 15 mg, administered as single dose every other day for the first 6 months of the 12-month treatment period. The dose will be stopped after 6 months and it will not be tapered.

ACEi: A maximally tolerated dose of the angiotensin converting enzyme inhibitor, lisinopril will be attempted in three steps at two-week intervals (see chart below). The initial daily dose will be instituted at commencement of the study. If tolerated the intermediate dose will be given two weeks later and the maintenance dose will be achieved two weeks later if no symptoms or side effects occur. For participants less than 25 kg a liquid formulation of lisinopril (1 mg/ml) may be utilized with an initial daily dose of 0.1 mg/kg, an intermediate dose of 0.2 mg/kg and a maintenance daily dose of 0.4 mg/kg. Doses for participants taking capsules are given below:

Participant Weight (Kg)	Initial Daily Dose (mg)	Intermediate Dose (mg)	Maintenance Daily Dose (mg)
<25	2.5	5.0	10
25 – 35	2.5	7.5	15
35 – 45	5.0	10	20
45 – 55	5.0	12.5	25
55 – 65	7.5	15	30
65 – 75	7.5	17.5	35
>75	10	20	40

This medication may be started prior to commencing therapy with the specific agents outlined for treatment Arms A and B. In the absence of toxicity, the ACEi dose will remain unchanged for the remainder of the 18-month treatment period. Participants who are unable to tolerate treatment with ACEi or who have been previously intolerant of ACEi will receive an angiotensin receptor blocker (ARB) losartan. Dosing of losartan per table below.

Participant weight	Initial daily dose	Maintenance daily dose
<50 kg	0.5 mg/kg	1 mg/kg
≥50 kg	50 mg	100 mg

Participants will not be administered ACEi and ARB therapy simultaneously during the trial.

Toxicity Related Indication for lisinopril or losartan Modification:

a) GFR: A decline in GFR of 30% or more below the baseline GFR to GFR ≤ 100 ml/min/1.73m^2 which is repeated and confirmed in a well hydrated participant requires modification

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 or serum potassium is greater than 6 mmol/L, dosage modification should be instituted.

c) BP: Symptoms of orthostatic hypotension.

d) Cough: Persistent cough unrelated to other causes. (lisinopril only)

Dosage Modification for lisinopril or losartan: If a, b or c above pertain, the dose of lisinopril or losartan should be reduced to 0.67 of the original dose for 2 weeks. If the indication for dosage modification persists, the dose should be reduced to 0.33 of the original dose for 2 weeks. If the abnormality persists, the medication should be discontinued and the Core Center notified. If d above pertains (i.e., the participant has persistent cough unrelated to other causes) and the participant is on lisinopril, then lisinopril should be discontinued and treatment with ARB should be instituted and toxicity monitored. If d above pertains and the participant is on losartan, then losartan should be discontinued.

Subsequent Dosing: 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 (see dosage modification above), treatment with ARB should be instituted (see table above) and toxicity monitored (as above).

Toxicity Related Indication for Prednisone/Prednisolone Modification:

Hyperglycemia: A fasting serum glucose above 140 mg/dl or random above 200 mg/dl repeated and confirmed after dietary modification requires prednisone dose modification.

Dosage Modification for Prednisone/Prednisolone: If sustained hyperglycemia persists as defined above, the alternate day prednisone should be discontinued and the Core Coordinating Center notified.

9.5. Treatment of Relapses

If a participant has achieved a partial or complete remission while on therapy, the participant will be considered to have developed a relapse if the following occurs:

a) A complete remission (Up/c < 0.2) is followed by the occurrence of a Up/c > 2.0.

b) A partial remission (Up/c of 0.2-2.0 and < 50% of baseline value) is followed by the occurrence of a Up/c > 2.0 which is two-fold greater than the nadir of the Up/c which is documented by the Core Lab.

If either (a) or (b) above occurs on 1 or more occasions and are associated with a serum albumin < 3 g/dl, the participant is eligible for relapse therapy while remaining on treatment arm A or B and common therapies.

Relapses may be treated with prednisone 2 mg/kg/day to a maximum of 60 mg daily for two weeks followed by same dose on alternate days for one week. The Up/c should be repeated at the end of the three weeks of therapy to determine the effect of the relapse treatment and the participant is to remain on either treatment arm A or B and common therapies whether or not the Up/c is changed.

Treatment of relapses is optional but if treated, this therapeutic regimen must be employed. Relapse therapy may be implemented on not more than two occasions during the first 12 months of the clinical trial. Additional relapses are to remain untreated. If a participant is receiving relapse therapy at 26 or 52 weeks, assessment of clinical status should be accomplished one week after completion of the relapse therapy regimen.

10. FOLLOW-UP EVALUATION (03/03/04)

10.1. General Principles

The purposes for follow-up visits are:

c) to ensure compliance with the protocol and to acquire data that ensures protocol adherence;

d) to assess the participant's clinical status including general well-being, the development of new symptoms or physical findings, and to ascertain the course of the underlying disease;

e) to evaluate possible adverse events and side effects related to the study medications and to evaluate abnormal laboratory values;

f) to make changes in the medications as defined by protocol, and

g) to identify participants who reach a Medication Stop Point.

Scheduling Follow-Up visits: If a visit or procedure is missed, the visit should be rescheduled as soon as possible within the allotted interval. An interval of +/- one week is targeted for all protocol visits. If participants are receiving relapse therapy at visit W26, W52 or W78, the visit will be delayed until one week after completion of the relapse protocol (see Section 9).

10.2. Schedule of Visits and Laboratory Tests

Visit Number	Weeks	Clinical Objectives	7 Basic Labs [2]	3 Addi-tional Labs[3]	8 Extended Labs[4]	Fasting Lipids[5]	Up/C[6]	Cyclo-sporine Drug Level[7]	Hematology (CBC)[8]	
									MMF Arm	CSA Arm
B1	-1 or –2	Informed consent baseline studies[1]	X	X	X	X	X		X	X
W0	0	Confirm pregnancy test Initiate RX	X				X		X	
W2	2	Interval Assessment	X				X	X	X	
W4	4	Interval Assessment	X			X	X	X	X	
W6	6	Interval Assessment	X				X	X	X	
W8	8	Interval Assessment	X	X			X		X	X
W14	14	Interval Assessment	X				X	X	X	
W20	20	Interval Assessment	X	X			X		X	X
W26	26	Interval Assessment	X	X	X	X	X	X	X	X
W32	32	Interval Assessment	X				X		X	
W38	38	Interval Assessment	X	X			X	X	X	X
W44	44	Interval Assessment	X				X		X	
W52	52	Interval Assessment	X	X	X	X	X	X	X	X
W65	65	Interval Assessment	X				X		X	
W78	78	Interval Assessment	X	X	X	X	X		X	X

1) Baseline studies: Studies to be performed at baseline are described in Section 7.
2) The 7 basic blood chemistries measured at each visit include: BUN, creatinine, sodium, potassium, chloride, CO_2, and glucose.
3) In addition to the 7 basic blood chemistries, serum albumin, aspartate transaminase (AST), and ALT will also be measured at visits B1, W8, W20, W26, W38, W52, and W78.
4) In addition to the 10 blood chemistries listed above, the following 8 extended measurements will be obtained at B1, W26, W52, and W78: total protein, alkaline phospatase, total bilirubin, calcium, phosphorus, uric acid, magnesium, gamma-glutamyltransferase. After W78, blood tests will be done at 6-month intervals and will include BUN, serum creatinine, and serum albumin.
5) Fasting lipid profiles will be included at visits B1, W4, W26, W52, and W78.
6) Up/c: Value will be determined on two early morning urine specimens and the average of the two determinations will be recorded as the value at visits B1, W26, W52, and W78. A single Up/c will be collected at each additional scheduled visit. Procedures for the collection or the first morning specimens will be the same as described in baseline evaluation (see Section 7). At visits with two Up/c measurements, a third urine sample will be obtained if the discrepancy between the Up/c on the first two urine samples is

such that the higher value is 1.5 x the lower value. The two samples closest in value will be averaged. After W78 Up/c will be done at 6-month intervals.

