

1. INTRODUCTION/GENERAL INFORMATION

The Manual of Operations (MOP) has been written to provide physicians, nurses, and others involved in the Focal Segmental Glomerulosclerosis Clinical Trial (FSGS-CT) with a detailed step-by-step description of the entire study. It is important that Study Coordinators and Principal Investigators (PI) in each of the participating sites become familiar with the entire contents of the MOP.

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

Contact Person	* Phone	* Fax
NIH Project Officer Marva Moxey-Mims, MD	(301) 594 7717	(301) 480 3510
Core Coordinating Center A SUNY at Stony Brook, NAPRTCS Richard Fine, MD Principal Investigator	(631) 444 2716	(631) 444 7865
Howard Trachtman, MD Co-PI	(718) 470-3491	(718)470-0887
Core Coordinating Center B University of North Carolina Debbie Gipson, MD Principal Investigator	(919) 966 2561 Extension 235	(919) 966 4104
Core Coordinating Center C Montefiore Medical Center Frederick J. Kaskel, MD Principal Investigator	(718) 655 1120	(718) 652 3136
Data Coordinating Center Jennifer Gassman, Ph.D. Principal Investigator	(216) 444 2275	(216) 445 2781
Drug Distribution Center / Central Pharmacy Fisher Clinical Services David Zimmerman Project Manager	(610) 871 8463	(610) 871 8590

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Contact Person	* Phone	* Fax
Core Lab Spectra Renal Research James Zazra Director	(800) 205 5005 Extension 5422	(201) 767 7358
NIDDK Biological Specimen Repository Fisher Clinical Services Sandra Ke Principal Investigator	(240) 686 4702	(301) 515 4049
NIDDK DNA Repository Rutgers Genetics Repository David Toke Project Director	(732) 445 2457	(732) 445 1149
NIDDK Database Repository RTI Jamie Cuticchia	(919) 316 3511	(919) 541 6178

*** For complete and updated contact information, please refer to the most recent FSGS-CT Address Directory.**

2. GLOSSARY OF TERMS/LIST OF ABBREVIATIONS — July 13, 2004

ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
ANC	Absolute Neutrophil Count
ARB	Angiotensin II Receptor Blocker
BCG	Tuberculosis Vaccine
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CL	Core Lab
CCC	Core Coordinating Center
CRF	Case Report Form
CSA	Cyclosporine
DCC	Data Coordinating Center
DM	Diabetes Mellitus
EAB	External Advisory Board
FDA	Food and Drug Administration of the USA Public Health Service in the Department of Health and Human Services
FBG	Fasting Blood Glucose
FSGS-CT	Focal Segmental Glomerulosclerosis-Clinical Trial
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin, Urine Pregnancy Test
HCT	Hematocrit
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
JAMA	The Journal Of The American Medical Association
LOV	List of Values
MOP	Manual of Operations
MMF	Mycophenolate Mofetil
NIDDK	National Institute Of Diabetes And Digestive Kidney Diseases
NSAIDS	Non Steroidal Anti-Inflammatory Drugs
OGTT	Oral Glucose Tolerance Test
PG	Plasma Glucose
PI	Principal Investigator
PPD	Tuberculin skin test
QOL	Quality of Life
SAE	Serious Adverse Event
SMA18	Biochemical test battery
SST	Serum Separator Tubes
Up/c	Urine protein divided by urine creatinine concentration
WHO	World Health Organization

3. BACKGROUND AND INTRODUCTION

3.1. 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 participants, this lesion is refractory to therapeutic interventions. Progression to end stage renal disease is an expected outcome for the vast majority of participants. Overall, FSGS accounts for approximately 15% of pediatric and 5% of adult cases of end stage renal disease in North American. The morbidity and mortality for participants with FSGS is compounded by the relative high recurrence rate for this lesion following renal transplantation. The outcomes for participants with recurrent FSGS are as poor if not worse than those for participants with primary FSGS.

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 participants included in most reports. 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 participants to the study. The rationale and background related to each of the drugs chosen to be a part of the Focal Segmental Glomerulosclerosis-Clinical Trial (FSGS-CT) therapeutic interventions are outlined in the study protocol.

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 participants. 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 cyclosporine (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 Nephrologists 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 participants 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.

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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 participants 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 Mycophenolate Mofetil (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 participants.

3.2. Purpose and Overall Study Design

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 corticosteroids in inducing remission of proteinuria in participants with steroid resistant FSGS. Both of the regimens will also include an ACE inhibitor (ACEi) 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 in participants with steroid resistant FSGS, when compared to similar participants receiving CSA, those who are treated with the MMF/oral pulse dexamethasone combination 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

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

The CSA and MMF/Pulse steroid treatment regimens will be implemented over the first 52 weeks after randomization, with the ACEi 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 for two successive central Up/c measurements obtained at least four weeks apart. For participants who do achieve a partial or complete remission at the week 26

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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.

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

4. TIMELINES

4.1. The Study Calendar Timeline

Month 1	Sept 2002	Funding begins
Month 2	Oct 2002	Steering Committee Meetings begin
Month 9	May13, 2003	Preliminary protocol submitted to Data Safety and Monitoring Board (DSMB)
Month 9	May 27, 2003	DSMB meeting
Month 12	Aug 2003	Core Lab and Core Pharmacy selected
Month 27	Nov 9, 2004	Participant enrollment begins
Month 55	Mar 1, 2008	Participant enrollment ends
Month 74	Oct 1, 2009	Final follow up data collection on last participants enrolled
Month 77	Jan 1, 2010	Completion of Study Close Out and primary analysis

Participants will be enrolled at the Participating Sites and all visits will be held at the Participating Site where the participant is enrolled. 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.

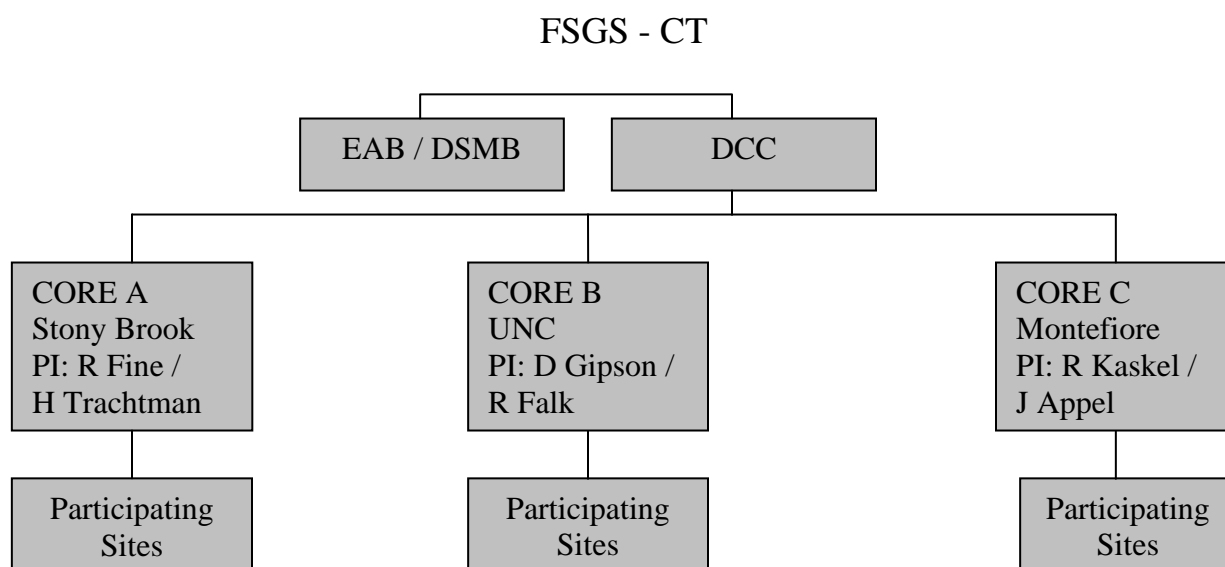
Visit	Study Week	Clinical Objectives	Labs	Up/c	Cyclosporine Drug Level
Screening*	-1 or -2	Informed Consent Baseline Studies	X	X	
Baseline*	-1 or -2	Informed Consent Baseline Studies			
Follow-up	0	Confirm Pregnancy Test Dispense Study Medications	X	X	
Follow-up	2	Interval Assessment	X	X	X
Follow-up	4	Interval Assessment	X	X	X
Follow-up	6	Interval Assessment	X	X	X
Follow-up	8	Interval Assessment	X	X	
Follow-up	14	Interval Assessment	X	X	X
Follow-up	20	Interval Assessment	X	X	
Follow-up	26	Interval Assessment End Prednisone/Prednisolone	X	X	X
Follow-up	32	Interval Assessment	X	X	
Follow-up	38	Interval Assessment	X	X	X
Follow-up	44	Interval Assessment	X	X	
Follow-up	52	Interval Assessment End Study Medications MMF/Dexamethasone/CSA Continue ACEi/ARB	X	X	X
Follow-up	65	Interval Assessment	X	X	

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Visit	Study Week	Clinical Objectives	Labs	Up/c	Cyclosporine Drug Level
Follow-up	78	Interval Assessment Stop ACEi/ARB	X	X	
Long-term Follow-up	104	Interval Assessment	X	X	
Long-term Follow-up	130	Interval Assessment	X	X	
Long-term Follow-up	156	Interval Assessment	X	X	
Long-term Follow-up	182	Interval Assessment	X	X	
Long-term Follow-up	208	Interval Assessment	X	X	

* These two visits may be combined

4.2. Organizational Overview



CORE LAB Spectra
Drug Distribution Center Fisher Clinical Services
REPOSITORIES DNA - Rutgers Biospecimens – Fisher BioServices

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4.3. Core Coordinating Centers

Principal Investigator (PI)
Co-Investigator(s)
Study Coordinator(s)

4.3.1. Responsibilities of the Core Coordinating Centers (CCC)

1. Maintain current IRB approved study related documents.
2. Assure proper personnel training for the requirements for the appropriate conduct of the trial by attending a central DCC training session or internal CCC training sessions prior the initiation of the participant recruitment as well as during the study.
3. Complete the process of activating each specific institution as a participating site for FSGS-CT, which includes signing a contract, financial arrangements, IRB approval, etc.
4. Train the participating site personnel for the requirements for the appropriate conduct of the study prior to the initiation of participant recruitment and during the study.
5. Perform the required study procedures, including data collection, data entry and resolution of data discrepancies related to the participants recruited by the CCC.
6. Oversee the participating site participant recruitment follow-up process.
7. Oversee the participating site data management process, which would entail data collection, data entry and resolution of data discrepancies.
8. Perform the actual data entry and data discrepancy resolution activities for the participating sites, which do not access the database.
9. In cases when the CCC cannot resolve a Participating Site's data discrepancy, the CCC personnel should communicate this to the DCC.
10. CCC should forward to the DCC any suggestions or changes deemed necessary to the MOP, the data collection instruments (data collection forms and data entry screen layouts) or any other study documents.

4.4. Participating Site

Principal Investigator (PI)
Co-Investigator(s)
Study Coordinator(s)
Data Entry Specialist

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4.4.1. Responsibilities of the Participating Site

1. Complete the process of activating the institution as a participating site for FSGS-CT, which includes signing a contract with the CCC, financial arrangements, IRB approval, etc.
2. Maintain current IRB approved study related documents.
3. Assure proper personnel training for the requirements for the appropriate conduct of the trial. It is recommended for the Participating Center personnel to attend CCC training sessions prior the initiation of the participant recruitment as well as during the study.
4. Perform the required study procedures for the recruited study participants.
5. If the Participating Site chooses, perform the actual data entry and data discrepancy resolution activities.
6. If the Participating Site chooses, facsimile the completed data collection forms to the CCC for data entry and resolve the data discrepancies by communicating with the CCC over the phone, fax or e-mail.
7. Communicate with the CCC any suggestions or changes deemed necessary to the MOP, the data collection instruments (data collection forms and data entry screen layouts) or any other study documents.

4.5. Data Coordinating Center

Principal Investigator(s)
Co-Investigator(s)
Biostatistician(s)
Study Coordinator(s)
Programmer(s)

4.5.1. Responsibilities of the Data Coordinating Center

Notes:

- All automated reports will be sent via e-mail as PDF attachments; with the exception of the Drug Allocation Report for McKesson, which will be faxed.
- All reports for a Participating Site will also be sent to their CCC.
- Participating Site recipients will be e-mailed addresses of all Principal Investigators and Study Coordinators with Active status listed on the Participating Site's Form 2.
- CCC recipients will be e-mailed addresses of all Principal Investigators and Study Coordinators with Active status listed on the Participating Site's Form 2.
- Enrollment reports (i.e. new Form 10s) with birthdates will be sent to Spectra, and a version with ages will be sent to Rutgers.
- A message detailing files received from the Core Lab, or stating that no files were received, will be sent to Spectra and fsgs_dcc@bio.ri.ccf.org.
- A log file from nightly processing will be sent to fsgs_dcc@bio.ri.ccf.org.

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1. Establish systems for data acquisition via a secure web-based data entry. Establish systems for data management.
2. Develop procedures to enhance the quality and completeness of the data collected. Provide regular quality control reports on the data collection process.
3. Establish systems for communications (drug distribution and reports) between the Central Pharmacy and the Participating Centers.
4. Establish systems for communications (study lab specimen shipment and reports) between the Core Lab and the Participating Centers.
5. Establish systems for communications (study lab specimen shipment and reports) between the Repositories and the Participating Centers.
6. Provide centralized training of the study personnel on entry of trial participants, completion of data collection forms, use of the data management system.
7. Establish report systems for monitoring the recruitment, retention and the adherence to the protocol, including dose modification, AE reporting, etc.
8. Establish an inquiry system for timely resolution of data discrepancies.
9. Provide regular data summary reports to the CCC, the Steering Committee and its subcommittees.
10. Provide regular data summary reports to the Data and Safety Monitoring Board.
11. Perform necessary statistical interim analyses and final analyses. Develop new statistical methodology as needed to properly analyze the data
12. Perform necessary statistical analyses for publications related to the study results.
13. Participate in the overview process of any ancillary study.

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4.6. Charter Statement

A Randomized Controlled Trial of Mycophenolate Mofetil (MMF) and pulse dexamethasone versus cyclosporine A in Participants with Focal Segmental Glomerulosclerosis

Charter Statement for the Safety and Monitoring Committee
(Version 1.0; December 19, 2003)

IND #68,498 (FDA – USA)

Control #pending (BPA – Canada)

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4.6.1. Functions of the DSMB

An 8-person Data Safety and Monitoring Board (DSMB) will regularly review safety data and results of interim analyses from this trial in order to ensure that subjects are not placed at undue risk by participation. This committee has previously reviewed and approved the final protocol for the trial, and will be responsible for determining if and when the study must be discontinued or the study protocol amended as a result of excessive adverse events relative to anticipated benefits as detailed in Section 1 of this charter. The committee will also be responsible for recommending whether the study should continue based on interim analysis results of the study's primary outcome variable.

4.6.2. Membership

The members of this committee are listed below:

- John Lewy, MD (Chair)
- James Balow, MD
- Katie Buchannan
- Marie Diener-West, PhD
- Agnes Fogo, MD
- Norman Fost, MD, MPH
- Andrew Levey, MD
- John Sedor, MD
- Irving Smoker, PhD
- Julie Ingelfinger, MD

4.6.3. Specific Aim of the Study

The study is a multicenter, randomized controlled clinical trial designed to test the hypothesis that treatment with mycophenolate mofetil (MMF) plus oral pulses of dexamethasone (MMF/D) will lead to a more significant improvement of proteinuria in participants with FSGS who are also treated with Angiotensin Converting Enzyme inhibitor (ACEi) compared to a group of participants receiving cyclosporine A (CSA) and a comparable dose of ACEi.

4.6.4. Study Design

This study is a multicenter, controlled, randomized clinical trial. In addition to the study drugs (either CSA or the MMF/D combination), all participants will receive treatment with lisinopril or losartan during a 12-month period of treatment with the active study drug and for a subsequent 6-month period of study. Participants who are unable to tolerate lisinopril will be converted to losartan and continue in the study. Each participant will receive a year of treatment with the study drug followed by at least 6 months follow-up off the study drug. The primary outcome is remission from proteinuria after 12 months on the study drug. The main secondary outcome is the persistence of remission at month 18 after withdrawal of the study drug.

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4.6.5. Participant Enrollment

It is anticipated that approximately 600 to 700 participants aged 2 to 40 years who have FSGS will be recruited for the screening phase of the study. It is anticipated that 500 of these participants will be randomized to either MMF/D or CSA after a screening phase. This number should be sufficient to detect a 10 to 12% absolute difference in remission rate of proteinuria between the two groups with 80% power.

4.6.6. Clinical Site Locations

Approximately 175 actively enrolling sites in the USA, Mexico and Canada will participate.