7) Cyclosporine drug levels will be measured only in the CSA arm.
8) CBC with platelet count will be obtained at all visits in the MMF arm, and at visits B1, W8, W20, W26, W38, W52, and W78 in the CSA arm.
9) Urine HCG pregnancy test for post-menarchal females done at visits B1, W0, W14, W26, W38, W52, and W65.
10) Quality of life (SF-36 in adults, PedsQL in children) at visits B1, W26, W52, and W78.
11) Extended follow-up: After week 78, visits will continue to be held at 6-month intervals until termination of trial. Visits M24, M30, M36, M42, and M48will include physical examinations, measurements of Up/c, serum creatinine, BUN and albumin, and medication use.
12) For those participants who consent to provide biologic samples for the biorepositories, urine, serum, and plasma specimens will be shipped to the NIDDK Biosample Repository at McKesson Bioservices at the W0, W26, W52, and W78 visits. Whole blood specimens for DNA extraction will also be obtained at the W0 visit and shipped to the NIDDK Genetics Initiative at the Rutgers University Cell and DNA Repository for those participants who provide consent.

10.3 Physical Examinations

A complete physical examination will be done at weeks 14, 26, 38, 52 and 78 (see Form 46). Blood pressure will be measured at each visit. A limited history and physical examination will occur at each follow-up visit and will include weight, vital signs, blood pressure, heart and lung exam, assessment for ascities or peripheral edema, and assessment for study related toxicities.

10.4. Monitoring of Hospitalizations

All hospitalizations, elective and acute, will be reported for trial participants. Hospitalization after randomization will constitute a SAE. In this instance a Hospitalization Form 62 and SAE Form 61 must be transmitted to the coordinating center within 24 hours of the participating sites awareness of the hospitalization. The information that will be collected for hospitalizations is described in Section 6.7.

10.5. Participant Questionnaires

Participants will be asked at each visit to volunteer symptoms experienced since the last visit including intercurrent illness and hospitalizations. An FSGS symptom checklist, coded using the MedDRA system, will be used to record specific and volunteered responses. Quality of life questionnaires will be administered at weeks 26, 52, and 78 (see Section 6.6).

10.6. Interim Visits

These visits will occur as frequently as necessary in between scheduled protocol Follow-Up visits for evaluation of safety issues, abnormal laboratory results, documentation of changes in proteinuria or for adjustment of medications. At a minimum, a limited evaluation will occur at each non-protocol visit. The reason for the non-protocol visits and the findings at these visits will be recorded in the database.

10.7. Missed Visit or Measurement

If any follow-up visit is missed and cannot be rescheduled within the allowable +/- one week tolerance interval, the visit should be rescheduled as soon as possible after the close of the tolerance interval.

10.8. Participant Transfers

If study participants move from one participating site to a different participating site, efforts will be made to maintain the treatment regimens specified in the Protocol, and to document the subsequent clinical course and renal function. If a participant moves into a geographic area served by a different participating site, the participant (with informed consent) will be reassigned to the care of the new center, in the treatment group to which they were originally randomized. Data will be reported to the Core Coordinating Center aligned with the new participating site. A Transfer Form must be completed.

10.9. Close Out/End of Study

At the end of the clinical trial, the results of the study will be provided to the Participating Sites. Participants will receive summaries of their own data and participant-friendly summaries of the study results. Study data forms and the study database will be archived.

11. ADVERSE EVENTS AND DEVIATIONS FROM ASSIGNED TREATMENT (03/03/04)

11.1. Adverse Events

All adverse events will be documented on study data forms, Adverse Event Form 60 or Serious Adverse Form 61. The forms will request information regarding the diagnosis, timing and whether or not the adverse event was related to the study participation or study medication. A serious adverse event is defined as:
a. Death
b. Life-threatening event
c. Requires or prolongs hospitalization
d. Results in disability significant, persistent or permanent
e. Pregnancy with a resultant birth defect
f. Causes cancer
g. Overdose of a study medication

In addition to the completion of the appropriate forms, any serious adverse event or unanticipated adverse event occurring during the study or in a post-study period of reasonable duration must be reported to the principal investigator of the Clinical Coordinating Center by telephone and to the local IRB within 2 business days.

The data base will automatically send electronic reports describing serious adverse events which are potentially related to the study drug to the NIDDK project officer, and if requested to designated contact persons from the manufacturers of the study drugs.

11.1.1. Deaths

A death of a study participant is a serious adverse event and must be reported to the local Institutional Review Board and to the Clinical Coordinating Center as for any Serious Adverse Event (See Section 11.1). A Death Report Form 63 will be completed and submitted within 2 business days of the participating site investigator's awareness of the occurrence. The Death Report Form requests information regarding the cause of death, date of death, and asks for the investigator's determination as to the relationship of the death to study participation. If complete information regarding the cause of death is unknown and awaiting autopsy results or other information, a second Death Report form must be submitted when a final determination has been made.

11.1.2. Hospitalizations

For the purposes of the study, a hospitalization is defined as an overnight stay as a patient in a hospital facility. All hospitalizations occurring after consent for participation has been obtained is considered a Serious Adverse Event and must be reported using the Hospitalization form and the SAE form. Hospitalization admission and discharge dates, up to 3 diagnoses and 3 procedures will be noted. A determination of the relationship of the hospitalization to the study participation will be made by the Participating Site investigator.

11.1.3. Other adverse events

Adverse events that do not meet criteria for Serious Adverse Event as defined in Section 11.1 will be reported using the Adverse Event Form 60 during the follow up visit. Information regarding the diagnosis, date of occurrence, severity of the event and therapy will be recorded.

A determination of the relationship of the adverse event to the study participation will be made by the Participating Site investigator.

11.2. Study Mandated Deviations from Assigned Treatment. Medication Stop Points.

11.2.1. Definition

A stop point can only occur after the participant is randomized and denotes the occurrence of an event, which necessitates altering the interventions of the study (i.e., cessation of CSA or MMF). Visits and data collection continue after stop points. 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 of the deviation if at all possible. If possible the participant will resume the intervention at a later time.

The Core Coordinating Center Principal Investigator and Study Coordinator will complete a Medication Termination Form 45. The DCC and Clinical Management Subcommittee reviewers jointly complete a stop point confirmation form.

General Stop Points:

1. Pregnancy
2. Decline in GFR: 50% decline from baseline in estimated GFR to GFR ≤ 75 ml/min/1.73m^2
3. Maintenance dialysis
4. Medication related toxicity (see Section 9)

11.3. Measurements at the Time of a Stop Point

When a Stop Point has been confirmed by Clinical Management Subcommittee Review, a measurement of serum SMA 18, cyclosporine level, CBC, lipids, and Up/c will be obtained

11.4. Follow-Up After Stop Point

Following treatment failures, which determine the primary and main secondary outcomes, participant follow-up will be scaled back to semi-annual assessments including the following information:

1. Labs tests including Up/c, serum creatinine, serum albumin, and BUN

2. Vital status and dialysis status will be ascertained

However, in accordance with the intent-to-treat analysis plan, the standard study measurement schedule described in Table 10.2 will be maintained following the pregnancy and medication stop points which do not define the primary or main secondary outcomes.

12. ANALYSIS PLAN (03/03/04)

12.1. General Methods

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Inferential analyses for continuous variables will generally be conducted using linear models such as analysis of variance and multiple regression. Highly skewed variables may be transformed prior to inferential comparisons [Carroll 88]. Categorical variables will be analyzed with logistic regression, general multinominal response models, and multinominal logit models for ordered categorical outcomes as appropriate [Agresti 90, Lloyd 99]. Cox regression and other survival analysis methods [Klein 97] will be used to analyze time-to-event data. Interpretation of multiple tests resulting from subgroup analyses and multiple endpoints will take into account the problem of multiple comparisons [Pocock 87].