4.6.7. Primary Efficacy Endpoint

Significant improvement in the study participants is defined as reduction in the indices of urinary protein excretion, associated with stable or improved renal function (GFR). The study baseline is the measurement taken prior to the start of study treatment.

4.6.8. Primary Safety Endpoint

Safety outcomes will be defined as combined Serious Adverse Events (SAE) including death and hospitalization.

4.6.9. Responsibilities of the DSMB

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.

Following each meeting the DSMB chairperson will prepare a brief document stating that the committee has performed the review and will provide a conclusion and recommendation from the pre-specified list given below:

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CONCLUSIONS

- I. No observations have been made that would alter the execution of the study.
- II. The primary study objective has been met and safety risks are minimal.
- III. Based on current data, there is a low probability that the primary study objective can be met and/or there is concern for safety.
- IV. Based on current data, there is a very low probability that the primary study objective can be met and/or there is a high probability subjects are at undue risk.

RECOMMENDATIONS

- I. No action recommended at this time.
- II. Changes to the protocol/analysis recommended without a suspension of participant enrollment.
- III. Changes to the protocol/analysis recommended with a suspension of participant enrollment.
- IV. Termination of study recommended.

4.6.10. Other

The DSMB Committee has reviewed and approved the final protocol for the trial, and has approved the interim analysis plan including the stopping rule. The DSMB Committee members will teleconference at least once prior to the start of regular teleconferences and meetings to agree on how responsibility for paperwork, etc. will be shared among committee members, and to review plans of the DCC regarding presentation of data.

5. STUDY POPULATION

5.1. 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 41st birthday)
3. Estimated GFR ≥ 40 ml/min/1.73 m² at most recent measurement prior to randomization (see Section 20 for formulas)¹
 - a. For participants < age 18 years: Schwartz formula
 - b. For participant's ≥ 18 years: Cockcroft-Gault formula
4. Up/c > 1.0 g protein/g creatinine on first morning void at time of randomization¹
5. Biopsy confirmed as FSGS (including all subtypes) by study pathologist (see Section 11). A minimum of 1 glomerulus demonstrating segmental sclerosis on 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 1,680 mg of prednisone or its equivalent.

It is recognized that the use of steroids may vary considerably from site to site and especially between pediatric and adult participants. Inclusion Criteria #6 is meant to provide a guideline to defining steroid resistance. If a participant receives a total dose of steroids that is equivalent to the amount detailed in Item #6 over a minimum of 8 weeks, then that participant would satisfy the criterion for steroid resistance and would be eligible for enrollment in the FSGS Clinical Trial.

The following Table defines total doses for each dosing system, i.e., mg/kg, or an actual daily dose of 60 mg/day for 4 weeks of daily therapy and 40 mg every other day for 4 weeks of alternate day therapy. These numbers are provided as guidelines for assessing equivalency of total steroid dose received by a prospective participant in defining steroid resistance.

Dosing Method	4 week Daily Dose	4 week Alternate Day Dose	Total Prednisone Dose
mg/kg	56 mg/kg	14 mg/kg	70 mg/kg
mg/m ²	1680/m ²	560/m ²	2240/m ²
Actual dose (60 mg / 40 mg)	1680	560	2240

All questions about steroid dose equivalency and patient eligibility should be addressed to the Core Coordinating Center before enrolling a participant.

5. STUDY POPULATION

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 treatment course demonstrating steroid resistance.

7. May be taking ACEi, ARB, Vitamin E, or lipid-lowering therapy
8. Willingness to comply with clinical trial protocol, medications, and follow-up visits, etc.

[†] 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 > 95th percentile for age/height while the participant is on less than three antihypertensive agents so long as the total number of agents does not exceed three.

5. STUDY POPULATION

5.2. Exclusion Criteria

1. Secondary FSGS
2. Prior therapy with sirolimus, cyclosporine, tacrolimus, MMF, or azathioprine (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 potential¹
5. Participation in another therapeutic trial concurrently or 30 days prior to randomization¹
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/height¹
9. Participant is receiving 4 or more antihypertensive agents for the primary purpose of controlling blood pressure¹
10. Participants with previously diagnosed diabetes mellitus (DM) 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 World Health Organization (WHO) criteria for the diagnosis of DM I and II will be used (see Section 20).

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/mm³, 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

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 > 95th percentile for age/height while the participant is on less than three antihypertensive agents so long as the total number of agents does not exceed three.

5. STUDY POPULATION

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/m² for age ≥ 21 years
16. Allergy to study medications
17. Inability to consent/assent

5.3. Study Exit

1. Serious adverse event
2. Participant or parent withdrawal of consent to participate
3. Pregnancy:

NOTE: If a study participant becomes pregnant during the course of the clinical trial, then the study medication should be discontinued and she must be followed until the time of delivery (premature or full-term) to determine the outcome of the pregnancy and the health status (e.g. if there are any birth defects) of in the infant.

6. IRB INFORMATION

The Catalog of Federal Domestic Assistance number is cited in the RFA. The Catalog of Federal Domestic Assistance Number is 93.849.

6.1. General Principles of Consent

1. 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 take part in the study activities.
2. The time frame of a participant signing an informed consent to actually being randomized must be ≤ 6 months. If this time frame is greater than 6 months, it will be necessary to re-consent the participant before being randomized into the FSGS-CT study.
3. Separate informed consent will be obtained for participation in the clinical trial and for obtaining and storing of biological samples (see Section 13.9. for Template Material Consent for Provision of Biorepository Samples). Although participants will be permitted to join in the therapeutic trial without granting permission for collection and storage of biological samples, they will not be invited to provide biological specimens without being part of the clinical trial. (Note: NIH approval is required for *Repository Consents* before specimens can be taken out of the Repository.)
4. For each participant in the FSGS-CT a de-identified copy of his/her informed consent signature page, specifying the assigned identification number, will be faxed to the DCC.
5. 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.

A template informed consent form is provided below.

Information about the Certificate of Confidentiality should be included in the informed consent document, and in fact is required by 21 CFR 50.25(a)(5): "In seeking informed consent, the following information shall be provided to each subject: A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained..." The revised consent document should, of course, be reviewed/approved by the IRB and used with any subjects who enroll in the study after the Certificate is obtained. See Section 20 of the MOP for examples of Application Instructions (20.7.) and Language describing Certificate of Confidentiality protection of privacy (20.8.).

In the event that the Certificate is obtained after the study has begun (for example, if a Participating Site did not initially know that certificates are available, and applied for one sometime after the study had started), sites could inform study subjects who are already enrolled that a Certificate has been obtained and provide these subjects with a description of the protections that the Certificate provides.

6. IRB INFORMATION

Please contact your CCC if you have any questions regarding the Certificate of Confidentiality.

Participating Site's interested in having the Consent Form translated into Spanish may contact:

ILT Translation Service

Home Office (336) 578-4198

Irina Lopez Teixeira

Email Address: ILTTrans@bellsouth.net

Participating Sites will need to pay for translations out of the funds allotted for "Start Up Costs". Refer to Section 19 for details on Financial Overview.

6.2. Privacy

1. At the beginning of the study, each participant is assigned an identification number and a study code.
2. In any individual tabulation, participants will be identified only by number.
3. The medical records of participants in the FSGS-CT will be confidential. Participant documentation and files will be stored in numerical order and stored in a secure and accessible place and manner.
4. Specific study related information may be made available to the Food and Drug Administration and the National Institutes of Health.
5. All procedures will be in compliance with HIPAA regulations.

TEMPLATE
INFORMED CONSENT
Focal Segmental Glomerulosclerosis Trial

1. Introduction

You (your child) are being invited to participate in this research study because you (your child) have a kidney disease known as focal segmental glomerulosclerosis (FSGS) and continue to have abnormal amounts of protein in your urine.

Several different medicines have been used to treat patients like you, but it is not clear whether any of these treatments change the long-term outcome. The purpose of this study is to compare two different treatments. One will use a medicine called Cyclosporine. The other plan will use two medicines – Mycophenolate Mofetil (MMF) and intermittent high doses of a steroid called Dexamethasone.

The medicines being used in this study are already being used to treat patients with FSGS, so if you decide not to be part of the study, your doctor may recommend one of these treatments or some other treatment. Experts disagree as to what the best treatment is for patients like you, and there is no strong evidence to prove which treatment is better.

The side effects of the treatments are different; these are explained in more detail later in this consent form. If you decide to join the study your treatment would be decided randomly (like flipping a coin). If you decide not to join the study, you may discuss alternative treatments with your doctor.

The major benefits of being in the study maybe: (1) you would be contributing to knowledge that could help other patients with FSGS in the future; (2) if the study shows that one treatment is better, you might benefit by being treated with that approach when you finish the study (in about 1.5 years). Similarly, you might avoid prolonged treatment with medicines that are not the most effective; (3) the medicines would be provided without charge.

It's important that you understand what the research is about, so don't be afraid to ask questions if you don't understand something.

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

You do not have to participate in this study. You may stop your participation at anytime without changing your current or future relations with "X" hospital or its doctors.

If you decide to participate in this study you will be told about any new information available to us during the course of the study that might cause you to change your mind about being in the study.

6. IRB INFORMATION

You are being invited to participate in this study because you have focal segmental glomerulosclerosis. You have had a kidney biopsy, which confirmed the fact that your kidneys have this abnormality. You have already had some therapy to try to decrease the amount of protein in your urine. This has not been successful and therefore other therapy is needed.

2. Why is this study being done?

The purpose of the study is to determine which of two treatment methods would be better in decreasing the amount of protein in your urine during the first six months of the therapy. In addition, we will determine the effect of these therapies on your kidney function and any side effects of the two treatments.

One therapy involves a drug called Cyclosporine. Cyclosporine has been used for kidney transplant patients for adults and children for many years. It has also been used to treat patients with focal segmental sclerosis. The other treatment consists of a drug called Mytopenalate Mofetil (MMF) and intermittent doses of a steroid, Dexamethasone. MMF is a drug that has been used in transplant patients and has been also used in patients with focal segmental sclerosis. The use of Cyclosporine and MMF has been reported in small numbers of patients, but the drugs have not been compared to each other. High doses of steroids have been used for many of years, again in small numbers of patients. This study will directly compare, in a standardized fashion, these two drug regimens, Cyclosporine vs. MMF and Dexamethasone. Whether you are in one treatment group or the other, you will also receive prednisone (a steroid) every other day for the first six months of the study. You will also receive a blood pressure medication known as Lisinopril (an angiotensin converting enzyme inhibitor). Lisinopril has been shown to control blood pressure and to decrease the amount of protein in urine of patients with kidney disease.

3. How many people will take part in the study?

Five hundred adults and children will be asked to participate in this study. This study will take place at five coordinating centers across the country, which will collaborate with smaller centers so that a wide representation of adults and children from 200 centers across the United States will take part in the study. “X” number will be asked to participate at “Y” university.

4. What is involved in the study?

If you (your child) agree to participate in this study you will be asked to have several studies done before you’re given any medication (Baseline studies). There will be urine studies done on at least two occasions and there will be blood studies done. These studies will evaluate the amount of protein in your blood and urine, measure kidney function, blood electrolytes, liver function and blood lipids (cholesterol/triglycerides). If you are a woman able to have children, a urine pregnancy test will be done, because one of the medicines used in the study (Lisinopril) can harm a developing fetus. You will also have a physical examination done to measure blood pressure and to look for swelling, cataracts and to listen to your heart and lungs. If you have not had a test to determine whether you have had tuberculosis, a skin test will be done to determine this. This will be a small amount of liquid injected directly into the skin that will raise a small welt on your forearm. You will need to have this checked in 48 to 72 hours. Also at this time

6. IRB INFORMATION

patient information will be collected about you, your family, the history of your kidney disease and data about you and your family lifestyle, education and finances. Your kidney biopsy will be sent to a pathologist at another center to be looked at.

There will be a total of 14 additional visits for the 78 week (1.5 years) duration of the study. At the first visit (week 0) you will be asked to give a urine specimen to determine the amount of protein in this urine, then you will be randomized into one of the two treatment groups. Randomization is similar to a flip of a coin. Two weeks later (week 2) you will return to clinic and have another urine collected for protein and you will have more blood studies done. These blood studies will consist of a blood count to evaluate the number of red blood cells, white blood cells (cells that fight infection) and platelets (cells which cause the blood to clot). The blood studies will also evaluate your kidney function, liver function, electrolytes, and the amount of protein in your blood. At week 4 these same lab studies will be drawn again and you will also have lipid studies done which will evaluate the amount of cholesterol and triglycerides and other lipids in your blood. You will need to come to the clinic not having anything to eat or drink for the previous 12 hours before you have the blood drawn. You will come to the clinic again at weeks 8, 14, 20, 26, 32, 38, 44, 52, 65 and 78 for the research study. The laboratory blood studies will be drawn at every visit. You will also be asked about any side effects of the medications or symptoms of the FSGS you may have had since your last visit. At weeks 14, 38, 65 urine will be obtained for a pregnancy test. Urine will be collected at every study visit to measure the amount of protein in your urine. At weeks 26, 52 and 78 blood will also be done for the lipid studies. You will need to come in the morning of these visits not having had anything to eat or drink for the previous 12 hours.

The amount of blood to be drawn for each visit will vary from one teaspoon to one and a half teaspoons. Thus the total amount of blood drawn for the study is about 4.5 tablespoons.

You will also be asked to answer questions about your quality of life at study visits week 26, week 52, and week 78. Some of these questions may be of a personal and sensitive nature; if you do not want to answer a question, you can skip it. This will take about 20 minutes. Regardless of which treatment group you are assigned to you will be asked to take prednisone (a steroid) every other morning for the first 26 weeks of the study. The dose will be based on your weight. Also you will be asked to take Lisinopril everyday. The dose will be based on weight.

If you are in the cyclosporine group, you will be asked to take cyclosporine every day for 52 weeks. The dose will be based on your weight, but may be modified based on any side effects you may have and on the blood levels of cyclosporine.

If you are in the MMF group, you will be asked to take MMF every day for 52 weeks. The dose will be based on your weight but may be modified based on any side effects you may have. You will also be asked to take Dexamethasone based on your weight; this will be 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.

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We would like to continue to collect data on you after the research study is over. This would include results from blood and urine samples that would be done anyway at your regular clinic visits and information about relapses and remissions.

5. What happens if I discontinue or withdraw from the study?

If you withdraw from the study before its completion, you will be asked to return all study medications and for your safety to come in for a final visit in order to have blood work done (1.0 teaspoon), urine protein and blood lipid studies (0.5 teaspoon) performed.

You may also be asked to leave the study if you do not take the drugs as instructed, if you consistently fail to come in for clinic visits, if the investigator feels that you are having unacceptable side effects from the medications or if you have failed to respond to the medications by week 26.

6. What are the risks of this study?

Your participation in this study involves the following risks:

The risks of taking Cyclosporine include: decreased kidney function, tremor (shakiness of the hands), increase in hair growth, high blood pressure and an increase in tissue around the teeth (gingival hyperplasia). It may also cause increases in the blood potassium, which can cause heart rhythm disturbances, and decreases in blood magnesium, which causes twitching or seizures. In studies of patients with other diseases taking Cyclosporine, the most common reactions (one or more occurring in greater than 3% of over 800 patients) are: decreases in kidney function, high blood pressure, increase hair growth, acne, shakiness, headache, seizures, diarrhea, nausea, vomiting, increase in liver enzymes suggesting an abnormality of the liver, stomach pain, decreases in white blood cells (cells that fight infections) and increases in breast tissue. Adverse reactions which have occurred in less than 2% of patients taking Cyclosporine include: decreases in red cell count (anemia), loss of appetite, confusion, redness of the eyes, swelling, fever, increases in blood sugar, decreases in platelet counts (cells that cause blood to clot) and ringing of the ears.

Because adverse reactions (side effects) may be related to the blood concentration, we will measure the blood concentration of Cyclosporine at frequent intervals particularly early in the course of the therapy. Blood concentration will be measured at week 2, week 4, week 6, week 8, week 20, week 26 and week 52 or anytime the physician feels that it is necessary or that you may be having a reaction related to the Cyclosporine. Based on side effects you may be having and on the blood levels, the investigators may change the amount or time Cyclosporine is given.

Lisinopril is a drug that controls blood pressure and has also been shown to decrease the amount of protein in the urine. All patients on this study will be taking Lisinopril in doses that are based on weight and blood pressure. Side effects noted in more than 3% of over 1,000 patients taking Lisinopril include: headache, dizziness and cough. A condition known as angio-edema has also occurred, this is swelling of the face, lips, tongue and or the larynx (voice box). Without treatment this can lead to death. Lisinopril can also cause damages to the fetal and newborn if a

6. IRB INFORMATION

woman becomes pregnant while taking this drug, and may cause death of a fetus. It is important that while in the study and taking Lisinopril, women do not become pregnant. It is important that appropriate methods of birth control be used if you are sexually active. The preferred methods would be barrier methods such as condoms and spermicides.