Baseline analyses. To assess external generalizability, demographic and clinical characteristics, which enter the baseline phase of the study, will be compared between participants who are subsequently randomized and participants who are screened but not randomized. The specific eligibility and exclusionary criteria by which participants are excluded from randomization will be tabulated. Demographic and clinical characteristics will be compared among the clinical coordinating centers and between the treatment groups to identify any imbalances.

12.2. Analysis of Primary Remission Outcome

12.2.1. Primary Analysis of Response Status

The primary statistical analysis will compare the six-level ordered categorical variable characterizing status during the first year of follow-up defined in Section 2.2 between the treatment groups. The six levels will be assigned scores ranging from 1 (for the most favorable category) to 6 (for the least favorable category). The mean response score will be compared between the CSA and MMF/Pulse steroid groups within each of the four randomization strata defined by baseline estimated GFR (GFR < 90 ml/min/1.73 m^2 vs. GFR $\geq$ 90 ml/min/1.73 m^2), and race (black vs. non-black). Standard errors for the difference in remission score between treatment groups will be obtained as linear combinations of multinomially distributed proportions of participants in the respective remission categories.

The comparison of the CSA and MMF/Pulse steroid regimens in the primary analysis will be carried out by intent-to-treat with participants retained in their randomized groups regardless of whether they have maintained and adhered to their randomly assigned treatment regimen. For participants missing either their 26-week or 52 week visits the primary remission score will be defined based on their next available first morning urines obtained after these visits. For participants who die, reach ESRD, or reach the 50% declining GFR stop point, all subsequent scheduled protocol assessments of proteinuria will be treated as non-remissions for the definition of the primary outcome. Thus, these participants will be assigned a score of either 4, 5 or 6, depending on whether they had a partial remission at week 26 or earlier in follow-up. The same procedure will be used for participants who are lost to follow-up for other reasons at or before the Week 26 visit. Participants who achieve at least a partial remission at week 26 but become lost to follow-up after their Week 32 visit will be assigned a score between 1 and 4 depending on their available Up/c measurements. The CSA group will be regarded as the reference group and the MMF/Pulse steroid groups as the treatment group for expression of treatment effects in the primary analysis. However, due to the expectation that beneficial effects

may be observed in either direction, a 2 sided test will be conducted at the 5% significance level.

12.2.2. Explanatory Analyses of the Primary Outcome

While the pre-specified analysis plan will be strictly adhered to for the primary analysis, additional explanatory analyses will be conducted to more fully characterize the relationship between the outcome, the treatment interventions, and prognostic covariates based on interactive analysis of the data. Multinomial logit regression methods for ordered categorical outcomes [Lloyd 99] will be developed to investigate multivariable models relating the odds or scores < k, for k = 2,3,4,5,6 to the randomized treatment groups and baseline variables. To simplify the statistical analysis and interpretation of the results, consideration will be given to combining levels 4, 5, and 6 into a single category designated treatment failure, and to combining levels 1 and 2 into a single category designated complete remission in these regression models.

In addition to the intent-to-treat analysis, which compares participants according to their randomized groups, the marginal structural modeling approach proposed by J Robins and colleagues [Robins 98, Gill 2001] will be used to relate response status to the components of the MMF and CSA regimens, which are actually received by the participant. The results of this analysis will be interpreted cautiously, in view of the well-known limitations of such as-treated analyses [Sheiner 95].

Due to the stipulated intent-to-treat strategy, we expect the primary outcome to be ascertained for at least 97% of randomized participants. Hence, the risk of bias in the primary analysis due to non-ascertainment of the primary outcome is low. However, a sensitivity analysis of the effects of loss-to-follow-up will be conducted using a standard multiple imputation procedure [Verbeke 2000] in which the level of the primary outcome for participants lost to follow-up prior to 52 weeks is projected based on baseline prognostic factors and the levels of Up/c observed while the participant remained in the study. Multiple imputations will also be used in sensitivity to estimate intermediate missing values of Up/c while patients remain in the study prior to computation of the levels of the primary and main secondary endpoints.

12.2.3. Power of the Primary Analysis

The determination of the power of the study depends on the proportions of participants, who fall into each of the five ordered categories of the primary outcome. Results for previous studies of CSA-based regimens in participants with biopsy proven include: [Cattran, 99] with 6% complete and 36% partial remissions at 12 months follow-up in 49 adult FSGS participants treated with a combination of CSA and prednisone; [Chishti 01] with 52% complete remission (defined by absence of dipstick proteinuria] and 24% partial remission at any time during follow-up; [Lieberman 96] with 4 complete and 8 partial remissions in 12 CSA treated participants, and [Inguilli 95] with approximately 33% complete remissions at any time during follow-up among 21 participants treated with CSA and low dose prednisone. The criteria for complete remission varied substantially among these studies, and no prior study has employed a 6-level categorization of remission status similar to that of this study. Generalizing these studies to the present trial is complicated by variations among studies in participants and treatment protocols, and responses in single center trials can be more favorable than in broader populations. The Chisti and Inguilli studies counted complete remissions at anytime during follow-up, and may have reported higher response rates than can be expected in the present study where remissions must be observed at 52 weeks. Therefore, we consider three difference scenarios

(labeled A, B, and C) corresponding to a range of response rates in the control group (CSA) to evaluate statistical power. The power calculations assume that a total of 500 participants will be randomized, of whom the primary outcome will be ascertained in 485. Observe (see Section 2.2) that the combination of levels 4, 5 and 6 correspond roughly to the definitions of treatment failure, and the combination of levels 1 and 2 to the definitions of complete remission that have been used in previous studies.

Smallest Detectable Treatment Effects Under Alternative Scenarios

Scenario	Level	Assumed percentage at this level in CSA group	Closest detectable event rates in MMF/Pulse Steroid Group (% difference in square brackets)		Minimum detect treatment effect (OR)	
			80% power	90% power	80% power	90% power
A	6	22.5	15.4 [-31%]	14.5 [-35%]	1.59	1.71
	5	22.5	18.5 [-18%]	17.8 [-21%]		
	4	22.5	22.7 [1%]	22.5 [0%]		
	3	22.5	28.3 [26%]	29.2 [30%]		
	2	5	7.3 [46%]	7.7 [54%]		
	1	5	7.7 [54%]	8.3 [65%]		
B	6	18.3	12.4 [-32]	11.7 [-36]	1.58	1.70
	5	18.3	14.4 [-22%]	13.7 [-25%]		
	4	18.3	16.8 [-8%]	16.4 [-10%]		
	3	25	28.1 [12%]	28.4 [13%}		
	2	10	13.4 [34%]	13.9 [39%]		
	1	10	15.0 [50%]	15.9 [59%]		
C	6	13.3	8.8 [-34%]	8.3 [-38%]	1.59	1.71
	5	13.3	9.8 [-27%]	9.3 [-30%]		
	4	13.3	10.9 [-18%]	10.5 [-21%]		
	3	30	30.0 [0%]	29.7 [-1%]		
	2	15	18.6% [24%]	19.1 [27%]		
	1	15	21.9 [46%]	23.2 [55%]		

For conciseness, the power calculations were performed assuming that the odds ratio for achieving a level < k between the MMF + pulse steroid vs. CSA groups is the same for k = 2, 3, 4, 5 and 6. Note, however, that common odds ratios are not an assumption for the statistical analysis. The minimum detectable odds ratios under the three scenarios considered are listed for 80% and 90% power in the final two columns of the table. The fourth and fifth columns list the corresponding event rates in the MMF + pulse steroids group, with percent differences in event rates between the MMF + pulse steroid and CSA groups provided in square brackets.
Under Scenario A, the study has 80% power to detect an increase in the overall remission rate (including levels 1, 2, or 3) from 32.5% to 43.3% (a relative percent increase of 33.2%). Similarly, the study has 80% power to detect an increase in the overall remission rate from 45% to 56.5% (a relative percent increase of 25.5%) under Scenario B, and from 60% to 70.5% (a relative increase of 17.5%) under Scenario C, recognizing that the assumed power depends in part also on the hypothesized differences among the specific categories of remissions and non-remissions.

As can be seen, the study design has sufficient power to detect moderate or large differences in response rates between the two treatment arms. However, there is limited power to detect relatively small treatment effects. This indicates that while this study design has sufficient power to identify a clearly superior intervention, the primary analysis is not powered to establish equivalence between equally efficacious interventions.

12.3. Description of Interventions

Characteristics of the treatment interventions to be summarized include the proportions of participants withdrawn from the primary medications at any time during the 52-week follow-up period, the average number of dosage adjustments required, the proportion of participants who tolerate the maximum dose, the time-averaged dose employed.

12.4. Secondary Outcomes

12.4.1. Other Analyses of Proteinuria

The 5-level main secondary outcome defined in Section 2.3 regarding the persistence of remissions following termination of immunosuppressive therapy will be analyzed by adapting the method used to analyze the primary outcome.

As described in Section 12.2, in accordance with the intent to treat principle remissions at weeks 52 or 78 may be counted in defining the primary and main secondary outcomes even if participants have previously discontinued their randomized therapy or initiated alternative treatments. Thus, secondary analyses will be conducted in which participants who deviate from their randomized treatment regimens will be classified as treatment failures (i.e., assigned to levels 1 or 2 depending on when the participant discontinued the randomized therapy) in the definitions of the outcomes.

Other secondary analyses of proteinuria will employ longitudinal methods to evaluate the effects of the treatment interventions on the pattern of change in proteinuria including all the protocol follow-up assessments. The effects of the randomized treatment groups on Up/c as a continuous variable will be characterized by developing longitudinal mixed effects models [Verbeke 00, Liang 95] for the change in the mean Up/c (or in the geometric mean, if Up/c is heavily positively skewed) from baseline throughout follow-up. The effects of treatment

assignment on the proportions of participants with the three types of remission status (none, partial, and complete) over time will be addressed with longitudinal models adapted for ordered categorical response variables [Liang 92, Toledano 99]. Standard survival analysis methods will be used to compare the amount of time until the first remission. Relapse rates (defined in Section 9.5) will be summarized for relevant periods during follow-up, with the recognition the comparison of relapse rates between the treatment groups will not be a true randomized comparison since they are defined conditionally based on the occurrence of a remission. In particular, the proportions of participants who experience relapses during the period from weeks 52 to 78 after termination of therapy will be compared between the treatment groups for the subsets of participants achieving either complete or partial remissions on the primary therapy at 52 weeks.

12.4.2. Analyses of Renal Function

Mixed effects models will be used to perform longitudinal analyses estimated GFR [Verbeke 00]. Analyses will be performed for the effects of treatment assignment both on mean change (slopes) in estimated GFR over time and on the rate of the composite renal outcome defined by ESRD or a 30% reduction in estimated GFR from the mean of two baseline values. In this setting where many participants may have normal renal function, the latter “event-based” approach may be the most informative [Greene 01]. The mean estimated GFR slope and the rates of the composite renal outcome will also be related to the primary and main secondary outcomes for remission of proteinuria.

12.4.3. Extrarenal Complications and Side Effects

The proportions of participants with specific adverse events will be compared between the treatment groups using exact tests for comparing binomial proportions [Agresti 92]. Adverse events to be investigated include side effects and toxicity of all medications (e.g., GI complaints, diarrhea, infection and cough, see Section 9) and any adverse events reported by Participating Sites. Changes between baseline and follow-up will be compared between the treatment group using mixed-effects models or generalized estimating equations as appropriate for the following parameters: systolic and diastolic blood pressure, body mass index, serum magnesium, serum potassium, fasting LDL, HDL, and total cholesterol, uric acid, and white blood cell count. The change from baseline to follow-up in the number of non-study medications required will be considered as a surrogate marker for other complications related to medications or the clinical course of FSGS.

The full profile of side effects and extra-renal complications will be compared between the randomized groups, recognizing the likelihood that different subsets of side effects and complications are likely to be increased in one or the other treatment arms. Multivariate statistical methods, including multivariate analysis of variance and structural equations models, will be used in an exploratory fashion to provide aggregate comparisons of the treatment groups across multiple side effects and complications.

The rate of hospital admissions will be compared between the treatment groups using appropriate methods (e.g., overdispersed Poisson regression, frailty models) for comparison of repeated event data [Therneau 00].

12.4.4. Quality of Life

In adults, the main analysis of quality of life will compare the effects of the interventions on the change in the physical and mental composite scores of the SF-36 from baseline to the average over the 26 and 52 week assessments, controlling for corresponding baseline SF-36 composite score and the randomization stratification factors as covariates. In children, the main quality of life analysis will compare the effects of the interventions on the change from baseline to the average over the 26 and 52 week assessments in the overall score from the PedsQL, with the same approach to covariate adjustment as for the SF-36 in adults. A pooled comparison of the treatment groups included both children and adults would be desirable for increased statistical power. However, a combined analysis including children and adults will be complicated by the absence of a well-validated overall quality of life composite index from the SF-36 (the SF-36 has distinct physical and mental composite scores rather than a single overall index), and more generally by the absence of a validated methodology for pooling quality of life results between children and adults. However, we plan to summarize the overall SF-36 results in adults using the first principal component based on the eight SF-36 subscales at baseline. Then, after standardizing the first principal component of the SF-36 and the overall PedsQL score to have the same variances, the treatment effects on the changes from baseline to follow-up in the standardized overall quality life scores may be compared between the children and adults. In the absence of a statistically significant interaction, consideration will be given to pooling the comparisons of the overall scores between children and adults.
In adults, additional analyses will be conducted to evaluate effects of the interventions on the the 8 specific subscales of the SF-36. In children, additional analyses will be conducted to test effects of the interventions on the physical functioning, social functioning and school functioning subscales. All of these analyses will be conducted using mixed effects models to account for multiple measurements in the same participants over time.

12.5. Subgroup Analyses

Interaction terms between the treatment comparison and baseline factors pre-specified participant subgroups will be used to test for differences in the treatment comparison of the primary outcome and other outcomes between different subgroups. The Steering Committee has pre-specified age, race, gender, level of baseline proteinuria, level of baseline estimated GFR, baseline blood pressure, time from diagnosis of FSGS to randomization, baseline hyperlipidemia, use of lipid lowering agents at baseline, family history of FSGS, and total amount of prior immuno-suppressive or ACEi/ARB therapy as factors to consider in subgroup analyses.

12.6. Interim Analyses

The External Advisory Committee/Data Safety and Monitoring Board will meet regularly to review the safety of the participants during the course of the study. The External Advisory Committee will review data regarding adverse events and other indicators of participant safety, recruitment, retention, deviations from assigned treatments, quality control, and interim analyses comparing the primary and main secondary outcomes between the CSA and MMF + pulse steroid arms. Meetings will be held at least annually after the initiation of enrollment. A formal stopping rule using a Lan-DeMetz (Lan et al, 1983) spending function constructed according to an O'Brien-Fleming design will be applied to the primary outcome of remission status at 1 year. A total of three looks at the primary outcome results (two interim looks and the final analysis) are planned.

The decision for an early termination of the trial due to demonstration of superiority of one of the interventions is recognized to be complex. Thus, in addition to the formal stopping rule a decision for early termination will take into account other secondary analyses, including comparisons between the treatment groups of the main secondary outcome of the persistence of a remission following withdrawal of therapy, and of extra-renal complications of the interventions.

13. QUALITY CONTROL (03/03/04)

13.1. Quality Control Introduction

In addition to the quality control methods and programs routinely used at the Core Lab, quality control mechanisms for the FSGS-CT are outlined in the following sections.