If Lisinopril does not control your blood pressure adequately or if you have adverse side effects, other drugs may be prescribed.

Prednisone/Dexamethasone. Adverse reactions to Prednisone or Dexamethasone include swelling due to sodium and fluid retention, decrease in serum potassium which may cause muscle weakness, increase in blood pressure, muscle weakness, loss of muscle mass, loss of bone mass (osteoporosis), compression fractures of the back, destruction (aseptic necrosis) of the femoral head (thigh bone), hip and/or knee pain, gastritis giving stomach pain, ulcer formation, perforation of the large and small bowel, inflammation of the pancreas with severe abdominal pain, abdominal distention, impaired wound healing, fragile skin, increased breakage of blood vessels and bruising, seizures, increase in pressure within the head, headache, increase in behavioral and psychiatric problems, irregularities of menstrual periods, increase in facial fat particularly around the cheeks, decrease in growth, decrease in the body's own steroid production, increase in blood sugar, increase in hair growth, formation of cataracts, glaucoma, weight gain, increase in appetite and nausea.

Mycophenolate Mofetil. Adverse events which may occur in more than 10% of patients taking Mycophenolate Mofetil include: hypertension, diarrhea, blood in the urine, decreased white blood cells (leading to increased risk of infection), decreased red blood cells (leading to tiredness, weakness) and decreased platelets (leading to increased risk of bleeding); tremor, nausea, heartburn, decreased serum potassium (leading to weakness, heart rhythm disturbance); increased blood sugar.

We cannot predict all the risks or potential side effects of these medicines. There may be unknown or delayed risks that may occur months or years after treatment.

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

As with all drugs, the study drugs may have interactions with other drugs, both prescription drugs, non-prescription drugs and herbal remedies found at health food stores. Before any medicine is taken whether it is purchased by you, prescribed by a physician or purchased from a health food store, your physician needs to be called or notified. Other prescribed or “over the counter” drugs or herbals may cause increases or decreases in effectiveness of the study drugs and therefore may increase the risk of side effects or decrease the effectiveness of the study drugs.

Reproductive Health/Sexual Activity

The effects on the developing fetus by using Lisinopril during pregnancy and the risk of birth defects are well known. This drug may cause damage or even death to a fetus. Therefore

6. IRB INFORMATION

women who are pregnant or breast-feeding may not participate in this study. Women should not become pregnant while participating in this study. If sexually active both men and women should use an effective method of birth control while taking lisinopril. Condoms, diaphragm, Depo-Provera, Norplant, oral contraceptives and complete abstinence are examples of effective methods. If you become pregnant while taking the study drug, it is important that you notify your study nurse/doctor immediately. You may be required to stop treatment, at which time other treatment options will be discussed with you.

Pregnancy tests will be performed at the time of the baseline study and at week 14, week 38 and at week 65.

7. Are there benefits to taking part in this study?

There may be benefits for you taking part in this study including: decreases in protein in your urine, increase in serum proteins, and reduction or even disappearance of swelling. This study may also benefit future patients by identifying which of these two treatment protocols would be more helpful to patients with focal segmental sclerosis.

You may receive no benefit by participating in this study, the protein in your urine may increase, may stay the same, or you may have relapses while on the study. You may also experience adverse effects from the study drugs while participating in the study.

8. What other options are there?

If you do not wish to participate in this study the following alternative treatments are available to you. Treatment with the medicines being used in this study, or other treatments that have been proposed for focal segmental sclerosis including: high dose intravenous steroids, no therapy, or other immunosuppressives.

9. What are the costs of the study?

You will not be charged for the study drugs that are provided to you. You will not be charged for visits for the study. Any visits and medications that are not related to the study will be charged to you or your insurance company.

After the study ends, you or your insurance company will be responsible for the cost of medications.

10. What happens if I am injured while participating in this study?

Medical care including hospitalization is available if you are injured or become ill because of research procedures. This medical care is not free. You will be responsible for the cost. You may call the Director of Risk Management if you have any questions about the cost of treatment in your case.

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11. Will I be paid for participating in this study?

You will not be paid or compensated for your participation in this study.

12. What about confidentiality?

We will make every effort to keep your research records private, but confidentiality cannot be assured. Records that identify you, and this consent form, may be looked at by regulatory agencies such as: the Food and Drug Administration; the Department of Health and Human Service Agencies; the Institutional Review Board; the National Committee for Quality Assurance; your records may be looked at by personnel from the National Institutes of Health. If the results of the study are published or presented in public your name will not be used.

Centralized data of collection or registry. The results of your tests will be stored in a centralized computer or data registry at the Cleveland Clinic Foundation for 7 years.

Insert information pertaining to Certificate of Confidentiality.

13. What are my rights as study participant?

Taking part in this study is voluntary. You have a right to choose not to take part in this study. If you do not take part in this study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled. If you withdraw from the study, with your permission, you will continue to be followed and clinical data will continue to be collected from your Medical Records. A data safety monitoring board (an independent group of experts) will be reviewing the data from this research throughout the study.

If you choose to take part, you have the right to stop at any time. You will be told of any new findings from this or other studies that may affect your health, welfare, or willingness to stay in this study.

If you are an employee or student, whether or not you take part in this study will not affect your job, current or future medical care or studies.

Insert language pertaining to HIPAA Regulations.

14. Conflict of Interest

15. Whom do I call if I have questions or problems?

If you have questions about any part of the study now or in the future, you should contact _____, who can be reached at _____. If you experience side effects or injuries while participating in this study, please contact _____, who may be reached at _____. For after hours, weekends, or holidays call _____. If you have questions about your rights as a research participant contact the Institutional Review

6. IRB INFORMATION

Board (which is a group of people who review the research to protect your rights) at _____.

16. Patient/Subject Acknowledgement:

The procedures, purposes, known discomforts and risks, possible benefits to me and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I understand it. I agree to participate in this study. I have been given a copy of this consent form.

Patient/Subject Signature

Date

Signature of Person Obtaining Informed Consent

Date

Optional:

Signature of Principal Investigator or Designate

Date

The procedures, purposes, known discomforts and risks, possible benefits to my child and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I understand it. I agree to allow my child to participate in this study. I have been given a copy of this consent form.

Subject Assents by Signature, when applicable

Date

Subject Age

Parent/Guardian Signature

Date

Parent/Guardian Signature

Date

Signature of Person Obtaining Informed Consent

Date

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Both parents need to sign for children to participate in a research study. If only one parent can sign this consent, indicate the reason that applies to the other parent.

- _____ decreased
 - _____ unknown
 - _____ legally incompetent
 - _____ no legal responsibility for the care and custody of the child
 - _____ not reasonably available – indicate why _____
- [Acceptable reasons for this category must not be based on convenience]

Optional:

Signature of Principal Investigator or Designate Date
[Affirming eligibility for the study and that informed consent has been obtained]

If child cannot reasonably assent or if well being of child is directly benefited by participation without assent, please explain.

Signature of Principal Investigator Date
or his/her authorized agent

6. IRB INFORMATION

Visits Weeks	Focal Segmental Glomerulosclerosis Trial			
	Laboratory Studies	H & P	Questionnaires	
	<u>Urine</u>	<u>Blood</u>		Patient information Disease profile Socio economic Biopsy sent to lab
<u>Baseline</u>	HCG Up x 2	CBC Chem 18 Lipids	X	
0 Randomization	Up			
+2	Up	CBC Chem 18		
+4	Up	CBC Chem 18, Lipids		
+6	Up	CBC, Chem 18, CBC		
+8	Up	Chem 18		
14	Up, HCG	CBC Chem 18	X	
+20	Up	CBC Chem 18		
*+26	Up x2, HCG	CBC Chem 18, Lipids	X	QOL
32	Up	CBC Chem 18		
38	Up, HCG	CBC Chem 18	X	
44	Up	CBC Chem 18		
+52	Up x 2	CBC Chem 18, Lipids	X	QOL
65	Up, HCG	CBC Chem 18		
78	Up x 2	CBC Chem 18, Lipids	X	QOL

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H & P – History and Physical Exam

HCG – pregnancy test

QOL – Quality of Life

Lipids – fasting 8-12 hours before test

* Alternate-day prednisone stopped

+ Cyclosporine levels drawn

Dexamethasone given 1st two days of weeks: 1 through 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 34, 38, 42, 46, 50

Cyclosporine/MMF given every day through week 52

Lisinopril given every day

TEMPLATE
Focal Segmental Glomerulosclerosis Trial
Child Assent

1. Introduction

You are being asked to take part in a research study because you have kidney disease. The name of this kidney disease is called focal segmental sclerosis (FSGS). This means that you have little scars in your kidneys. This causes abnormal amounts of protein to be in your urine and because of this you have less protein in your blood, which causes you to have, swelling of your face and legs and maybe your stomach.

The purpose of this study is to compare two different ways to treat this kidney disease. One way involves a drug called Cyclosporine the other way involves two medicines, one medicine is called Mycophenolate Mofetil (MMF) and the other high dose is of a drug like Prednisone which you have taken before. We don't know which is the best way to treat this and that is why we are comparing these two ways.

Like all drugs, these two drugs have different side effects; these will be explained to you.

We don't know which of these treatments is better but we think either one may be helpful. By taking part in this study, you may help us learn the best way to treat this disease, which will help other people in the future.

It is important that you understand what the research is about so if there are any questions you need to ask.

You do not have to stay in the study if you start the study. You can stop at any time and you can continue to be seen by Dr. X at Y hospital.

If you do decide to be part of this study you will be told about any new information as the study goes along. You will be in the study for approximately a year and a half.

2. How many participants will take part in the study?

About 500 adults and children will be asked to take part in the study. The study will take place at five large medical centers across the country. They will collaborate with other hospitals and medical centers.

3. What is involved in the study?

You will have several blood and urine studies done before you take any of the new medicines. We will want to measure your kidney function, your liver function, the amount of protein in your blood, and the amount of protein in your urine. We will want to do a test to make sure that you have not had tuberculosis. We will also want to ask you and your mother and father questions about where you live, what school you go to and about your home life. There will be a total of

6. IRB INFORMATION

14 other visits over the one and a half years of the study. At these visits you will have blood taken every time and you will be asked to give a urine sample. We will measure the amount of protein in your urine and we will take a small amount of blood to measure how your kidneys are working and to check for side effects from the drugs. When we measure the amount of fat in your blood, you will not have breakfast or anything to eat or drink the morning that you come to clinic.

Three times during the study you will also be asked questions about how well you are doing, any effects that you are having from the medicines and generally how you feel.

Depending upon which study you are in you will be asked to take drugs every day, every other day, at the first of the week and not at the end of the week. We will decide which of the two treatment protocols you are going to be on by flipping a coin.

Even if you aren't in the study, your doctor will probably suggest that you be treated with one or more of these medications. The main differences from being in the study is that you will be asked to come to your doctor's clinic/office 15 times to be seen, examined, have blood and urine taken for the study.

4. What will happen if I discontinue or withdraw from the study?

If you decide that you don't want to take part in the study anymore, we would ask that you bring all the medicines back that we have given you and we would ask you to allow us to draw one final blood specimen.

5. What are the risks of the study?

When you take part in this study and take these drugs there are certain other effects the drugs have other than helping you. These are called adverse effects.

Cyclosporine, one of the drugs that you might take, can cause shakiness of the hands, it can increase the amount of hair that you have on your body, it can increase your blood pressure, which will give you headaches, and it can increase the amount of tissue around your teeth.

A blood pressure medicine called lisinopril may also cause headache, make you dizzy and make you cough.

Prednisone or Dexamethasone may cause you to get puffy, have puffy cheeks, increase blood pressure, give you headaches, give you muscle weakness, it may weaken your bones, it may give you stomach upset, it may make you bleed more easily and cause your skin to bruise more easily, it can make you irritable, make you get angry more easily and it can stop you from growing as well as you might.

Mycophenolate Mofetil can cause you to have diarrhea, blood in the urine, it can make you get infections more easily, and it can make you shaky and can make your stomach upset.

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You may have some or none or all of these reactions.

Also we will need to withdraw blood from a vein in your arm or hand and this may cause some pain or discomfort, we will minimize this by making sure that only people who draw blood do a really good job.

6. Are there benefits in taking part in this study?

There may be benefits for you to take part in this study. It may decrease the amount of protein in your urine; it may increase the amount of protein in your blood and therefore decrease swelling in your face and feet.

7. What are the other options?

You do not have to take part in this study and your doctor can talk to you about other ways that your disease might be treated.

8. What are the costs?

Many of the drugs will be given to you and your parents free.

9. What about privacy?

All of your studies, blood studies, urine studies, will be kept private between you and your doctor. The results of your study will be sent off to another hospital in the country, but it will not be identified with you.

Insert information pertaining to Certificate of Confidentiality.

Insert language pertaining to HIPAA Regulations.

10. Whom can I call if I have questions?

If you have any questions about any part of this study you can call your doctor and ask him or her any questions that you might have.

11. Participant/Subject Acknowledgment

The procedures, purposes, known discomforts and risks, benefits to me and to others, and the availability to alternate procedures regarding this research study have been explained to me and my child. My child and I have read this consent form or it has been read to me and I understand it. My child and I agree to participate in this study and have been given a copy of the consent form.

Participant/Subject Signature

Date

6. IRB INFORMATION

Signature of Person Obtaining
Informed Consent

Date

Optional:

Signature of Principal Investigator
or Designate

Date

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

7.1. Purpose

This section describes the procedures that are to be performed 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 Sites and include: confirmation of pathology, laboratory studies including the correct collection of first morning urine samples for measurement of Up/c, and measurement of blood pressure.

7.1.1. First Morning Urine (FMU) Samples

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

1. First morning urine collections for measurement of the urine protein:creatinine ratio (Up/c) should be obtained at each protocol visit as indicated in Section 10.2. The urinary protein and creatinine concentrations should be measured as mg/dl.
2. **In order to obtain the most reliable estimate of urinary protein excretion and to eliminate any orthostatic component, this determination will be done in early morning specimens rather than random spot urine samples.** The early morning urine sample should be collected as soon as the participant awakes in the morning prior to engaging in any activity. It is advisable to place a specimen cup in the bathroom in the evening prior to specimen collection.
3. A specimen should be collected on two mornings prior to (urine should be less than seven days old when brought in for their visit) the Baseline and W26, W52, and W78 Follow-up visits. Participants should bring these specimens in to the clinic. All other Follow-up study assessments of proteinuria will require only a single early morning specimen.
4. The baseline or follow-up Up/c ratio will be calculated as the average of the values measured in the two early morning urine samples. Average Up/c will not be calculated if the two baseline samples vary by more than 1.5 times. If the higher value of the two is 1.5 times or more than the lower value, a third sample will be requested. (Note: 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 values is 1.5 x the lower value, unless both the first two Up/c values are greater than 8 or both are less than 0.2.)
5. Increases in proteinuria will be documented in the Core Lab report, containing the Up/c measurement, **prior to** initiation of relapse therapy, novel therapy or a medication stop point (withdrawal of the participant from the protocol's treatment regimen).

Participants should be instructed to avoid drugs that interfere with creatinine excretion (e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septa, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. *Common H₂ blockers include:* Tagamet (cimetidine). *Common NSAIDS include:* ibuprofen (Advil) and naproxen (Aleve).

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Participants should be contacted prior to a scheduled visit to inquire if he/she has any of the following problems:
 - a. Intercurrent illness
 - b. Fever
 - c. Temporary use of a medication that interferes with creatinine excretion (see list of medications above).

These conditions might cause a transient increase in proteinuria or alter the Up/c. **If any of these circumstances apply, then reschedule the planned visit.**

If the participant is found to have fever or an intercurrent illness at a scheduled follow-up visit, then the urine samples should be discarded without being sent to the Core Lab and repeat samples should be obtained. These repeat samples may be collected and shipped to the Core Lab from the participant's home.

Instructions for shipping urine specimens to the Core Lab are specified in Section 10.

7.1.2. Blood Pressure Determinations

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

The normal values for blood pressure in pediatric age participants should be based on the Second Task Force on Blood Pressure in Children (Pediatrics 1996) and in adults on the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JAMA 2003) (see Section 20.1. and 20.2. for normal blood pressure levels).

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7.1.3. Laboratory Tests

1. 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.
2. Indication of fasting status and duration prior to blood draw should be documented on the Blood and Serum Mailing Form (Form # 83).
3. Blood samples for measurement of trough cyclosporine levels should be drawn between 10 to 14 hours after the last dose and immediately before the next scheduled dose.
4. Blood and urine assays will be conducted in the Core Lab. The following tests have been included in the study:
 - a. SMA18 (or equivalent)
 - b. CBC with platelet count and Up/c (refer to “Schedule of Visits and Lab Tests” table in Section 7.4)
 - c. Cyclosporine level at 7 visits and a fasting lipid profile at 5 visits. See Section 10.2 of the Protocol for details.