13.2. Certification of Participating Sites

A site will be considered certified when the following have been submitted to the DCC database:

1. Name of investigator
2. Name of study coordinator (or, if no study coordinator is designated, name of back up investigator)
3. Date of contract with Core Coordinating Center (Contracts will include the plans for payments and data entry, and will note that the Participating Site agrees to abide by the study's publications policies.
4. Date the IRB affiliated with the Participating Site has approved the FSGS-CT Protocol

13.3. Training and Certification of Personnel at Participating Sites

Core Coordinating Center and participating site personnel are trained and certified for the specific tasks they perform and undergo certification as to their competence. Individuals who have multiple titles and responsibilities with regard to this study must be trained and certified for each responsibility. The training and certification requirements for each member of the study team are given below:

Investigators
No specific training and certification measures are required for Principal Investigators and Co-Investigators unless they are responsible for performing study measurements or procedures. All investigators are expected to be actively involved in study activities at their center, in study-wide committees (as assigned), and in meetings of the Steering Committee.

Study Coordinator
The primary Study Coordinator from each of the core centers must attend a Study Coordinator training.

13.4. Pregnancy Testing

Urine pregnancy tests will be assessed centrally at the Core Lab at Baseline and specified follow-up visits in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized).

13.5. Check In Calls for Participating Sites

For every participating site that has less than two participants currently being followed, the Core Coordinating Center will check in on that Participating Site at least once every calendar quarter. A Check In call will include the Core Coordinating Center's study coordinator or designate talking to the Participating Sites' PI or Study Coordinator to make sure that the Participating Site remembers that the study is going on, remembers the treatment regimens to which participants are being randomized, and remembers the study schedule of measurements.

13.6. Site Visits

Site visits are to be made to each of the Core Coordinating Centers in years 1 and 2. The primary goals of the site visits are:

1) to observe the clinic under normal operating conditions for adherence to protocol;
2) to increase/improve communication between the study administration, the clinic personnel and the DCC; and
3) to demonstrate the study's concern for the quality of data collection.

Site visit teams consist of a DCC staff member familiar with the FSGS protocol and an NIH representative. A Study Coordinator from another core center may be included. All site visits teams will compile a report, which is given to the Core Coordinating Center PI and to the DCC. These reports will be reviewed by the Quality Control Subcommittee and the Steering Committee. Participating Sites will be site visited on an as-needed basis. Sites selected for site visits will be those with especially large enrollment or those having difficulty with study procedures. The CCC will have regularly scheduled contact with all Participating Sites.

A special committee will be formed to site visit the DCC on a regular basis. The exact membership of this committee will be determined by NIDDK. It is expected to include a representative from NIDDK, representatives from one or more of the Core Coordinating Centers, a representative from the External Advisory Committee, a biostatistician and a clinical trials expert. The Chairman of the Steering and Planning Committee may be included.

13.7. Quality Control of the Core Lab

Data from the Core Lab will be securely transmitted in batches and quality controlled in the same manner as Core Coordinating Center data; i.e. data will be entered and verified in the database on the Cleveland Clinic Foundation SUN with a subset later selected for additional quality control. Appropriate edit checks will be in place at the key entry (database) level.

The Core Lab is to have an internal quality control system established prior to analyzing any FSGS samples. This system will be outlined in the Manual of Operations for the Core Lab(s) which is prepared and submitted by the Core Lab to the DCC prior to initiating of the study.

At a minimum this system must include:

1) The inclusion of at least two known quality control samples; the reported measurements of the quality control samples must fall within specified ranges in order to be certified as acceptable.

2) Calibration at FDA approved manufacturers' recommended schedules.

13.8. Quality Control of the Biopsy Committee

The chair of the pathology committee will circulate to all of the study pathologist (see Section 5.5) samples biopsy specimens for evaluation after criteria to establish diagnosis of FSGS has been agreed. This internal review process will serve to ensure common criteria and assessment of biopsy specimens for confirmation of diagnosis of FSGS.

13.9. Quality Control of the Data Coordinating Center

Any and all paper forms or copies of forms (i.e., copies of de-identified informed consent signature pages) that pertain to the FSGS-CT will be filed in a logical and consistent manner in the participant's file at the DCC. Participant files will be stored in numerical order and stored in a secure and accessible place and manner.

13.9.1. Participant Recruitment

The Data Coordinating Center will produce summary recruitment reports weekly and detailed reports monthly. These reports should be verified by each Core Coordinating Center and discrepancies reported to the DCC.

13.9.2. Data Forms and Data Entry

In the FSGS-CT, all data will be entered electronically. This may be done at a Core Coordinating Center or at the participating site where the data originated. Original study forms will be entered and kept on file at the participating site. A subset will be requested later for quality control; when a form is selected, the participating site staff will pull that form, copy it, and sent the copy to the DCC for re-entry.

Any and all paper forms or copies of that pertain to the FSGS-CT are to be filed in the participant's FSGS file in a logical and consistent manner to provide accessibility for the duration of the study. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 3 years after completion of the study.

13.9.3. Data Transmission and Editing

The data entry screens will resemble the paper forms approved by the Steering Committee. Data integrity will be enforced through a variety of mechanisms. Referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks) will be supported. The option to chose a value from a list of valid codes and a description of what each code means will be available where applicable. Checks will be applied at the time of data entry into a specific field and/or before the data is written (committed) to the database. Modifications to data written to the database will be documented through either the data change system or an inquiry system. Data entered into the database will be retrievable for viewing through the data entry applications. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password.

13.9.4. Data Discrepancy Inquiries and Reports to Core Coordinating Centers

Additional errors will be detected by programs designed to detect missing data or specific errors in the data. These errors will be summarized along with detailed descriptions for each specific problem in Data Query Reports, which will be sent to the Data Managers at the Core Coordinating Centers (or, for those participating sites who enter their own data, directly to the participating sites) via e-mail. Reports regarding the length of time required to resolve queries as well as reports indicating those centers and their specific queries that are still open will be prepared monthly.

The Data Manager who receives the inquiry will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original (paper) form entering a response to the query. Note that it will be necessary for Data Managers to respond to each inquiry received in order to obtain closure on the queried item.

The Core Coordinating Center **and** participating site personnel will be responsible for making appropriate corrections to the original paper forms whenever any data item is changed. No data revisions will be made over the telephone. Written documentation of changes will be available via electronic logs and audit trails.

Feedback to the Core Coordinating Centers will occur at various times depending upon the specific information being disseminated. Most reports will be distributed over electronic mail. Core Coordinating Centers will receive recruitment and retention reports. As required for individual participants, Baseline Appointment schedules, Eligibility Reports, and Follow-Up Appointment Schedules will be generated as needed.

Biopsy and biochemistry reports will be sent via e-mail when data are received from the Core Lab.

Reports identifying participants who have reached an adverse event condition will also be sent to the Core Coordinating Centers (or, for those participating sites who enter their own data, directly to the participating sites) via e-mail. The detection and reporting of such events will be based on data stored in the DCC database.

Queries will be sent when needed due to discrepant data.

Monthly reports summarizing subject recruitment, retention, participant compliance, clinic performance, and progress will be sent to the Core Coordinating Centers (or, for those participating sites who enter their own data, directly to the participating sites) via e-mail, the Core Lab, and the NIH Project Office. Summaries of recruitment will assess the success rates of specific recruiting methods used at each Core Coordinating Centers.

Missed Visit Reports will be provided to each Core Coordinating Center monthly specifying participants completing and missing scheduled visits at that Center. This report should enhance the completion of follow-up visits.

Missing Query Response Reports will be provided to each Core Coordinating Center (or, for those participating sites who enter their own data, directly to the participating sites) via e-mail monthly and will consist of queries, which have been identified by the DCC and have not yet been responded to by the Core Coordinating Center or participating site. These will highlight any query requests, which are over 14 days delinquent.

Thorough analyses of quality control will be prepared by the DCC in a quarterly report, which will be reviewed by the Quality Control Subcommittee. Frequency of missing data, missing forms, and missed visits will be monitored.