Although Urine Analysis is recommended as standard of care, it is not mandatory at the screening visit.

5. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should 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). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference.

Note: Although there is a formal requirement to repeat a pregnancy test at specified follow-up visits – Baseline, Week 0, Week 14, Week 26, Week 38, Week 52, and Week 65 -- it is advised that the test be repeated as often as deemed clinically necessary to avoid unanticipated teratogenic effects of the drugs used in the treatment protocol, especially ACEi and ARB.

6. Instructions for shipping blood and urine specimens to the Core Lab are specified in Section 10.

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7.1.4. Estimation of Glomerular Filtration Rate

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

1. Determine eligibility for the study AND
2. Provide an estimate of renal function for longitudinal analyses of the effects of the treatment intervention on GFR as a side effect of therapy or progression of disease.

It is important that all participants should be in their usual state of health and that they be carefully examined to ensure that they are free of any clinical signs of dehydration at visits requiring estimation of GFR. This precaution is critical to avoid unnecessary adjustments in the doses of the study medications, based on spuriously low estimated GFR levels.

To determine GFR:

1. The average of serum creatinine values at the Baseline visit, and the Week 0 visit will be used for the calculation of the study estimated GFR baseline.
2. GFR will be estimated by the Schwartz formula for participants age < 18 years and by the Cockcroft-Gault formula for participants age ≥ 18 years.
3. The local investigator should use the formulas (see Section 20.6) when calculating the GFR to determine eligibility during the Screening Evaluation.

Note: After enrollment, all other GFR calculations will be performed by the DCC using laboratory results forwarded by the Core Lab. The age-appropriate criterion will be applied in children who are screened in the study when they are < 18 years but whom become 18 years or older during the course of the follow-up period.

7.1.5. Additional biological samples for special studies

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 Fisher 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. Refer to Section 13 of the MOP for further details on Repository collections. 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).

7.1.6. Questionnaires

The questionnaires to be used include a disease history and a quality of life instrument. The disease history will be completed at baseline and the quality of life survey will be administered 4 times during the course of the study – at Baseline, W26, W52, and W78.

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1. Disease History (Form # 14) - This questionnaire will be administered by study personnel and document the age of onset of proteinuria, past treatment for FSGS and family history of proteinuria, nephrotic syndrome, FSGS, and end-stage renal disease. Family members will only be identified as first-degree relative or other relative.

To be completed at Baseline only.

2. The SF-36 is a 36-item quality of life questionnaire for adults age 18 and above. This is a self-administered questionnaire.

To be completed at Baseline, Follow-up visits on weeks 26, 52 and 78.

3. The PedsQL is a 23-item quality of life questionnaire self-reported for children ages 5–18 and parent proxy-reported for ages 2–4.

To be completed at Baseline, Follow-up visits on weeks 26, 52 and 78.

Validated translations of the SF-36 and PedsQL will be provided in English, Spanish, and French.

7.1.7. Monitoring of hospitalizations

See Section 9, Adverse Events and Deviations from Assigned RX, for detailed description of procedure to be followed in the event that a study participant requires hospitalization.

7.1.8. Medication use

All medications will be recorded at the baseline evaluation and all scheduled and unscheduled study visits during Treatment and Follow-up Periods using WHODRUG coding system. WHODRUG is a computerized database that will be used centrally by the DCC to facilitate identification and tabulation of all formulations of the medications prescribed to participants enrolled in the clinical trial. For Participating Sites using paper forms, only documentation of the name of medications will be required.

Note:

In patients assigned to the cyclosporine arm of the study, the drug dose will be adjusted based on plasma levels at select visits and on side effects. Because cyclosporine is metabolized in the liver primarily by the Cytochrome P450 (CYP 450) system, the drug level may be altered by medications that increase or decrease the activity of this enzyme system. In light of this potential confounding effect, it is advised that caution be used in prescribing the following drugs:

Agents that inhibit CYP 450 activity and increase cyclosporine levels:

ketoconazole, fluconazole, erythromycin, diltiazem, verapamil, nicardipine, metoclopramide.

Agents that stimulate CYP 450 activity and lower cyclosporine levels:

antiseizure medications (e.g. phenytoin, phenobarbital and carbamazepine), rifampin, and non-steroidal anti-inflammatory drugs.

These drugs are not contraindicated by the protocol but should be avoided if possible. If a CYP 450 modulating agent must be used it is advised that their use be taken into account in determining the dose of cyclosporine and interpreting the drug level.

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7.2. Baseline Period Evaluation

7.2.1. General Principles

The Screening and Baseline periods are expected to last at most two weeks. Before entering the Baseline period, participants will be screened to ensure that they meet the inclusion criteria and that none of the exclusion criteria are present. Using existing medical records and/or participant interviews, the Screening Form will be completed (see Form 10). Some eligibility criteria will require confirmation by laboratory tests at the Baseline visit (see Section 10.2).

All participating PIs are encouraged to make every effort to expedite participant screening and to complete the Baseline Evaluation as quickly as possible. It is recommended that this phase be completed within 2 weeks.

7.2.2. Laboratory Tests From Screening Through Randomization

Lab tests will include both blood and urine studies. Analyses will be done by the Core Lab for HCG (at Baseline and specified follow-up visits) and CBC, serum chemistries, lipid profile and early morning Up/c. GFR will be calculated by the DCC using the appropriate formulas.

Urine protein excretion

1. A first morning urine sample should be collected on two mornings prior to the Baseline visit brought to their visit. The urine samples should be refrigerated until the appointment.
2. The baseline Up/c ratio will be calculated as the average of the values measured in the two early morning urine samples.

KEY POINT: 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 1.5x the lower value. Under these circumstances, the Up/c ratio will be calculated as the average of the two closest values.

Additional biological samples for special studies at the Baseline assessment

HIV, Hepatitis B and C
SMA18 or equivalent
CBC including differential, ANC and platelet count
Urine HCG

HIV testing

Rhode Island state regulation of HIV testing only allows testing at the Rhode Island State Department of Health. For Participating Sites in Rhode Island, the HIV sample must be sent to the Rhode Island Department of Health and the results should be sent to the DCC on Form # 77.

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PPD (tuberculosis skin test)

Potential subjects without a history of a previously positive PPD skin test (tuberculosis skin test) must receive a PPD test during the screening period unless the participant 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 is an acceptable alternative. Results of the Local TB test should be reported on Form # 91.

Screening Medication Status

Participants should be queried about use of any of the immunosuppressive medication that would disqualify them from participating in the study. Participants who are receiving concomitant treatment with an ACEi and ARB for control of blood pressure or to lower proteinuria will be required to discontinue the particular brand and convert to lisinopril, which will be provided by the study. ACEi are the preferred therapy if the participant tolerates this class of drugs. In addition, if the participant is on an ACEi at the time of enrollment, then the medication must be switched to the formulation that is being provided as part of the clinical trial, namely lisinopril. If the participant is on an ARB but has no clinical history of intolerance of ACEi, then ARB should be discontinued and replaced with lisinopril. If the participant is on an ARB because of prior ACEi intolerance, then the ARB medication must be switched to the ARB formulation that is being provided as part of the clinical trial, namely losartan.

During the screening visits:

1. Review all prescribed medications and record on Medication Form (Form # 44)
2. Ensure that the participant is not receiving medication that would result in exclusion from the study
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. If it is clinically indicated and the participant is not yet taking an ACEi, then this drug can be started during the Baseline period. *The study provided ACEi first becomes available after randomization.* The Up/c must be > 1.0 g protein/g creatinine while on ACEi (or ARB in ACEi intolerant participants) to be eligible for inclusion in the study. After entry into the study, the dose should be adjusted to the full target dose, as outlined in Section 8.

History and Physical Examination

A full history (at Baseline) and physical examination (at Baseline and specified follow-up visits) including measurement of blood pressure must be performed using the Disease History Form (Form # 14) and the Physical Exam Form (Form # 46).

Participant Questionnaires

Participant questionnaires administered at Baseline include the Baseline Visit Form (Form # 11) with information on symptoms, medications, and TB history. The questionnaire items concerning socio-economic variables will be optional. Also, Quality of Life questionnaires will be

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administered using the appropriate QOL Form(s), SF-36 Form (Form # 36), and PedsQL Forms (Form # 37 – 43) at Baseline and specified follow-up visits.

Assessment of Eligibility and Randomization

Participants will be considered eligible for randomization if they provide consent to participate, if all of the required baseline data is collected and validated, and no additional exclusion criteria are identified during baseline.

Special studies

As part of the trial, for those participants who consent to this procedure, an extra sample of plasma, serum, urine, and DNA will be collected at the baseline visit. These samples should be obtained at the Week 0 visit, after randomization but prior to administration of the first dose of study medications. **Please note:** Participants can enroll in the clinical trial without agreeing to the collection and storage of these additional biological specimens. However, they cannot provide these special samples without enrolling in the clinical trial.

The DNA samples will be stored in an NIDDK DNA Repository, which is the Rutgers Cell and DNA Repository. The other biological repository specimens will be entered into the NIDDK Biological Specimen Repository, which is at the Fisher Biological Specimen Management (see Section 13 for specific details).

General standard of medical care

The study protocol does not define the specific care to be provided for the following problems that are likely to arise in the participants identified during the Screening Period or the Treatment and Follow-up Periods: (1) hypertension; (2) hyperlipidemia; (3) bone disease related to the underlying disease or the treatment protocol; or (4) edema.

All participating PIs are encouraged to treat these problems in the best manner possible, in accordance with the prevailing practice patterns at their institution. The therapy for these problems can be initiated during the Baseline period.

1. For hypertension, effective doses of up to three medications should be prescribed to maintain the blood pressure below the 95 percentile for age and gender (see Sections 20.1. and 20.2.). Preference should be given to prescribing an ACEi. Although the need for a fourth medication to control blood pressure is an exclusion factor during Screening and Baseline Evaluations, more than three antihypertensive medications can be prescribed during the Treatment and Follow-up Periods. The only restriction is concomitant use of an ACEi and ARB.
2. Modification of diet and the use of cholesterol lowering medications are encouraged to achieve target lipid levels. These can include statins or cholesterol-binding agents, whatever is deemed appropriate for the specific participant.
3. Bone disease related to the FSGS or steroids can be treated with oral calcium supplements, vitamin D preparations including calcitriol, and oral osteoclast inhibitors as single drugs or in combination. They are all acceptable means of treating this problem and alleviating bone

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complications encountered in the study participants. Bone densitometry studies (e.g. DEXA scans) can be performed at the discretion of the attending nephrologist.

4. It is anticipated that edema will be a persistent or recurrent problem in participants enrolled in the clinical trial. This may be managed using dietary sodium restriction, diuretics as single agents or in combination therapy, and/or alternative medication supplements. It is advised, if possible, that diuretic medication should not be changed within one week of a scheduled visit.
5. Dietary advice and the use of antacids and H2-blockers to prevent gastrointestinal side effects of steroids, especially in participants randomized to receive oral dexamethasone pulses, will be left to the discretion of the Participating Site PI. However, H2-blockers must be held for 48 hours before each follow-up visit in order to enable accurate measurement of the serum creatinine concentration and Up/c ratio.

7.3. Randomization Procedure

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

The randomization schedules have been prepared by the DCC prior to the start of recruitment. Allocation to the treatment groups will be equal and stratified by the CCC, baseline estimated GFR (GFR <90 mL/min/1.73 m² *versus* GFR ≥90 mL/min/1.73 m²), and participant's self-reported race (black *versus* 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 DCC staff.

Once all baseline period studies have been completed, the forms corresponding to these studies have been entered into the database, and the forms have been checked to be sure the participant meets eligibility requirements, the Principal Investigator or the study coordinator shall access the On-Line Randomization Form (Form # 30). Once the required questions on Form # 30 are entered, the form will verify through a defined set of questions whether the participant is eligible 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 CCC and the Core Lab. Randomization marks the participant's official and irrevocable entry into the Follow-up Period.

Note: The time frame of a participant signing an informed consent to actually being randomized must be less than 6 months. If this time frame is greater than 6 months, it will be necessary to re-consent the participant before being randomized into the FSGS-CT study.

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Once a participant has been randomized, efforts should 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 one or all medications must be stopped.

It is advisable that randomization should occur prior to the first visit (study week 0) so that the participant can be given the appropriate study medications during the initial visit of the treatment phase of the study. It is strongly recommended to randomize the participant when you are confident that the W00 visit and the drug dispensing can occur within 4 weeks from time of randomization.

7.4. Follow-up Evaluation

Permitted time windows for scheduling Follow-Up visits

Baseline and follow-up visits can be scheduled at any time of the day in order to maximize convenience for the participants and their family. This is especially true in adolescents in high school or young adults attending college or those participants who are employed. However, it is recommended that those visits that require measurement of a fasting lipid profile and trough cyclosporine levels be performed in the morning. If a visit or procedure is missed, the visit should be rescheduled as soon as possible within the allotted interval.

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

TIME WINDOW FOR VISITS:

A tolerance interval of ± 1 week will be allowable for all protocol visits.

Missed Visit or Measurement

If any routine follow-up visit or associated measurements is missed and cannot be rescheduled within the allowable \pm one-week tolerance interval, the visit should be rescheduled as soon as possible after the close of the tolerance interval. The individual participant appointment schedules will be automatically e-mailed to the Participating Site once the W00 has been held (CRFs entered); which indicates target windows for each routine visit. The Report program to generate appointment schedules (on demand) is located on the web site where Form # 02 is. See Section 16 for Database and Data Entry instructions.

If participants are receiving relapse therapy at visit Week 26, Week 52 or Week 78, the visit will be delayed until one week after completion of the relapse protocol (see Section 8.4.7.).

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W26 Treatment Failure Follow-up

Once the lab results determine the W26 outcome for your participant, the DCC will instruct you as to whether the participant is a treatment failure which would require the participant to come off the study medications. Even if the participant is a treatment failure, follow-up will continue but will be scaled back to semi-annual assessments including the following information:

1. Labs tests including Up/c, serum creatinine, serum albumin, and BUN (specimens should be sent to the Core Lab, Spectra)
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 of the Protocol will be maintained following the pregnancy and medication stop points which do not define the primary or main secondary outcomes.

For Treatment Failure Follow-up - W52 CRFs to be completed:

F16 – Follow-up Visit, F44 – Medication; F46 – Physical Exam (Q1-8, Q200 – 201); F52 – Long Term Monitoring; F80 – Urine Mailing; F83 – Serum Mailing; F89 – Results of Pregnancy Test (if applicable); F95 – Biological Specimen Repository Mailing (to Fisher – if participant consented); QOL (PedsQL) should be completed if the participant is willing.

Patient Management at Completion of the W52 Treatment Phase

Medications

According to the protocol, the main study medications – cyclosporine (CSA), mycophenolate mofetil (MMF), and dexamethasone -- should be completely stopped at the 52 week visit, at the end of the treatment phase. This design was implemented to enable determination of the durable response rate to a 1-year course of therapy. The alternate prednisone dosing will have been stopped at 26 weeks. Thus, the only study medication that should be administered according to the protocol is lisinopril or losartan in patients who are intolerant of ACEi.

The protocol does not detail any taper regimen and instead requires complete cessation of the drug at the W52 visit. Abrupt discontinuation of cyclosporine (CSA) or mycophenolate mofetil (MMF) should not cause acute clinical problems and the dexamethasone dosing will have been gradually reduced in intensity over the final 4-6 months of the Treatment Phase. If there are questions about this regimen for a specific patient please contact the Core PI who can solicit the input of the Clinical Management Committee.

Patients who required ACEi or ARB dose reduction for hyperkalemia or GFR decline during the 0-52 week treatment period may have the dose of the ACEi (or ARB if intolerant to ACEi) increased up to the maximally tolerated dose after the 52 week visit at the discretion of the participating site physician. Additional monitoring of GFR and serum potassium will be determined by the participating site physician and protocol adjustments for recurrent hyperkalemia or decline in GFR should follow the study protocol until the final study visit at week 78.

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Study visits

The only study visits required by the protocol during the first 6 months after discontinuing study medications are at weeks 65 and 78 and every 6 months thereafter. The decision to schedule additional interim visits for an individual patient is left entirely at the discretion of the site PI. Laboratory testing during these supplemental evaluations is not part of the protocol. The patient's clinical status after completion of the Treatment Phase is contingent only on the results of laboratory testing (urine protein excretion and blood work) performed at weeks 65 and 78.

Repeat Testing (which tubes to use)

1. If a cyclosporine (CSA) level or a CBC needs to be repeated, then the blood sample should be drawn into a lavender top tube.
2. If a serum potassium or creatinine concentration needs to be repeated, then the blood sample should be drawn in a small SST.
3. If a urine for protein:creatinine (Up/c) ratio needs to be repeated, use the urine collection kit but send only a single tube of urine (do not send the urine cup).

Ordering Extra Tubes or Kits

If repeat tests are necessary, the Site Investigator should use tubes and supplies from kits already available at the Site. If additional supplies are needed to handle repeat testing, then the Site Investigator should contact Spectra to request a shipment of the required number of tubes or replacement mailing boxes. See Section 10.4. for the supply order form.

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Scheduling of Visits

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

Schedule of Visits and Lab Tests

<u>Visit Number</u>	<u>Weeks</u>	<u>Clinical Objectives</u>	<u>Labs</u>	<u>Up/c</u>	<u>Cyclosporine Drug Level</u>
B1	- 1 or - 2	Informed consent baseline studies	X	X	
W0	0	Confirm pregnancy test & Initiate Rx	X	X	
W2	2	Interval Assessment	X	X	X
W4	4	Interval Assessment	X	X	X
W6	6	Interval Assessment	X	X	X
W8	8	Interval Assessment	X	X	
W14	14	Interval Assessment	X	X	X
W20	20	Interval Assessment	X	X	
W26	26	Interval Assessment	X	X	X
W32	32	Interval Assessment	X	X	
W38	38	Interval Assessment	X	X	X
W44	44	Interval Assessment	X	X	
W52	52	Interval Assessment	X	X	X
W65	65	Interval Assessment	X	X	
W78	78	Interval Assessment	X	X	

- 1) Baseline studies: Studies to be performed at Baseline are described in Section 7 of the Protocol.
- 2) Labs: All blood tests will be done at the Core Lab.
- 3) Serum biochemical testing: A complete SMA18 will be done 7 times during the course of the study: at the Baseline visit and the follow-up visits on weeks 8, 20, 26, 38, 52 and 78. At all other visits an SMA7 including electrolytes, BUN, creatinine and calcium will be performed.
- 4) Hematology: CBC with differential and platelet count will be done at every visit in the MMF-treated participants. In the CSA-treated participants, the hematology tests will be done at the Baseline visit and the follow-up visits on weeks 8, 20, 26, 38, 52 and 78.
- 5) Fasting lipid profile will be done at the Baseline visit and the follow-up visits on weeks 4, 26, 52, and 78.

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- 6) Cyclosporine levels will be measured in the CSA-treated participants at the follow-up visits on weeks 2, 4, 6, 14, 26, 38, and 52.
- 7) 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 the Baseline visits, and the follow-up visits on weeks 26, 52, and 78. Procedures for the collection of the early morning specimens will be the same as described in Baseline Evaluation (see Section 7.1.1.). 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 1.5x the lower value. The two samples closest in value will be averaged. A single Up/c will be collected at each additional scheduled visit.
- 8) Urine HCG: Test will be done at the Baseline visit, Week 0 (if applicable), and follow-up visits on weeks 14, 26, 38, 52, and 65 (see Section 7.1.3. for details).
- 9) QOL forms (SF-36 in adults, PedsQL in children) at the Baseline visit, and follow-up visits on weeks 26, 52, and 78.
- 10) Extended follow-up: After week 78, visits will continue to be held at 6-month intervals until termination of trial. These visits will include physical examinations, laboratory tests, i.e., serum creatinine and Up/c, and medication use.
- 11) For those participants who consent to provide biological samples for the biorepositories, urine, serum, and plasma specimens will be shipped to the NIDDK Biosample Repository at Fisher BioServices at weeks 0, 26, 52, and 78. Whole blood specimens for DNA extraction will also be obtained at the W0 visit and shipped to the NIDDK Genetics Initiative at Rutgers University Cell and DNA Repository for those participants who provide consent.

Physical Examination

A complete physical examination will be done at Baseline and Follow-up visits on weeks 0, 14, 26, 38, 52 and 78 (see Physical Exam Form, Form # 46). Participants and their parents should be questioned about unexplained fevers, infections, rash, headaches, abnormal behavior or ideation, or change in appetite. 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 ascites or peripheral edema, and assessment for study related toxicities.

Study medication use

Participants will be encouraged to return all bottles of dispensed medication in order to review how much medication was administered to the participant and to monitor compliance with the protocol. Although no formal pill counts are required, local investigators are urged to review all aspects of the medication regimen with the study participants at all scheduled visits.

Unscheduled Interval Visits

These visits will occur as frequently as necessary in between scheduled protocol Follow-Up visits for evaluation of safety issues, abnormal lab results, documentation of changes in proteinuria, adjustment of medications, or participant education. These visits should be arranged at the discretion of the Participating Site's PI with the purpose of increasing compliance with the protocol. At a minimum, a limited evaluation will occur at each non-protocol visit including weight, temperature, blood pressure, significant changes in physical exam, and relevant lab data.

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The reason for the non-protocol visits and the findings at these visits will be recorded. If the visit is indicated for an AE/SAE event evaluation or follow-up, the AE/SAE Form should be completed (see Forms # 60 and 61).

Monitoring of Hospitalizations

If a participant is hospitalized during study participation, the DCC and the CCC must be informed immediately (within 2 working days) because this represents a Serious Adverse Event (SAE). The initial notification of the hospitalization should be recorded on the Hospitalization Form (Form # 62) and entered into the database or faxed to the CCC for data entry within 2 working days.

At the first visit after discharge, the following information about the hospitalization will be recorded: reason for admission, duration of hospitalization, changes in study medication, and participant status at the time of discharge.

Missed Medication

If the study medications need to be withheld for any reason during a hospitalization or while the participant is at home, the study medication may be resumed in some cases. See Section 8 that provides algorithms for restarting CSA, MMF and dexamethasone.

Participant Questionnaires

Participants will be asked at each visit to volunteer symptoms experienced since the last visit including intercurrent illness and hospitalizations. Record this information on the Follow-Up Visit Form (Form # 16). Quality of life questionnaires will be administered at Baseline, and Follow-up visits on weeks 26, 52, and 78.

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 site, 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 (Form # 05) must be completed.

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.

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7.5. Visit Breakdown

Study Visit 1: Baseline Visit (B1)



Prior to Baseline Visit, call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To fast for at least 12 hours (10 hours for children less than 10 years of age) prior to visit.
3. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)].
 - b. Two first morning urine specimens

Forms to be completed at this visit:

- Form 10 Preliminary Screening Form (participant alpha code assigned)
- Form 11 Baseline Visit
- Form 14 Disease History
- Form 36–43 QOL Questionnaire (dependent on age of participant)
- Form 44 Medication (Non study medication section only)
- Form 46 Physical Exam
- Form 75 Results of Local PCR Testing for Hepatitis C (if applicable)
- Form 80 Core Lab Urine Mailing Form (one form for each specimen)
- Form 83 Blood and Serum Mailing Form
- Form 86 Biopsy Mailing Form
- Form 89 Pregnancy Test Results
- Form 91 Results of Local Tuberculin Skin Test
- Run Eligibility Report (Form 2 database → Reports)

If the participant is eligible then -

- Form 30 On-Line Randomization Form (enter items 1 and 2, and once prompted enter items 101 through 103)

Detailed description of what is expected from the Baseline Visit (B1) –

1. Explain the study protocol in detail to the participant and parent (if applicable). Go over the inclusion and exclusion criteria to verify that the participant meets all criteria.
2. If the participant is a post-menarcheal female, discuss the participant's chances for pregnancy and the need to avoid pregnancy if she enters this study. To maximize the likelihood of obtaining accurate information, provide the participant with complete confidentiality. Note that post-menarcheal females must have a negative urine pregnancy test within 7 days prior to start of the study medications.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

3. If no known disqualifying criteria are found, invite the participant and/or parent (if applicable) to ask any questions they may have about the study and then to sign and date the age appropriate consent and/or assent form(s). Provide them with a copy of their signed consent/assent form(s). Assign the participant with a unique FSGS participant ID number from the list of IDs set up by the DCC for each Participating Site. Each Participating Site will have 100 Participant ID numbers available. The ID number will consist of 6 digits. The first 3 digits represent the Participating Site number. The last 3 digits are sequentially numbered, starting from 001 to 100. At the beginning of the study the DCC will set up a list of 10 potential Participant ID numbers from 001 to 010 for each Participating Site. For example, for the Participating Site 501 the numbers 501001 through 501010 will be set up. If a Participating Site has used all the ID numbers that were initially set up by the DCC, e-mail fsgs_dcc@bio.ri.ccf.org and more ID numbers will be set up for your Participating Site. Once an ID number has been assigned to a specific participant, this participant cannot be assigned a different number throughout the study and this number cannot be reused for another participant in the study. Once the Preliminary Screening Form (Form # 10) has been entered (Saved) into the database, a 2 digit alpha-numeric code will be assigned automatically to that participant. The combination of the Participant ID and the alpha-numeric code is used to uniquely identify each participant in the study. The reference to the alpha-numeric code in the MOP and on the forms is “alpha code” for convenience purposes.

At this time Form # 10 – Preliminary Screening Form may be completed. This form establishes the patient as a participant in the study. Once Form # 10 is entered into the database, the participant is assigned a two-digit alpha code. Each participant’s assigned alpha code will need to be documented, along with the Participant ID number, on all forms.

As soon as a Form # 10 – Preliminary Screening Form is entered into the database the Participating Site may generate an Eligibility Report (Form 2 ➔ Reports ➔ Eligibility Report). The Eligibility Report can be generated as many times for the same participant as necessary. Generating this report initially after entering the Form # 10 allows the Participating Site to see what has been done, and what specifically needs to be done before determination of participant eligibility.

4. Complete Form # 11 – Baseline Visit, Form # 14 – Disease History, and age appropriate QOL Questionnaire – Forms 36-43.
5. Perform a physical exam of the participant, including weight, height and BP. Complete Form # 46 – Physical Exam Form, and Form # 44 – Medication Form (non-study medications section only).

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Note: Prior to each individual participants' shipment of specimens (blood and/or urine) to Spectra (the Core Lab), a Form 10 (Preliminary Screening Form) must be entered into the Oracle data base. A hard copy of page 1 of Form 10 must be included inside the shipping container (along with the appropriate Mailing Form). This step is for each first shipment (per participant) to Spectra.

6. Using the supplies in the Core Lab sample kit for screening visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
B1	- 1 or - 2	Screening	1 - 8.5 mL SST 1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 8.5 mL SST 1 - 3.5 mL SST 1 - 2 mL Lav. Top	14 mL	14 mL	2

Complete Form # 83 – Blood and Serum Mailing Form.

Refer to Section 10 of the Manual of Operations (MOP) for Blood Collection Procedures.

Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. Confirm that two first-morning urine specimens were obtained at least 24 hours apart. Refer to Section 10 of the Manual of Operations (MOP) for Urine Collection Procedures. Document the date and time of each specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. **Each** Urine Mailing Form must have a barcode different from the other as well as different from the Serum Mailing Form barcode. So when two first-morning urines and blood/serum is collected for the protocol visit, there must be three mailing forms with three different barcodes.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

8. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at baseline and specified follow-up visits in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results.
9. Submit kidney biopsy specimens to Core Coordinating Center's Study Pathologist. Complete Form # 86 – Biopsy Mailing Form. Upon receipt and review of the biopsy materials submitted, the F87 – Biopsy Results Form will be completed by the Core Pathologist who will enter the results into the database or fax to the designated Core Coordinator for data entry; once results have been entered into the database the Biopsy Results Report will be generated and e-mailed to the Participating Site and Core.
10. Complete Form # 91 – TB Test Results.
11. Complete Form # 75 – Results of Local PCR Testing for Hepatitis C, if applicable. This form is completed in Baseline for participants whom:
 - 1) The Core Lab reports that the patient has Hepatitis C antibodies, and
 - 2) The Participating Site does a local laboratory PCR test that shows that the participant does not have active Hepatitis C in spite of the presence of Hepatitis C antibodies.
12. Give participant/parent the Participant Handbook (if not already provided prior to Visit B1)
13. Once all required Case Report Forms and lab result reports have been entered into the Oracle Clinical database, run the Eligibility Report to determine participant eligibility (located <https://clinapps.bio.ri.ccf.org/fsgs/index.html>, Reports ➔ Eligibility).
14. Once the Eligibility Report indicates that the participant is eligible and ready to be randomized, run the On-Line Randomization Form (Form # 30) – enter questions 1 and 2, and questions 101 through 103. It is strongly recommended to randomize the participant when you are confident that the W00 visit and the drug dispensing can occur within 4 weeks from time of randomization. (Note: allow 30 minutes for the database to refresh when updates and new entries have been made prior to running the Eligibility Report – this is so the report will reflect the most recent information.)

Note: The time frame of a participant signing an informed consent to actually being randomized must be ≤ 6 months. If this time frame is greater than 6 months, it will be necessary to re-consent the participant before being randomized into the FSGS-CT study.

If a Participating Site is working with its local pharmacy, the Participating Site should notify the pharmacy when a participant has been randomized so the pharmacy will know that the drug will arrive in one or two business days.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

15. Schedule the date and time of Visit W0 within two weeks of B1 (W0 occurs once a participant has been randomized. Receipt of study drug is within 1 – 2 business days from date randomized). Record this information in the Participant Handbook.

Note: Once the participant has been randomized all visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 2 (W0), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen (note: an additional “fresh” urine specimen will be obtained for the Repository on consented participants)

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 2: Entry Visit (W0)

Forms to be completed at this visit:

- Form 16 Follow-Up Visit
- Form 44 Medication
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form (Spectra)
- Form 89 Pregnancy Test Results
- Form 94 Consent for Repositories Form (to be completed for all participants)
- Form 95 Biological Specimen Repository Mailing Form (Fisher)
- Form 96 (DNA) NIDDK Genetics Initiative Phlebotomy Mailing Form (Rutgers)

Detailed description of what is expected from the Entry Visit (W0) –

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP. Complete Form # 46 – Physical Exam Form.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the Manual of Operations (MOP) for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. NOTE: Females of childbearing potential must have a negative pregnancy test within 7 days prior to starting study medications. If pregnancy test obtained at B1 was greater than seven days ago, repeat pregnancy test to confirm participant is not pregnant. Complete Form # 89 – Pregnancy Test Results.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Using the supplies in the Core Lab sample kit for screening visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W0	0	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1

Complete Form # 83 – Serum Mailing Form.

Refer to Section 10 of the Manual of Operations (MOP) for blood collection procedures.

Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

6. A F94 – Consent for Repositories Form must be completed for all participants, to document whether they have or have not agreed to collection for the Repositories. For **participants who have consented** to collection of biological specimens for the Repository, complete a Form # 95 – Biological Specimen Repository Mailing Form. And a one-time DNA sample will be obtained from **participants who have specifically consented** to the collection of their DNA. Complete Form # 96 – (DNA) NIDDK Genetics Initiative Phlebotomy Mailing

<u>Study Week</u>	<u>Destination</u>	<u>Tubes Filled</u>		<u># of Urine Samples</u>
		<u>MMF Arm</u>	<u>CSA Arm</u>	
0	Fisher Biosample Repository*	4 - 4 mL SST 4 – 4.5 mL PST	4 - 4 mL SST 4 – 4.5 mL PST	1
	Rutgers Cell and DNA Repository*	2 - 8.5 mL ACD	2 - 8.5 mL ACD	none

Form. Refer to Section 13 for instructions on biorepository sample collection. The sample collection is age dependent.

* Indicated are quantities for participants age 13 years or greater.

For participants age 7-12 years, repository amounts are as follows:

Fisher: 2 – 4.0 mL SST tubes, 2 – 4.5 mL PST tubes;

Rutgers: 3 - 3.5 mL ACD tubes.

For participants age 6 years or less, repository amounts are as follows:

Fisher: 1 – 4.0 mL SST tubes, 1 – 4.5 mL PST tubes;

Rutgers: 2 - 3.5 mL ACD tubes.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

7. If no new problems are identified at the W00 visit, instruct the participant not to start taking the study medications that has been dispensed until the Core Lab results from this W00 visit confirms there are no patient safety issues. Complete Form # 44 – Medication Form.

Once the participant's W00 data has been entered into the database an appointment schedule can be generated, printed and used for scheduling visits. To generate the participant appointment schedule; go to the Form 2 → Reports → Visit Schedule Report. (Note: initially the appointment schedule is automatically e-mailed to the Participating Site.)

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 3 (W2), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W2 visit blood draw for CSA level measurements.
3. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 3: W2

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit (W2) –

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP sitting and standing. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first-morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W2	2	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Complete Form # 83 – Blood and Serum Mailing Form.

Refer to Section 10 of the Manual of Operations (MOP) for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 4 (W4), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To fast for at least 12 hours (10 hours for children less than 10 years of age) prior to visit.
3. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W4 visit blood draw for CSA level measurements
4. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 4: W4

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit (W4) –

1. Complete Form # 16 – Follow-up Visit Form.
2. Perform a physical exam of the participant, including weight, height and BP sitting and standing. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	
W4	4	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Complete Form # 83 – Blood and Serum Mailing Form.