13.9.5. Security and Back-Up of Data

The need for strict confidentiality of all study records will be emphasized to the staff of the DCC. All forms, diskettes and tapes related to study data will be kept in locked cabinets. Access to the study data will be restricted. In addition, Core Coordinating Centers will only have access to their own center's data. A password system will be utilized to control access to all computer accounts as well

as database accounts. These passwords will be changed on a regular basis. All reports prepared by the DCC will be prepared such that no individual subject can be identified.

A complete back up of the primary DCC database will be performed twice a month. These tapes will be stored off-site in a climate-controlled facility and will be retained indefinitely. Incremental data back-ups will be performed on a daily basis. These tapes will be retained for at least one week on-site. Back-ups of periodic data analysis files will also be kept. These tapes will be retained at the off-site location until the Study is completed and the database is on file with NIH. In addition to the system back-ups, additional measures will be taken to back-up and export the database on a regular basis at the database management level. The Oracle database management system provides extensive back up and documentation.

13.9.6. Study status reports

The DCC will send weekly email reports with information on missing data, missing forms, and missing visits. Personnel at the Core Coordinating Center and the Participating Sites should review these reports for accuracy and report any discrepancies to the DCC.

13.9.7. Reporting Study Results

All reports for external distribution (e.g., manuscripts) will be prepared in duplicate and reviewed by the DCC Director or Deputy Director. All files, programs and data sets will be archived. Reports summarizing the status of the trial but which provide no information that may compromise the blinding of outcome variables will be provided on request to suppliers of the study medications.

13.9.8. Description of Hardware at DCC

A SUN Workstation environment is maintained in the department with a SUN SPARCstation 10 model 41 as the server. All computers within the department are networked via Ethernet using the TCP/IP protocol. Core Coordinating Centers and Core Lab will access the departmental network through the Internet.

Access and predictable utilization of data processing facilities are adequate to service the needs of this study and to ensure the production of periodic reports on the data that are collected. Primary access to the departments computing facilities will be through the Internet, a world-wide cooperative network of computers, modem connection allowing sites to dial into the system directly, will serve as a back-up to the Internet method. These modes of accessibility allow authorized individuals access to the computing resources within the department with relative ease from other workstations within the department, other computers within The Cleveland Clinic Foundation, and from computers at other registered Internet sites at virtually no cost.

Extensive computer software is available for this project. For maximum programming efficiency, the Oracle database management system and the SAS and BMDP statistical analysis systems will be employed for this study. In this manner, special purpose programming will be kept to a minimum. Specific details regarding software packages to be used in the proposed project are provided as follows:

Oracle is an American National Standards Institute (ANSI) compliant relational data base management system, which operates across platforms. It is a premier database product on the Sun workstation environment. The Oracle products in use at the Cleveland Clinic's Department of

Biostatistics and Epidemiology include the computer assisted system engineering (CASE) tools, forms and report writer products

Oracle, coupled with the hardware available within the department, is well suited for the development of large databases with sophisticated data integrity checks

Oracle facilitates sophisticated integrity checks through a variety of mechanisms including stored procedures, stored triggers, and declarative database integrity--for between table verifications. Oracle allows data checks to be programmed once in the database rather than repeating the same checks among many applications. Oracle provides multi-user support, ANSI standard SQL, journaling for database recovery and database transaction rollback. Security is enforced through passwords and may be assigned at different levels to groups and individuals. A query optimizer automatically selects the most efficient way for performing all database transactions. Oracle provides a utility that allows for bulk loading data into the database while enforcing any integrity checks previously defined in the database. This feature will be useful in loading the Core Lab data, which will be electronically output from the labs computerized analyzers. The CASE tools allow the generation of more reliable applications in less time. An established CASE tools methodology for developing applications within the department provides a consistent and methodical approach to building data entry systems. Additionally, Oracle is compatible (via SAS access) with the SAS system, which will be the primary statistical analysis tool.

SAS is the predominant analysis tool and has a very solid reputation within the field of statistical analysis. In addition to the base SAS product several add-on features are available including: SAS/STAT, SAS/GRAPH, SAS/IML. All are necessary to run currently developed analyses and for the development of future analyses. Means for importing/exporting SAS data from/to other platforms are provided.

SAS/ACCESS software provides an interface between the SAS System and the ORACLE database management system by directly accessing data in ORACLE tables from within a SAS program.

S-Plus is available within the department and is used primarily for sophisticated data modeling. Its interactive graphics capabilities make it a superior product and allow it to contribute significantly to the types of analyses that are able to be conducted. It is an excellent tool for the purpose of and programming new statistical methods because of its extensive selection of mathematical and array manipulation routines.

14. ANCILLARY STUDIES POLICIES (03/03/04)

14.1. General Policy

To enhance the value of the FSGS Clinical Trial (FSGS-CT), the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of the FSGS-CT, ancillary studies must be reviewed and approved by the Ancillary Studies Committee (ASC) and the Steering Committee before their inception or submission of a proposal for external funding consideration.

14.2. Definition of Ancillary Study

An ancillary study will be used for the collection of additional data not collected or analyzed as part of the routine FSGS-CT data set. Ancillary studies may be submitted by the investigators within the FSGS-CT or by investigators who are not a part of the FSGS-CT. Ancillary studies require external (non-FSGS-CT) funding. Examples include studies funded by investigator-initiated NIH research awards (RO1s), grants from academic institutions or private sources (e.g. private foundations, pharmaceutical companies). Any ancillary study must have sufficient funding to cover the costs incurred by the FSGS-CT Core Coordinating Centers, Participating Sites, Core Lab (e.g., to process shipments and ship samples), and by the DCC (for tasks such as sample selection, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data back into the combined FSGS-CT database). Funds are not available for these purposes within the FSGS-CT.

14.3. Requirements and Procedures for Approval of an Ancillary Study

14.3.1. Overview

Participation in, and approval of an ancillary study is subject to review by the ASC and formal approval by the FSGS-CT Executive Committee. In unexpected select situations (e.g. an imminent funding deadline), the FSGS-CT Executive Committee may serve as the proxy for the ASC. Approval by the Executive Committee will be defined by majority vote. Concerns about a proposal will be discussed with the applicant and opportunities for clarification will be provided. If approved, all Core Coordinating Centers of the FSGS-CT agree to cooperate in the ancillary study. An ancillary study must receive approval before grant funding is submitted. Investigators are encouraged to discuss potential proposals with the Chair of the ASC prior to submitting a proposal. All ancillary study proposals must include at least one FSGS-CT investigator as a liaison.

14.3.2. Requests for Ancillary Studies as Part of Training or Career Awards

The FSGS-CT investigators and the NIH anticipate that the FSGS-CT will be an important resource for career development and training among members of the academic community. Special consideration, therefore, will need to be given to requests for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources. As these funding mechanisms typically provide funding only for investigator effort, not additional data collection, such proposals will generally propose research questions and analyses that could be considered part of the core FSGS-CT. In these cases, consideration of what analyses will be authorized could present a conflict with the interests of the FSGS investigators. Evaluation should consider the scientific gain to the FSGS-CT from the addition of the proposed ancillary analyses as well as the training and career development opportunities

afforded to the applicant by the proposed ancillary study. Proposals for ancillary studies as part of training or career awards must be reviewed and approved by the ASC.

14.3.3. Considerations for Approval

The proposed study must meet requirements of the highest scientific merit.

Relevance to FSGS.

Opportunity for acquisition of new scientific knowledge.

Adequacy of experimental design, methodology and data analysis.

Adequacy of the investigator and research environment.

Participant (enrolled participants and participating site providers) burden.

The proposed study must be acceptable to the participants (e.g. time, discomfort, privacy).

The proposed study must not interfere with other parts of the main FSGS-CT.

The proposed study must not hamper continued participation in the main Clinical Trial.

The proposed study must put minimal demand on scarce FSGS-CT resources such as blood samples.

The proposed study must require the unique characteristics of the FSGS-CT cohort to accomplish its goals.

The investigators must have adequate resources to effectively complete the project, including both financial support and personnel.

The ancillary study investigators must agree to return the complete ancillary data set back to the DCC, if requested.

The proposed study must not interfere with or impede the completion of the primary or secondary objectives of FSGS-CT.

The proposed study must not adversely affect participant cooperation or compliance with FSGS-CT protocols.

The proposed study must not create a serious diversion of study resources (personnel, equipment or study samples) or investigator/staff time at the Participating Sites, Core Coordinating Centers or DCC.

14.3.4. Instructions for Preparation of Requests for an Ancillary Study

All proposed ancillary studies must be reviewed by the FSGS ASC and approved by the Steering Committee before submission to a funding agency. Studies should be submitted a minimum of 8 weeks before a deadline.

<u>Ancillary Study Proposal Format</u>

A written request for approval of an ancillary study should be submitted in two to four (excluding biosketches and budget) pages containing the following information:

1) Principal investigator and other co-investigators (include biosketch in NIH format)
2) FSGS-CT liaison investigator
3) Hypothesis to be tested
4) Background and significance (maximum of one page)

5) Design-Methods-Key References (maximum of two pages)
6) Description of specimen or data request (maximum of two pages)
    a) Specific type(s) of samples
    b) Volume of each sample
    c) Time of sample collection (baseline vs. post-baseline)
    d) Use of thawed vs. unthawed specimens - for blood and urine, proposals must indicate whether previously thawed specimens can be used.
    e) Number of participants
    f) Type of storage – for urine, -20 or -70^{0}F
    g) Proposed laboratory that will perform the assays
    h) DNA specimens – special needs should be delineated.
7) Need for other study data (e.g. baseline and/or follow-up data) and other study resources
8) Time table with key dates (grant submission, target date for receipt of specimens, and completion of study
9) Documentation of local IRB approval [required prior to release of specimens]
10) Agreement to return any unused biological specimens and data sets
11) Budgetary issues
    a) Source(s) of funding
    b) Draft budget – See required elements in Ancillary Proposal Budget below

The investigator should send the ancillary study proposal to the Chair of the ASC. To ensure thorough scientific review, the Chair of the ASC may elect to seek outside expert opinion. The ASC members will have fourteen days from receipt of the proposal to provide an opinion to the DCC. No response will be considered an affirmative vote. A proposal, which receives an affirmative majority from the ASC, will be forwarded to the Executive Committee for authorization. Each FSGS-CT Executive Committee member should respond to the DCC within 15 days. Approval or disapproval is based on majority opinion. A failure to provide an opinion to the DCC will be considered an affirmative vote.

If a proposal is not approved, the Chair of the ASC may discuss potential revisions with the ancillary studies investigator. If resubmitted, the ASC will reconsider the proposal on one additional occasion only. If an affirmative majority is obtained after re-review, the proposal will be sent to the Executive Committee for authorization. The investigator may only proceed with the ancillary study after it has been authorized by the FSGS Steering Committee.

Changes to Proposed Study

Once an ancillary study is approved, if a change occurs in the structure or concept of the study, such changes should be disclosed to the ASC, and the FSGS Executive Committee, for review and approval.

Ancillary Proposal Budget

The investigator applying for an ancillary study must supply all additional funds needed to complete the study. Provision of funds for expenses incurred by the FSGS-CT is essential. Once a study concept is approved, ancillary studies are expected to collaborate with the DCC to develop a budget, which adequately provides for expenses incurred by the FSGS-CT. Such costs include, but are not limited to:

Statistical and data management staff for coordinating the additional data management and analyses with the DCC.

Expenses involved in modifying identifying data to protect subject confidentiality and maintain HIPPA compliance.

Costs for notification of alert values.

Costs incurred by Participating Sites including space, personnel, equipment, and IRB approval.

Costs relative to visits or examinations outside of the primary study protocol.

Human Subjects/Data Confidentiality

Confidentiality of FSGS-CT enrolled participants must be guaranteed. Individually identifiable data may not be released. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main FSGS Clinical Trial.
Any investigator or personnel having access to FSGS Clinical Trial subject data should have received an orientation on the FSGS Clinical Trial confidentiality policy. Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.

A copy of the IRB letter for the ancillary study should be sent to the DCC. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the FSGS-CT record. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the FSGS-CT DCC.

The principal investigator of an ancillary study will be responsible for:

a) monitoring the study to assure continuing compatibility with FSGS-CT,
b) maintaining communications with the FSGS liaison investigator and
c) provide written progress report on the ancillary studies.

14.4. Analysis and Publication of Results of Ancillary Studies

Unless specifically arranged for and specifically provided for in the Ancillary Study consent form, all data analyses will take place at the DCC. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical sites will be situations in which data analysis requires special consideration. In such circumstances, the investigator of the ancillary study will provide interim reports on analyses to the DCC during data analysis to ensure consistency with data in the FSGS-CT database and to ensure the quality of analysis approaches.

Proposals for manuscripts resulting from all ancillary studies will be submitted for review to the Publications Committee and will require approval by the Executive Committee prior to submission for publication or presentation. The phrase "FSGS Clinical Trial" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts should also contain an appendix listing FSGS investigators when appropriate.

14.5. Feedback of Results of Ancillary Studies to Participants

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

14.6. Handling of FSGS Clinical Trial Data and Specimens

At the time of distribution of FSGS-CT specimens and/or information, the FSGS-CT Liaison Investigator, in coordination with the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the FSGS-CT data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of biological materials after the ancillary study has been completed. An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the FSGS-CT DCC Coordinating Center at the conclusion of the data analysis and publication of ancillary studies. Once transferred back to the FSGS-CT, these ancillary data will become part of the aggregate FSGS-CT data. Subsequent access to these data will be governed by the FSGS-CT Study Policy on Use of Archived Study Data.

15. COMMITTEES AND ADMINISTRATIVE STRUCTURE (03/09/04)

The following committees will oversee the conduct of the trial:

Steering Committee Attendees, Chair – Norman J. Siegel

Executive Committee of the Steering Committee**,** Chair – Norman J. Siegel, members include principal investigators from each Core Coordinating Center, the Data Coordinating Center, and the NIDDK project director.

Ancillary Studies Committee, Chair – Frederick Kaskel

Pathology Committee, Chair – Vivette D'Agati

Retention and Recruitment Committee: Chair - Sandra Watkins

Financial Committee, Chair – Sandra Watkins

Training Committee, Chair – Ronald Hogg

Data Forms Committee, Chair – Debbie Gipson

Clinical Management Committee, Chair – Debbie Gipson

Updated lists of the members of each committee will be maintained in the FSGS-CT address directory throughout the conduct of the trial.

16. PROTOCOL CHANGES (5/1/03)

16.1. General Principles of Protocol Change

During the conduct of the study, protocol changes are not desirable and should not be made unless the safety of the participants is compromised or new information becomes available and strongly suggests that such changes would strengthen the scientific validity of the study. In the event that alterations are necessary, the following procedures will be followed:

16.2. Protocol Change Procedures

Recommendations for protocol changes may originate from one of the core coordinating centers, the Participating Sites, the External Advisory Committee/DSMB, the Data Coordinating Center, or one of the FSGS-CT Committees. All proposed changes will be submitted to the Steering Committee for consideration. The Steering Committee will decide whether the proposed modifications should be implemented and will determine the method of incorporating the proposed changes in the Protocol. Approval by the Steering Committee must have support from 5 of 8 of the voting members. For major changes, the recommendations of the Steering Committee will be presented to the External Advisory Committee who will advise the NIDDK as to whether the Protocol changes are advisable. The NIDDK may seek further advice from other experts outside of the FSGS-CT before making the final decision as to whether the recommended Protocol changes are approved. Major protocol changes will be made known to FDA and IRB (if modified informed consent is required).

17. PUBLICATION POLICY (03/03/04)

17.1. Introduction

The FSGS-CT publication's policy has five objectives:

1) To assure timely publication of the results of the FSGS-CT,

2) To avoid premature publication of results that might compromise the performance of the study (such as publication of trends before they become statistically convincing) or that might compromise later publication in high quality peer reviewed journals (as by premature release to the lay press),

3) To maintain high quality of material published by the FSGS-CT,

4) To prevent duplicate publication of results, and

5) To assure equitable attribution of credit to the FSGS-CT participants.