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 5 (W6), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W6 visit blood draw for CSA level measurements
3. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septtra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 5: W6

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit (W6)–

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP sitting and standing. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W6	6	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Complete Form # 83 – Blood and Serum Mailing Form.

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This is especially important in the first 8 weeks of the study when the visits are planned for every two weeks. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 6 (W8), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen
3. **Note:** if the participant is on the study drug dexamethasone, review the MOP section 8.4.3. Starting at W08 the interval should change to 2xMO (every other week) for Weeks 8, 10, 12, 14, 16, 18, 20, 22, 24.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 6: W8

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visits (W8)–

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W8	8	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Complete Form # 83 – Blood and Serum Mailing Form.

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Complete Form # 44 – Medication Form. As a reminder if the participant is on the study drug dexamethasone, review the MOP section 8.4.3. Starting at W08 the interval should change to 2xMO (every other week) for Weeks 8, 10, 12, 14, 16, 18, 20, 22, 24.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 7 (W14), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
3. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W14 visit blood draw for CSA level measurements
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 7: W14

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form
- Form 89 Pregnancy Test Results

Detailed description of what is expected from the Follow-up Visit (W14)–

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP sitting and standing. Complete Form # 46 – Physical Exam Form.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at this follow-up visit (W14) in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results.
5. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W14	14	Visit	1 3.5 mL SST 1 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 8 (W20), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 8: W20

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visits (W20)–

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.
Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W20	20	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1

Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 9 (W26), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To fast for at least 12 hours (10 hours for children less than 10 years of age) prior to visit.
3. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W26 visit blood draw for CSA level measurements
4. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. Two (2) first morning urine specimens (note: an additional “fresh” urine specimen will be obtained for the Repository on consented participants)
5. **Note:** if the participant is on the study drug dexamethasone, review the MOP section 8.4.3. Starting at W26 the interval should change to 1xMO (once a month) for Weeks 26, 34, 38, 42, 46, and 50.

Study Visit 9: W26

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 36–43 QOL Questionnaire (dependent on age of participant)
- Form 44 Medications
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form (one for each specimen)
- Form 83 Blood and Serum Mailing Form
- Form 89 Pregnancy Test Results
- Form 95 Biological Specimen Repository Mailing Form (Fisher)

Detailed description of what is expected from the Follow-up Visits (W26) -

1. Complete Form # 16 – Follow-up.
2. Complete appropriate SF-36/PedsQL Form(s) 36 – 43.
3. Perform a physical exam of the participant, including weight, height and BP. Complete Form # 46 – Physical Exam Form.
4. Confirm that two first morning urine specimens were obtained at least 24 hours apart. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of each specimen collection. Complete Form # 80 – Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. **Each** Urine Mailing Form must have a barcode different from the other as well as different from the Serum Mailing Form barcode. So when two first-morning urines and blood/serum is collected for the protocol visit, there must be three mailing forms with three different barcodes.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at this follow-up visit (W26) in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W26	26	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	2

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. For **participants that have consented** to collection of biological specimens to be sent to the Repository, complete a Form # 95 – Biological Specimen Repository Mailing Form. Refer to Section 13 for instructions on biorepository sample collection. The sample collection is age dependent.

* Indicated are quantities for participants age 13 years or greater.

<u>Study Week</u>	<u>Destination</u>	<u>Tubes Filled</u>		<u># of Urine Samples</u>
		<u>MMF Arm</u>	<u>CSA Arm</u>	
26, 52, and 78	Fisher Biosample Repository*	4 - 4 mL SST 4 – 4.5 mL PST	4 - 4 mL SST 4 – 4.5 mL PST	1

For participants age 7-12 years, repository amounts are as follows:

Fisher: 2 – 4.0 mL SST tubes, 2 – 4.5 mL PST tubes;

For participants age 6 years or less, repository amounts are as follows:

Fisher: 1 – 4.0 mL SST tubes, 1 – 4.5 mL PST tubes;

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

8. Complete Form # 44 – Medication Form. As a reminder, if the participant is on the study drug dexamethasone, review the MOP section 8.4.3. Starting at W26 the interval should change to 1xMO (once a month) for Weeks 26, 34, 38, 42, 46, and 50.
At W26 the study drug, prednisone/prednisolone, should be discontinued (see Section 8.4.4. of the MOP).

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

Once the lab results determine the W26 outcome for your participant, the DCC will instruct you as to whether the participant is a treatment failure which would require the participant to come off the study medications. Even if the participant is a treatment failure, follow-up will continue but will be scaled back to semi-annual assessments (next visit W52) including the following information:

1. Labs tests including Up/c, serum creatinine, serum albumin, and BUN (specimens should be sent to the Core Lab, Spectra)
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 of the Protocol will be maintained following the pregnancy and medication stop points which do not define the primary or main secondary outcomes.



Prior to Visit 10 (W32), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 10: W32

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit (W32) –

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.
Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W32	32	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1

Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 11 (W38), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W38 visit blood draw for CSA level measurements
3. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

Study Visit 11: W38**Forms to be completed at this visit:**

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form
- Form 89 Pregnancy Test Results

Detailed description of what is expected from the Follow-up Visits (W38) –

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP sitting and standing. Complete the Physical Exam Form (Form # 46).
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at this follow-up visit (W38) in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results
5. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W38	38	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	1

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 12 (W44), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 12: W44

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medications
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit (W44) –

1. Complete Form # 16 – Follow-up.
2. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.
Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W44	44	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1

Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

5. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

For Treatment Failure Follow-up - W52 CRFs to be completed:

F16 – Follow-up Visit, F44 – Medication; F46 – Physical Exam (Q1-8, Q200 – 201); F52 – Long Term Monitoring; F80 – Urine Mailing; F83 – Serum Mailing; F89 – Results of Pregnancy Test (if applicable); F95 – Biological Specimen Repository Mailing (to Fisher – if participant consented). Refer to Section 7.4 of MOP.



Prior to Visit 13 (W52), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To fast for at least 12 hours (10 hours for children less than 10 years of age) prior to visit.
3. Remind participant (if on cyclosporine) not to take CSA no less than 10 hours and no more than 14 hours before their W52 visit blood draw for CSA level measurements
4. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. Two (2) first morning urine specimens (note: an additional “fresh” urine specimen will be obtained for the Repository on consented participants)

Study Visit 13: W52

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 36–43 QOL Questionnaire (dependent on age of participant)
- Form 44 Medication
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form (one for each specimen)
- Form 83 Blood and Serum Mailing Form
- Form 89 Pregnancy Test Results
- Form 95 Biological Specimen Repository Mailing Form (Fisher)

Detailed description of what is expected from the Follow-up Visits (W52) -

Refer to Section 7.4 Follow-up Evaluation – Patient Management at Completion of the 52 week Treatment Phase.

1. Complete Form # 16 – Follow-up.
2. Complete age appropriate QOL Questionnaire (SF 36) – Form(s) 36-43.
3. Perform a physical exam of the participant, including weight, height and BP. Complete Form # 46 – Physical Exam Form.
4. Confirm that two first-morning urine specimens were obtained at least 24 hours apart. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of each specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. **Each** Urine Mailing Form must have a barcode different from the other as well as different from the Serum Mailing Form barcode. So when two first-morning urines and blood/serum is collected for the protocol visit, there must be three mailing forms with three different barcodes.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at this follow-up visit (W52) in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W52	52	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	2

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. For **participants that have consented** to collection of biological specimens to be sent to the Repository, complete a Form # 95 – Biological Specimen Repository Mailing Form. Refer to Section 13 for instructions on biorepository sample collection. The sample collection is age dependent.

* Indicated are quantities for participants age 13 years or greater.

<u>Study Week</u>	<u>Destination</u>	<u>Tubes Filled</u>		<u># of Urine Samples</u>
		<u>MMF Arm</u>	<u>CSA Arm</u>	
26, 52, and 78	Fisher Biosample Repository*	4 - 4 mL SST 4 – 4.5 mL PST	4 - 4 mL SST 4 – 4.5 mL PST	1

For participants age 7-12 years, repository amounts are as follows:

Fisher: 2 – 4.0 mL SST tubes, 2 – 4.5 mL PST tubes;

For participants age 6 years or less, repository amounts are as follows:

Fisher: 1 – 4.0 mL SST tubes, 1 – 4.5 mL PST tubes.

8. Complete Form # 44 – Medication Form.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

For Treatment Failure Follow-up - W52 CRFs to be completed:

F16 – Follow-up Visit, F44 – Medication; F46 – Physical Exam (Q1-8, Q200 – 201); F52 – Long Term Monitoring; F80 – Urine Mailing; F83 – Serum Mailing; F89 – Results of Pregnancy Test (if applicable); F95 – Biological Specimen Repository Mailing (to Fisher – if participant consented); QOL (PedsQL) should be completed if the participant is willing. Next semi-annual visit should be W78.



Prior to Visit 14 (W65), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H₂ blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. First morning urine specimen

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

Study Visit 14: W65

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form
- Form 89 Pregnancy Test Results

Detailed description of what is expected from the Follow-up Visit (W65) –

1. Complete Form # 16 – Follow-up Visit.
2. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
3. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

4. Urine pregnancy test, Human Chorionic Gonadotropin (HCG), should be **assessed centrally by the Core Lab** at this follow-up visit (W65) in women of childbearing potential (post pubertal, premenopausal, not surgically sterilized). Any other additional pregnancy tests should be done at the local site using the per patient reimbursement funds. This includes testing done in accordance with local IRB requirements or investigator preference. To document that a urine HCG pregnancy test was performed, complete Form # 89 – Pregnancy Test Results
5. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.
Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W65	65	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1

Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

6. Complete Form # 44 – Medication Form. At W52 the study drug, CSA (see Section 8.4.1. of MOP) or MMF and Dexamethasone (see Sections 8.4.2. and 8.4.3.) should be discontinued.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

For Treatment Failure Follow-up – W78 CRFs to be completed:

F16 – Follow-up Visit; F44 – Medication; F46 – Physical Exam (Q1-8, Q200 – 201); F52 – Long Term Monitoring; F80 – Urine Mailing; F83 – Serum Mailing; F89 – Results of Pregnancy Test (if applicable); F95 – Biological Specimen Repository Mailing (to Fisher – if participant consented); QOL (PedsQL) should be completed if the participant is willing. Refer to Section 7.4 of MOP.



Prior to Visit 15 (W78), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To fast for at least 12 hours (10 hours for children less than 10 years of age) prior to visit.
3. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. Two (2) first morning urine specimens (note: an additional “fresh” urine specimen will be obtained for the Repository on consented participants)

Study Visit 15: W78**Forms to be completed at this visit:**

- Form 16 Follow-up Visit
- Form 36–43 QOL Questionnaire (dependent on age of participant)
- Form 44 Medication
- Form 46 Physical Exam
- Form 80 Core Lab Urine Mailing Form (one for each specimen)
- Form 83 Blood and Serum Mailing Form
- Form 95 Repository Specimen Mailing Form (Fisher)

Detailed description of what is expected from the Follow-up Visits (W78) –

1. Complete Form # 16 – Follow-up Visit.
2. Complete appropriate SF 36/PedsQL form(s) (Form # 36 – 43).
3. Perform a physical exam of the participant, including weight, height and BP. Complete Form # 46 – Physical Exam Form.
4. Confirm that two first morning urine specimens were obtained at least 24 hours apart. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of each specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form for each specimen. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. **Each** Urine Mailing Form must have a barcode different from the other as well as different from the Serum Mailing Form barcode. So when two first-morning urines and blood/serum is collected for the protocol visit, there must be three mailing forms with three different barcodes.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits draw:
Complete Form # 83 – Blood and Serum Mailing Form.

<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
W78	78	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	2

Refer to Section 10 of the MOP for blood collection procedures. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. For **participants that have consented** to collection of biological specimens to be sent to the Repository, complete a Form # 95 – Biological Specimen Repository Mailing Form. Refer to Section 13 for instructions on biorepository sample collection. The sample collection is age dependent.

* Indicated are quantities for participants age 13 years or greater.

For participants age 7-12 years, repository amounts are as follows:

Fisher: 2 – 4.0 mL SST tubes, 2 – 4.5 mL PST tubes;

For participants age 6 years or less, repository amounts are as follows:

Fisher: 1 – 4.0 mL SST tubes, 1 – 4.5 mL PST tubes.

<u>Study Week</u>	<u>Destination</u>	<u>Tubes Filled</u>		<u># of Urine Samples</u>
		<u>MMF Arm</u>	<u>CSA Arm</u>	
26, 52, and 78	Fisher Biosample Repository*	4 - 4 mL SST 4 – 4.5 mL PST	4 - 4 mL SST 4 – 4.5 mL PST	1

7. Complete Form # 44 – Medication Form. At W78 the study medication ACEi lisinopril (see Section 8.4.5. of MOP) or ARB losartan (see Section 8.4.6. of MOP) should be discontinued.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.

For Treatment Failure Follow-up – W78 CRFs to be completed:

F16 – Follow-up Visit; F44 – Medication; F46 – Physical Exam (Q1-8, Q200 – 201); F52 – Long Term Monitoring; F80 – Urine Mailing; F83 – Serum Mailing; F89 – Results of Pregnancy Test (if applicable); F95 – Biological Specimen Repository Mailing (to Fisher – if participant consented); QOL (PedsQL) should be completed if the participant is willing. Refer to Section 7.4 of MOP.



Prior to Visit 16 (Month 24), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. A first morning urine specimen

Study Visit 16: Month 24

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 52 Long-Term Monitoring Form
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit – (M24).

Follow up visits continue to be held after a participant's course of study drug ends (every six months until the FSGS-CT ends).

1. Complete Form # 16 – Follow up Form.
2. Complete Form # 52 – Long-Term Monitoring Form.
3. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
4. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits:
 - a. Draw one 3.5 mL serum separator tube. (note: additional blood would be necessary if additional lab tests are requested)
 - b. See Section 10 of the MOP for blood collection procedures. Complete Form # 83 – Blood and Serum Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 17 (Month 30), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. A first morning urine specimen

Study Visit 17: Month 30

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 52 Long-Term Monitoring Form
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visit – (M30).

Follow up visits continue to be held after a participant's course of study drug ends (every six months until the FSGS Study ends).

1. Complete Form # 16 – Follow up Form.
2. Complete Form # 52 – Long-Term Monitoring Form.
3. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
4. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits:
 - a. Draw one 3.5 mL serum separator tube. (note: additional blood would be necessary if additional lab tests are requested)
 - b. See Section 10 of the MOP for blood collection procedures. Complete Form # 83 – Blood and Serum Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 18 (Month 36), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. A first morning urine specimen

Study Visit 18: Month 36

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 52 Long-Term Monitoring Form
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visits – (M36).

Follow up visits continue to be held after a participant's course of study drug ends (every six months until the FSGS Study ends).

1. Complete Form # 16 – Follow up Form.
2. Complete Form # 52 – Long-Term Monitoring Form.
3. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
4. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits:
 - a. Draw one 3.5 mL serum separator tube. (note: additional blood would be necessary if additional lab tests are requested)
 - b. See Section 10 of the MOP for blood collection procedures. Complete Form # 83 – Blood and Serum Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 19 (Month 42), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. A first morning urine specimen

Study Visit 19: Month 42

Forms to be completed at this visit:

- Form 16 Follow-up Visit
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 52 Long-Term Monitoring Form
- Form 80 Core Lab Urine Mailing Form
- Form 83 Blood and Serum Mailing Form

Detailed description of what is expected from the Follow-up Visits – (M42).

Follow up visits continue to be held after a participant's course of study drug ends (every six months until the FSGS Study ends).

1. Complete Form # 16 – Follow up Form.
2. Complete Form # 52 – Long-Term Monitoring Form.
3. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
4. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits:
 - a. Draw one 3.5 mL serum separator tube. (note: additional blood would be necessary if additional lab tests are requested)
 - b. See Section 10 of the MOP for blood collection procedures. Complete Form # 83 – Blood and Serum Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

6. Complete Form # 44 – Medication Form.

Note: All visits should be scheduled as early as possible within the allowable window. This procedure will enable repeat testing, if needed, to be performed within the allowable window for the visit.



Prior to Visit 20 (Month 48), call and remind participant –

1. Ask whether participant has had a fever or illness within the past 2 days. If so, this may prompt a rescheduling of this visit.
2. To bring to visit:
 - a. List of medications currently being taken [remind participant to avoid medications that would interfere with creatinine excretion e.g., pyridium, most cephalosporins (except cephalexin), Bactrim/Septra, H-2 blockers and NSAIDS for 48 hours prior to Up/c determination. Common H₂ blockers include Tagamet (cimetidine). Common NSAIDS include ibuprofen (Advil) and naproxen (Aleve)]
 - b. A first morning urine specimen

Study Visit 20: Month 48

Forms to be completed at this visit:

- Form 16 Follow up Form
- Form 44 Medication
- Form 46 Physical Exam (initial portion only – questions 1 through 8, 200 and 201)
- Form 52 Long-Term Monitoring Form
- Form 80 Urine Mailing Form
- Form 83 Serum Mailing Form

Detailed description of what is expected from the Follow-up Visits – (M48).