17.2. Scope of Policy, and Exception for Local Publicity Materials

All material to be presented orally or submitted for publication or dissemination by individuals associated with the FSGS-CT and dealing with any aspect of the FSGS-CT must receive prior review and approval by the PC with the following exception:

The PC need not review material prepared for publicity purposes, either nationally, or within the recruitment region of an FSGS Center, or presented to inform professional audiences of the FSGS-CT. Such material must not include FSGS-CT outcomes, which have not previously been presented or published.

17.3. Source of Suggestions for Publications of the FSGS-CT

The PC may suggest topics for abstracts, original peer reviewed papers, or reviews. In addition, all participants in the FSGS-CT are invited to suggest topics to the DCC and the Chair of the PC, who shall review the request, to assure there is no overlap with existing writing committee assignments. When overlap exists, the Chair of the PC may recommend to the Study Chair that the suggestion be referred to an existing writing committee, that additional participants be added to existing writing committees, or make other suggestions to resolve the overlap. The final decision will be made by the Study Chair after consultation with the Chair of the PC.

The PC will maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the FSGS-CT are reported to the scientific community in a timely fashion. This list will be circulated quarterly to members of the Steering Committee.

17.4. Assignment of Writing Committees

Topics suggested for presentation or publication will be circulated to the PIs of the CCCs, the DCC, Core Lab and the NIH. These groups are requested to suggest and justify names for authors to be reviewed by the PC. A recommendation for a writing committee will then be made to the Study Chair who will decide on the final composition of the writing committee after

consultation with the Chair of the PC. If a topic is suggested by a participant of the FSGS-CT, the writing committee will be formed as just described except that the person making the suggestion may be considered as the lead author. The PI of an ancillary study should be considered for lead author of material derived from this study. Disputes regarding authorship will be settled by the Study Chair after consultation with the Chair of the PC. All writing committees requiring analysis of FSGS-CT data will be assigned a member of the DCC.

17.5. Reports of the FSGS-CT: Classes of Reports

There are three classes of reports of the FSGS-CT:

A. Reports of the major outcomes of the Study.
B. Reports addressing in detail one aspect of the FSGS-CT, but in which the data are derived from the entire study.
C. Reports of data derived from a subset of centers by members of the FSGS-CT, (e.g., sub-studies or ancillary studies), or reports of investigations initiated outside of the FSGS-CT, but using data or samples collected by the FSGS-CT. The investigators may be FSGS-CT or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the FSGS-CT itself. Writing committees for this type are formed in accordance with the general policy rules for FSGS publications. However, the PI of an ancillary study should take primary responsibility in publishing the results of the study.

17.6. Authorship Policy

The authors of FSGS publications will be listed as detailed below.

Type A publications:

abstracts: from the FSGS Clinical Trial Group[1], presented by XXXX.
papers: from the FSGS Clinical Trial Group[1], prepared by XXXX.
[1]The FSGS participant box, detailed below, must be included in these papers. If a journal's publication policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:

abstracts and papers: Authors' names, from the FSGS Clinical Trial Group[1]
[1]The FSGS participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers.

Type C publications:

abstracts and papers: authors' names and the FSGS-CT
[1]The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers.

17.7. Authorship: Professional Participants Listing in the FSGS Participant Box

The FSGS participant box will list all professionals that have participated in the FSGS-CT for a minimum of one year. The participants for each participating center will be listed together, with the center PI listed first, followed by the other center staff listed alphabetically with academic degrees. The centers will be listed in the following order:

NIH
Study Chair
Core Coordinating Centers (in alphabetical order)
DCC
Core Labs (in alphabetical order)

17.8. Acknowledgement of Support

Acknowledgement of grant support to be used in all papers reporting results of the FSGS-CT. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The FSGS-CT is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH. Additional support is provided by the (list of any industrial or other support).

17.9. Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time a writing committee is constituted, the PC will establish a timetable for the completion of the writing assignment that takes into account deadlines for publication, the time required for data analysis, other commitments of the DCC, and priority of the publication. The Chair of the Writing Committee should provide the Chair of the PC a general outline of the proposed publication within a month of receiving its assignment, to permit the PC to identify any overlap with assignments of other writing committees. The Chair of the PC will report at each meeting of the Steering Committee on the progress of the various writing committees.

If the timetable is not met, the chair of the PC can name a new chair for the writing committee or reconstitute the membership of the writing committee.

17.10. Review of Abstracts and Presentations by the PC

The following procedure will be used to expedite reviews of abstracts and presentations:

1) The writing committee wanting to submit an abstract or other material for which there is an explicit submission deadline shall contact the Chair of the PC. In the event that the Chair is unavailable, the Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of two to three members of the PC to review the submitted material. The submitted material should be provided to the reviewers no fewer than seven (7) days prior to the deadline for submission.

2) The members of the subcommittee shall review the material and notify the Chair of their approval or disapproval. The PC Chair (or Alternate Chair) shall inform the submitter of the decision of the PC.

3) All materials submitted for approval in this fashion will be distributed, together with notice of the disposition, to all members of the PC and to the Chair of the Steering Committee. Approved materials will be forwarded to the NIH Project Coordinator and for record purposes to the Principal Investigator of the DCC, and will be distributed to the entire membership of the Steering Committee at the next meeting of that Committee.

All presentations will be developed in coordination with the DCC. Following approval for presentation, material may be provided to participating pharmaceutical companies.

17.11. Review of Papers by the PC

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

1) The Chair of the PC shall appoint two to three primary reviewers, including at least one PC member. The Chair of the PC will circulate the submitted material to the entire PC committee and to the PI of each FSGS-CT CCC. The primary reviewers will each send to the Chair a written critique of the submitted material for distribution to the entire PC. The PIs of the CCCs will be given a deadline by which comments of any study personnel at their center must be received by the Chair of the PC.

2) The Chair of the PC shall schedule a meeting of the PC (generally by conference call), including review of papers as Agenda items. The primary reviews and any comments received from the center PIs will be distributed to the committee with the agenda. The discussion of the submitted papers and other materials will be led by the primary reviewers.

3) Three dispositions may be made: a) approval of the material as submitted (possibly with minor recommendations for revision that do not require re-review), b) non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and c) disapproval of the material.

4) The Chair of the PC will communicate the decision of the Committee to the authors, together with a summary of suggestions for revision, if any.

5) If the decision of the PC is contested by the author(s), the Chair of the PC will report this outcome in writing to the Executive Committee for final action. In this case the Chair of the PC will provide a copy of the submitted material and a summary critique to Executive Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal. In these circumstances, the decision regarding final approval rests with the Steering Committee, or the Executive Committee in the interim between meetings of the Steering Committee.

6) All materials receiving approval for submission for publication will be forwarded to the NIH Project Coordinator, and for record purposes to the PI of the DCC.

7) If a scientific journal to which an approved FSGS manuscript is submitted requires revisions to the manuscript, the Chair of the PC will determine whether the revised manuscript should again be reviewed the PC prior to resubmission. If the Chair of the PC determines that a review of the revised manuscript is necessary, the Chair will attempt to appoint the same reviewers that first read the paper to review the revision, and will make every effort to expedite repeat reviews.

17.12. Criteria for Review of Materials by the PC

Materials submitted to the PC will be reviewed for acceptability on two grounds:

1) Materials shall be evaluated for scientific accuracy, quality, importance, and style.

2) Material shall be reviewed to assure that it conforms to the assignment to the writing committee, does not encroach on assignments to other writing groups, and does not divulge prematurely the findings of the FSGS-CT or compromise the eventual publication of FSGS findings in high quality peer reviewed journals.

17.13. Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all official publications and presentations of the FSGS. This listing will be updated at least quarterly and will be distributed to the PI of each CCC, together with copies of any papers, chapters, or abstracts accepted for publication since the last update.

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