Follow up visits continue to be held after a participant's course of study drug ends (every six months until the FSGS Study ends).

1. Complete Form # 16 – Follow up Form.
2. Complete Form # 52 – Long-Term Monitoring Form.
3. Perform a physical exam of the participant, including weight, height and BP. Complete the initial portion only (questions 1 through 8, 200 and 201) of Form # 46 – Physical Exam Form. Record information for any abnormalities in questions 9 through 21, if applicable.
4. Confirm that a first morning urine specimen was obtained. Refer to Section 10 of the MOP for urine collection procedures. Document the date and time of the specimen collection. Complete Form # 80 – Core Lab Urine Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

5. Using the supplies in the Core Lab sample kit for follow up visits:
 - a. Draw one 3.5 mL serum separator tube. (note: additional blood would be necessary if additional lab tests are requested)
 - b. See Section 10 of the MOP for blood collection procedures. Complete Form # 83 – Blood and Serum Mailing Form. Note: A different sheet of Barcode with accession numbers are provided for EACH mailing form. The Serum Mailing Form barcode must be different from the Urine Mailing Form barcode.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

6. Complete Form # 44 – Medication Form.

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

7.6. Unplanned Visits and Multiple CRF Entries

The DCC anticipates that there will be many circumstances in which a Participating Site will need to complete and enter multiple CRFs within any given appointment scheduled target window. (Refer to Section 16.4. pertaining to generating appointment schedules.) The Oracle Clinical Production database will enable a Participating Site to insert either a specific “Page” (CRF) and/or an additional “Visit” (sub-visit) for a participant. (Refer to Section 16.4. pertaining to Sub-visit Numbering.)

Section 7.5 (Visit Breakdown) reflects each typical Baseline and Follow-up Protocol Visit. It does not take into account the circumstances that arise which would require an Unplanned Visit for the participant. An Unplanned Visit is defined as any contact with the participant outside of the actual Protocol planned Visit. Note that the Follow-Up Visit Form # 16 states that it should be completed at every face-to-face participant study visit in follow-up (including unscheduled visits that occur in follow-up). An example of an Unplanned Visit would be that the participant’s study medication dose was modified, in which case an additional Medication Form # 44 would be completed and entered into the database. If the dose modification was implemented in person, a Form # 16 would also be required for completion/entry.

Naming a few other possible examples of Unplanned Visits would include:

- A repeat Urine sample was needed (Form # 80)
- A study dose modification was necessary (Form # 44)
- An adverse event occurred (Form # 60)
- A serious adverse event occurred (Form # 61)
- Participant was hospitalized (Form # 62)
- Participant wanted to discuss the study treatment or to complain about symptoms (Form # 16)

7.6.1. Instruction on How to Insert an Unplanned Visit or Page

First determine whether you need to insert either:

- 1) “Page” – a specific CRF that would not be displayed in a typical follow-up visit (i.e. Forms for AE, SAE, Hospitalization, Toxicity, Death, etc.)
- 2) “Visit” – a duplicate set of CRFs displayed in the database for an actual protocol visit (i.e. Follow-up Forms including Follow-Up Visit, Medication, Physical Exam, Urine Mailing, Blood and Serum Mailing)

Then, while logged into the Oracle Clinical Production database and with a specific PID selected (patient number highlighted) and making sure that you are within the appropriate visit tab, **click** on **Insert** located on the top Menu bar → select by **clicking** either **Page** or **Visit**.

When “Page” is selected a pop-up window appears. **Click the down arrow button**, and using the **Scroll bar** select by **clicking** on the desired **CRF**. This will insert the desired CRF into that participant’s visit window.

When “Visit” is selected a pop-up window appears stating that “This will add an unplanned visit after the current one”. **Click OK** if you want to create an unplanned visit, click Cancel if you do not want to create an unplanned visit. Clicking OK creates the unplanned visit and a duplicate set of Follow-up (or if the case, Baseline) Forms will appear. Notice however, that the tab displays the Visit type and number followed by a sequentially numbered decimal space. (So, the participants’ first unplanned visit’s sub-visit number in follow-up would be W00.01). Even

7. PARTICIPANT MANAGEMENT AND STUDY VISITS

though when an Unplanned Visit is created, the database displays each Follow-up form expected at a scheduled follow-up protocol visit, it is only necessary to enter the desired follow-up forms that are applicable. Once the CRF is saved in the database, and upon reentry into the database, only the entered CRFs for that Unplanned Visit (sub-visit) will be displayed.

For more detailed instructions on how to insert an unplanned visit or page refer to Section 16.5.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

Participants randomized to the CSA arm will receive 3 study medications: CSA, prednisone (or prednisolone liquid formulation), and either the ACE inhibitor lisinopril or the ARB losartan. Participants randomized to the MMF arm will receive 4 study medications: MMF, dexamethasone, prednisone or prednisolone, and either the ACE inhibitor lisinopril or the ARB losartan. This chapter summarizes the dose adjustment regimens of each of these drugs and describes the logistics of the drug distribution and monitoring of dose levels.

8.1. Formulations of Study Drugs

The formulations provided for each study drug are summarized in Table 8.1:

Table 8.1

Medication	Treatment Group	Supplier	Formulations ¹	Drug Packaging
Cyclosporine (CSA)	CSA	Donated by Novartis	Neoral 100 mg/mL liquid	
			Neoral 25 mg gel pack	25 mg cap / 30 cap box
			Neoral 100 mg gel pack	100 mg cap / 30 cap box
MMF	MMF	Donated by Roche	Cellcept 200 mg/mL liquid	200 mg mL/btl
			Cellcept 250 mg capsules	250 mg cap / 500 cap btl
Dexamethasone	MMF	Purchased from Roxanne	1mg/mL ²	1 mg mL / 30 mL btl
			4 mg tablet ²	4 mg tab/ 100 tab btl
Prednisone/ Prednisolone	Both Treatment Groups	Purchased from Roxanne	15 mg/5mL liquid (Orapred)	237 mL btl
			5 mg tablets	5 mg tab / 100 tab btl
Lisinopril	Both Treatment Groups	Donated by Merck	1 mg/mL liquid	
			5 mg tablets	5 mg tab / 90 tab btl
			10 mg tablets	10 mg tab / 90 tab btl
Losartan (for pts who do not tolerate ACEi)	Both Treatment Groups	Donated by Merck	2.5 mg/mL liquid	
			25 mg tablets	25 mg tab / 90 tab btl
			50 mg tablets	50 mg tab / 90 tab btl

¹ Exact expiration dates will be provided after all drugs are delivered to the Central Pharmacy.

² Dexamethasone Preparation: If dexamethasone tablets are not tolerated, it is recommended that dexamethasone tablets be crushed and administered in any vehicle tolerated. Parents should be instructed to crush tablets using a pill crusher, which can be obtained from their local pharmacy. Simple liquids like water or juice are discouraged because fragments of the crushed tablets may not dissolve and will settle to the bottom of the cup or glass. Since dexamethasone is extremely bitter, the best option for masking its flavor is to mix the crushed tablets with a small amount of chocolate syrup. Alternative options include mixing the crushed tablets with grape jelly or applesauce. If the child weighs less than 20 kg the 4 mg tablets may need to be split in half in order that doses can be rounded to the nearest 2 mg. Thus it is recommended that pharmacies

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provide a tablet splitter for children under 20 kg. If the liquid formulation of dexamethasone must be used, flavor-masking additives, using the Flavorx™ system, will be provided for addition to the dexamethasone liquid. Kits containing four 1 oz bottles each of a Flavorx™ sweetening enhancer and two alternative flavors (bubblegum and watermelon) will be distributed to Participating Sites in conjunction with the liquid dexamethasone. The Participating Site pharmacist should dispense the undiluted dexamethasone solution along with one bottle of the sweetening enhancer and one bottle of the preferred flavor to the participant's parents. For consistency and ease of use, parents should be instructed to add the following amounts of sweetening enhancer and flavoring, using a 1 mL or 3 mL oral syringe, depending on the amount to be measured:

Liquid Dexamethasone Amount	Sweetening Enhancer Amount	Flavor Amount
3 mL	0.3 mL	0.3 mL
4 mL	0.4 mL	0.3 mL
5 mL	0.6 mL	0.4 mL
6 mL	0.7 mL	0.5 mL
7 mL	0.8 mL	0.6 mL
8 mL	0.9 mL	0.7 mL
9 mL	1.0 mL	0.8 mL
10 mL	1.1 mL	0.8 mL
11 mL	1.2 mL	0.9 mL
12 mL or greater	divide dexamethasone amount by 9	divide dexamethasone amount by 12

Note: The strong taste of the liquid dexamethasone will only be partially masked by the Flavorx™. Therefore, strong consideration should first be given to crushing the dexamethasone tablets and mixing in a tolerated vehicle, as noted above.

Dexamethasone solution should be stored at room temperature. Parents should be instructed to add the flavorings to the measured dexamethasone dose just prior to administering the dose to their child.

Preparation of liquid formulations of lisinopril and losartan

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

DIRECTIONS FOR PREPARATION OF A LIQUID LISINOPRIL SUSPENSION

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

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

DIRECTIONS FOR PREPARATION OF A LIQUID LOSARTAN SUSPENSION

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

The Package Inserts for each of these drugs can be downloaded from the Study Documents section on the DCC web page.

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8.2. General Considerations for Both Treatment Arms

All study medications will be shipped by the Central Pharmacy, Fisher BioServices, directly to the participating site for distribution to participants. Three primary drug shipments will be done for each participant: (1) to last through week 32 of the study; (2) to last through week 52; and (3) to last through week 78. Each bottle of study medication will be labeled with the participant identification number.

The duration of immunosuppressive therapy will be 52 weeks. Prednisone (or prednisolone) will be administered for only the first 26 weeks after randomization, while the ACEi or ARB therapy extends to 78 weeks. All study medications are administered orally.

In both treatment groups, efficacy will initially be assessed after 26 weeks 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.

8.2.1. Patient Management at Completion of the 52 week Treatment Phase

Medications

According to the protocol, the main study medications – cyclosporine (CSA), mycophenolate mofetil (MMF), and dexamethasone -- should be completely stopped at the 52 week visit, at the end of the treatment phase. This design was implemented to enable determination of the durable response rate to a 1-year course of therapy. The alternate prednisone dosing will have been stopped at 26 weeks. Thus, the only study medication that should be administered according to the protocol is lisinopril or losartan in patients who are intolerant of ACEi.

The protocol does not detail any taper regimen and instead requires complete cessation of the drug at 52 weeks. Abrupt discontinuation of CSA or MMF should not cause acute clinical problems and the dexamethasone dosing will have been gradually reduced in intensity over the final 4-6 months of the Treatment Phase. If there are questions about this regimen for a specific patient please contact the Core PI who can solicit the input of the Clinical Management Committee.

Patients who required ACEi or ARB dose reduction for hyperkalemia or GFR decline during the 0-52 week treatment period may have the dose of the ACEi (or ARB if intolerant to ACEi) increased up to the maximally tolerated dose after the 52 week visit at the discretion of the participating site physician. Additional monitoring of GFR and serum potassium will be determined by the participating site physician and protocol adjustments for recurrent hyperkalemia or decline in GFR should follow the study protocol until the final study visit at week 78.

Study visits

The only study visits required by the protocol during the first 6 months after discontinuing study medications are at weeks 65 and 78 and every 6 months thereafter. The decision to schedule additional interim visits for an individual patient is left entirely at the discretion of the site PI. Laboratory testing during these supplemental evaluations is not part of the protocol. The

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patient's clinical status after completion of the Treatment Phase is contingent only on the results of laboratory testing (urine protein excretion and blood work) performed at weeks 65 and 78.

8.3. Birth Control

At the time of enrollment, all women of childbearing age must have a negative pregnancy test or have proof of surgical sterilization. Women who are able to conceive and who are sexually active during the treatment period of the study must use two acceptable methods of birth control. These include: (1) birth control pills; (2) an intrauterine device (IUD); (3) condoms; or (4) hormone implants. Follow-up pregnancy tests will be performed during the course of the trial at the following visits – Baseline 1, Week 0, Week 14, Week 26, Week 38, Week 52, and Week 65 -- in all post-menarchal females. Additional tests will be performed at the discretion of the investigator. Women with a vasectomized partner or who are abstaining from heterosexual intercourse may be enrolled provided the participating site's PI supports their entry into the study based on his/her clinical judgment and familiarity with the participant.

8.4. Maintenance Dose Levels and Dose Modifications

The protocol stipulates maintenance dose levels for each of the study drugs listed in Table 8.1 depending on the participant's weight and, in the case of CSA on whole blood trough levels. Dose adjustment instructions for toxicities are also provided for each drug. The dose adjustments for toxicities follow a common sequence in which the dose level is first reduced to approximately 67% of the maintenance dose level. Then, if the toxicity persists, the dose is reduced to approximately 33% of the maintenance dose, and finally, if the toxicity continues to persist, the study drug is discontinued. In cases where potential toxicities may result from causes other than the study drug, the instructions contain an additional step prior to dose reduction in which the alternative causes are addressed. If toxicities remit following dose reductions or discontinuation, then, depending on the nature of the toxicity, a rechallenge procedure may be instituted in which the dose level is increased in a stepwise fashion. The protocol also designates initial titration phases for establishing the maintenance doses for three of the study drugs: MMF, lisinopril, and losartan. The target dose levels and general descriptions of the dose adjustment instructions are provided below. Precise descriptions of the sequence of steps to be followed in the dose adjustment algorithms are provided in the flow charts provided in Section 8.5.

8.4.1. Cyclosporine (CSA)

Note:

In patients assigned to the cyclosporine arm of the study, the drug dose will be adjusted based on plasma levels at select visits and on side effects. Because cyclosporine is metabolized in the liver primarily by the Cytochrome P450 (CYP 450) system, the drug level may be altered by medications that increase or decrease the activity of this enzyme system. In light of this potential confounding effect, it is advised that caution be used in prescribing the following drugs:

Agents that inhibit CYP 450 activity and increase cyclosporine levels:

ketoconazole, fluconazole, erythromycin, diltiazem, verapamil, nifedipine, metoclopramide.

Agents that stimulate CYP 450 activity and lower cyclosporine levels:

antiseizure medications (e.g. phenytoin, phenobarbital and carbamazepine), rifampin, and non-steroidal anti-inflammatory drugs.

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These drugs are not contraindicated by the protocol but should be avoided if possible. If a CYP 450 modulating agent must be used it is advised that their use be taken into account in determining the dose of cyclosporine and interpreting the drug level.

Period of Administration

CSA is administered to participants randomized to the CSA group from time of randomization through Week 52.

Maintenance Dose

At randomization, participants assigned to the CSA arm are initially prescribed a dose of 5-6 mg/kg per day, divided into two daily doses. Subsequently, dose levels are adjusted to maintain the whole blood CSA trough level in the therapeutic range of 100 – 250 ng/mL. For children given the liquid formulation, the exact starting and maintenance doses will be rounded to the nearest 10 mg. For older children and adults receiving capsules, doses will be rounded off to the nearest 25 mg unit without exceeding the 6-mg/kg upper dose level. See Table 8.7.2. in Section 8.7. for recommendations for how the CSA dose should be rounded following dose adjustments for participants taken capsules. For participants weighing more than 50 kg the CSA dose increases should not exceed 50 mg increments.

Dose Adjustments Based on 12 Hr Trough Level

The CSA trough levels are obtained 12 hours (with a maximum allowable window of 10 – 14 hours) following the last administration of CSA. The CSA whole blood trough levels will be measured by the Core Lab at the Week 2, 4, 6, 14, 26, 38 and 52 visits, and within 2 weeks of any CSA dose modification made because of an out-of-range trough measurement. If the CSA trough level is below the therapeutic range, the dose will be increased in 1-mg/kg/day increments until the CSA trough level reaches the 100 – 250 ng/mL therapeutic range. If the level is above 250 ng/mL, but less than 400 ng/mL, then the dose will be lowered in 1-mg/kg/day decrements until a CSA between 100 – 250 ng/mL is achieved. If the level is equal to or greater than 400 ng/mL, then the CSA dose will be lowered according to the dose modification algorithm for toxicities described below. See Table 8.7.1 in Section 8.7 for recommendations for how the CSA dose should be rounded following dose adjustments. For participants weighing more than 50 kg the CSA dose increases should not exceed 50 mg increments.

Remember

A repeat trough CSA level must be obtained from the Core Lab within 2 weeks of any dose modification done because of abnormal 12-hour trough levels.

Toxicities

Because a declining GFR and elevated serum potassium may be toxicity indications for both CSA and ACEi or ARB therapy, when the CSA level is in the therapeutic range, the CSA dose should be modified in response to these toxicities only if they persist after implementing the dose-reduction algorithms for ACEi or ARB therapy (described below). There are four categories of toxicities for CSA:

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- a. Declining GFR: A decline in GFR which is 30% or more below the baseline GFR and $\leq 100 \text{ ml/min/1.73m}^2$ 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 and the value is confirmed on repeat testing, 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 CSA trough blood levels (greater than 400 ng/mL)
- d. Significant side effects: If thought to be related to CSA, an Adverse Event Form (Form # 60), or a Serious Adverse Event Form (Form # 61) should be completed. Contact the CCC if a question regarding indications for dose adjustment arises. With significant side effects it is clinically acceptable to reduce CSA and ascertain whether the adverse event resolves at a lower dose.
 1. Other significant adverse events: If a complication occurs that is thought to be related to CSA and clinical practice requires complete and temporary cessation of the drug rather than stepwise tapering, then the drug should be stopped. Examples include exposure to chickenpox in a child who has not been immunized or a patient with herpes zoster infection. And Adverse Event Form (Form # 60) or a Serious Adverse Event Form (Form #61) should be completed. Contact the CCC if a question regarding indications for drug cessation arises.

Gingival hyperplasia and hirsutism are not considered adverse/toxic events requiring CSA dose modification. Unless the side effect is extreme as judged by the primary nephrologist, participants should be encouraged to stay on the medication. Instructions for good oral hygiene, including flossing, frequent brushing of teeth, and dental visits should be given. Participants with hirsutism should be reassured that it will regress after the study is completed; advice regarding cosmetic measures such as hydrogen peroxide treatment and hair removal can be given.

Dosage Modifications for Toxicity:

If a, b, c or d above pertain, the dose of CSA should be reduced to 67% of the original dose for 2 weeks. If the indication for dosage modification persists, the dose should be reduced to 33% of the original dose for 2 weeks. If the abnormality persists, the medication should be discontinued. A Study Medication Termination Form (Form # 45) should be completed and the CCC notified. In participants who take pills rather than liquid formulations, doses will be rounded to the nearest 25 mg. See Table 8.7.1 in Section 8.7 for recommendations for how the CSA dose should be rounded following dose adjustments for toxicity.

If d1 (above) pertains, the drug should be withheld until the adverse event resolves and the participant is clinically cleared to resume the medication. The drug should be restarted at the full dose that applied prior to occurrence of the adverse event.

Please consult the flow diagrams labeled CSA1 – CSA3 in Section 8.5 for directions as to the sequence of steps for implementing CSA dose adjustments. The algorithm for making dose adjustments in response to hyperkalemia is provided in the flow diagram labeled HYP. Recommendations for dietary modification in response to hyperkalemia are provided in Section 8.6.

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Remember

1. In the event that there is decline in GFR which is 30% or more below the baseline GFR and ≤ 100 ml/min/1.73m² or hyperkalemia, the ACEi dosage should be modified first in accordance with the hyperkalemia flow diagram (HYP). The cyclosporine dose should only be altered if the abnormality persists after reduction in the ACEi dosage.
2. Follow the directions indicated in the flow diagrams regarding the time intervals for repeat lab testing following a dose reduction in cyclosporine dosage in order to assess reversibility of the drug-induced toxicity or the possible need for additional dose reductions.

Subsequent Dosing:

The dose of CSA at which a, b, c above is corrected should be maintained indefinitely without attempting to reestablish the maintenance dose. If significant side effects (item 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.

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8.4.2. Mycophenolate Mofetil (MMF)

Period of Administration

MMF is administered to participants randomized to the MMF group from time of randomization through Week 52.

Titration and Maintenance Dose

The maintenance dose of MMF is 25 - 36 mg/kg per day with a maximum dose of 2 g/day, divided into two to three daily doses. The dose range reflects the use of fixed size (250 mg) capsules and application of defined daily doses to specific weight ranges. In younger children or those participants who are unable to swallow capsules, a liquid formulation will be used to provide 36 mg/kg/day (rounded to the nearest 0.2 mL or 40 mg) to a maximum of 2 g per day.

The starting MMF dose should be 50 – 67% of the full dose for 2 weeks before advancing to the full dose for the duration of the 12-month treatment period. This up-titration is done to improve participant tolerance of the medication. The following table is the dosage schedule by subject weight that will be used in participants over 12 years of age.

Initial and Maintenance Dose of MMF

<u>Weight (Kg)</u>	<u>Initial Dose (mg)</u>		<u>Full Dose (mg)</u>		<u>Full Dose in mg/kg/day</u>
	<u>AM</u>	<u>PM</u>	<u>AM</u>	<u>PM</u>	
25 – 29.9	250,	250	500,	250	25 – 30
30 – 39.9	250,	250	500,	500	25 – 33
40 – 44.9	500,	250	750,	500	28 – 31
45 – 49.9	500,	500	750,	750	30 – 33
50 – 54.9	500,	500	1000,	750	32 – 35
≥ 55	500,	500	1000,	1000	≤ 36

Toxicities

The protocol designates three categories (a, b and c) of toxicities for MMF:

- 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 as outlined in the Table below.
- Leukopenia: ANC < 1,000 – Discontinue MMF
ANC 1,000-1,500 – Modify dose as outlined in the Table below
- Anemia: If HCT < 25%, MMF dose should be modified as outlined in the Table below
- Significant side effects: If thought to be related to MMF, an Adverse Event Form (Form # 60), or a Serious Adverse Event Form (Form # 61) should be completed. Contact the CCC if a question regarding indications for dose adjustment arises. With significant side effects it is clinically acceptable to reduce MMF and ascertain whether the adverse event resolves at a lower dose.

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- d. 1. Other significant adverse events: If a complication occurs that is thought to be related to MMF and clinical practice requires complete and temporary cessation of the drug rather than stepwise tapering, then the drug should be stopped. Examples include exposure to chickenpox in a child who has not been immunized or a patient with herpes zoster infection. And Adverse Event Form (Form # 60) or a Serious Adverse Event Form (Form #61) should be completed. Contact the CCC if a question regarding indications for drug cessation arises.

Dosage Modifications for Toxicity

Dosage Modification for MMF: If a, b, or c above pertain, the dosage of MMF should be reduced according 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 for 2 weeks. If the abnormality persists, the medication should be discontinued. Instructions for restarting MMF are summarized in Section 8.4.7. The Study Medication Termination Form (Form # 45) should be completed and the CCC notified.

If d1 (above) pertains, the drug should be withheld until the adverse event resolves and the participant is clinically cleared to resume the medication. The drug should be restarted at the full dose that applied prior to occurrence of the adverse event.

Recommended MMF Daily Dose Reduction Guidelines

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

See the flow charts designated MMF1 and MMF2 in Section 8.5 for directions as to the sequence of steps for implementing MMF dose adjustments.

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Note

Clinical assessment and laboratory testing must be repeated within 2 weeks of a reduction in the MMF dosage in order to assess reversibility of the drug-induced toxicity or the possible need for additional dose reductions

Subsequent Dosing:

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). If this is not possible, MMF should be increased gradually until an optimal tolerable dose is found.

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8.4.3. Dexamethasone

Period of Administration

Dexamethasone is administered to participants randomized to the MMF group from time of randomization through Week 52.

Maintenance Dose

The maintenance dose of dexamethasone is 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. A maximum of 10 dexamethasone tablets is required at a single dose, based on supply of the drug as 4-mg tablets. For participants taking dexamethasone tablets, the dose will be rounded to the nearest 4 mg for participants weighing over 20 kg, and to the nearest 2 mg for participants under 20 kg.

Toxicities

The protocol designates three categories of toxicities for dexamethasone:

- 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 if the random glucose is not less than 200 mg/dl during study weeks 1 to 26, the alternate day prednisone dose should be modified as outlined Section 8.4.4. If the fasting serum glucose remains above 140 mg/dl or random glucose above 200 mg/dl after following the modifications to prednisone, the dexamethasone dose modification should be instituted (see Dosage Modification for Dexamethasone Toxicity, below).
- 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 neurologic/ophthalmologic evaluation and imaging study

A psychiatric consultation is advised for all participants who have significant changes in behavior to assist in evaluating the need for reduction in the dexamethasone dose.

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

An ophthalmological consultation is advised for all participants who have new-onset significant headaches, alterations in vision, or cataracts to assist in evaluating the need for reduction in the dexamethasone dose.

Dosage Modifications for Dexamethasone Toxicity:

If any of the toxicities defined as a, b, or c above pertain, the dose of dexamethasone should be reduced to 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 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. A Study Medication Termination Form (Form # 45) should be completed and the Core Coordinating Center notified.

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See the flow charts designated DEX1 and DEX2 in Section 8.5 for directions as to the sequence of steps for implementing dexamethasone dose adjustments.

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.

If the dexamethasone has to be discontinued to achieve resolution of toxicity after week 10, then the drug should not be restarted.

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8.4.4. Prednisone

Period of Administration

Prednisone is administered in BOTH the CSA and MMF groups from randomization through week 26. The dose will be stopped after 6 months and it will not be tapered.

Maintenance Dose

The maintenance dose of 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. Dose levels for participants taking tablets must be rounded to the nearest 5 mg. The study medication formulation of prednisolone (Orapred) is the same strength as prednisone. If the participating site PI decides to use methylprednisolone, the dose should be 80% of the prednisone dose.

Toxicities

The protocol designates one category of toxicity for prednisone:

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

Dosage Modifications for Toxicity:

If sustained hyperglycemia persists as defined above, the alternate day prednisone should be discontinued and the Study Medication Termination Form (Form # 45) should be completed. The Core Coordinating Center should be notified.

Subsequent Dosing:

Prednisone should not be re-instituted if it was previously discontinued due to sustained hyperglycemia.

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8.4.5. Lisinopril

Period of Administration

The ACE inhibitor lisinopril is administered in BOTH the CSA and MMF groups from randomization through week 78. Any participant who wants liquid medication or cannot tolerate pills may receive liquid lisinopril.

Titration and Maintenance Dose

A maximally tolerated dose of the angiotensin converting enzyme inhibitor (ACEi), 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, which can occur during the Baseline period. If the starting dose is tolerated, the intermediate dose will be given two weeks later (see below for specific instruction regarding participants who are receiving an ACE inhibitor prior to entering the trial). Finally, 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 tablets and for children taking the liquid formulation who are over 25 kg are given below:

<u>Participant Weight (Kg)</u>	<u>Initial Daily Dose (mg)</u>	<u>Intermediate Dose (mg)</u>	<u>Maintenance Daily Dose (mg)</u>
<25	2.5	5.0	10
25 – 34.9	2.5	7.5	15
35 – 44.9	5.0	10	20
45 – 54.9	5.0	12.5	25
55 – 64.9	7.5	15	30
65 – 74.9	7.5	17.5	35
>75	10	20	40

Lisinopril may be started in the Baseline Period prior to commencing therapy with the specific agents outlined for the CSA and MMF groups, with the understanding that the participant must satisfy the Up/c criterion and other criteria for enrollment at the time of randomization. In the absence of toxicity, the maintenance ACEi dose (see above targets) must remain unchanged for the remainder of the 18-month treatment period.

If a participant is already receiving an ACE inhibitor at the time of enrollment into the trial, then the participant can continue on the same dose of the medication if he/she is receiving lisinopril. If the participant is receiving another ACE inhibitor, then an equivalent dose of lisinopril should be prescribed. During the switch to lisinopril, the dose of lisinopril can be advanced as quickly as necessary based on clinical circumstances. In particular, the lisinopril can be increased to the target dose without advancing the dose at 2-week intervals as outlined in the protocol. The previously prescribed ACE inhibitor can be tapered at the discretion of the local investigator. If a participant develops hyperkalemia or a reduction in the calculated GFR during this process, the

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dose of the non-lisinopril ACE inhibitor should be reduced accordingly. However, the conversion to lisinopril should be completed by 6 weeks. After this time, a subject on an ACE inhibitor other than lisinopril will be considered a protocol violation.

The following Table summarizes the estimated equivalent doses for the most commonly prescribed ACE inhibitors and is provided to assist in the switch between specific medications. It should be emphasized that most of the ACE inhibitors other than lisinopril are not approved for use in children and adolescents and the pediatric dose equivalent to lisinopril is provided as a suggested guideline not an established dose. **Please note: (1) other than during a switch in specific medications, patients cannot receive two ACE inhibitors; and (2) participant cannot receive doses of lisinopril in excess of the maximum amounts permitted by the protocol.**

Drug (Brand name)	Adult dose equivalent to lisinopril 10 mg	Pediatric dose equivalent to lisinopril 0.1 mg/kg
Benazepril (Lotensin)	10	0.1
Fosinopril (Monopril)	10	0.1
Quinapril (Accupril)	10	0.1
Enalapril (Vasotec)	5	0.05
Moexepil (Univasc)	7.5	0.075
Ramipril (Altace)	2.5	0.025
Perindopril (Aceon)	2	0.02
Trandopril (Mavik)	1	0.01
Captopril (Capoten)	50	0.5

Toxicities

The protocol describes 5 classes of toxicities for lisinopril:

- GFR: A decline in GFR which is 30% or more below the baseline GFR and ≤ 100 ml/min/1.73m² which is repeated and confirmed in a well-hydrated participant requires modification.
- 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.
- BP: Symptoms of orthostatic hypotension.
- Cough: Persistent cough unrelated to other causes.
- Angioedema: Lisinopril or losartan should be discontinued and a Serious Adverse Event Form (Form # 61) and a Study Medication Termination Form (Form # 45) should be completed. The Clinical Coordinating Center should be informed.

Dosage Modifications for Lisinopril Toxicity:

If a, b, or c above pertain, the dose of lisinopril should be reduced to 67% of the original dose for 2 weeks. If the indication for dosage modification persists, the dose should be reduced to 33% of the original dose for 2 weeks. If the abnormality persists, the medication should be discontinued.

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A Study Medication Termination Form (Form # 45) should be completed and the CCC notified. If item d (above) pertains (i.e., the participant has persistent cough unrelated to other causes), then lisinopril should be discontinued and treatment with ARB should be instituted and toxicity monitored.

See the flow chart designated A2 in Section 8.5 for directions as to the sequence of steps for implementing lisinopril dose adjustments.

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 of cough (see dosage modification above), treatment with ARB should be instituted (see table below) and toxicity monitored.

If the lisinopril has to be discontinued to achieve resolution of toxicity, then the drug should not be restarted.

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8.4.6. Losartan

Period of Administration

Participants who are unable to tolerate treatment with ACEi or who have been previously intolerant of ACEi will receive an angiotensin receptor blocker (ARB), namely losartan.

Titration and Maintenance Dose

For children weighing less than 25 kg, a liquid formulation of losartan (2.5 mg/mL) may be utilized. Doses for participants taking tablets and for children taking the liquid formulation who are over 25 kg are outlined in the following table:

	LOSARTAN DOSING	
Participants taking tablets		
Body weight	Initial daily dose	Maintenance daily dose
<50 kg	25 mg	50 mg
≥50 kg	50 mg	100 mg
Participants taking liquid	0.5 mg/kg	1.0 mg/kg

If a participant is already receiving an ARB because of a documented intolerance of ACE inhibitors at the time of enrollment into the trial then the participant can continue on the same dose of the medication if he/she is receiving losartan. If the participant is receiving another ARB, then an equivalent dose of losartan should be prescribed. During the switch to losartan, the dose of losartan can be advanced as quickly as necessary based on clinical circumstances. In particular, the losartan can be increased to the target dose without advancing the dose at 2-week intervals as outlined in the protocol. The previously prescribed ARB can be tapered at the discretion of the local investigator. If a participant develops hyperkalemia or a reduction in the calculated GFR during this process, the dose of the non-losartan ARB should be reduced accordingly. However, the conversion to losartan should be completed by 6 weeks. After this time, a subject on an ARB other than losartan will be considered a protocol violation.

The following table summarizes the estimated equivalent doses for the most commonly prescribed ARB and is provided to assist in the switch between specific medications. It should be emphasized that most of the ARB other than losartan are not approved for use in children and adolescents and the pediatric dose equivalent to losartan is provided as a suggested guideline not an established dose. Please note that if a participant is receiving an ARB because of convenience, then they should be switched to lisinopril and the dose should be titrated as outlined in section 8.4.5.

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Drug (Brand name)	Adult dose equivalent to losartan 25 mg	Pediatric dose equivalent to losartan 0.5 mg/kg
Candesartan (Atacand)	4	0.08
Eprosartan (Tevetan)	400	8
Irbesartan (Avapro)	75	1.5
Olmesartan (Benicar)	5	0.1
Telmisartan (Micardis)	20	0.4
Valsartan (Diovan)	40	0.8

Toxicities

The same potential toxicities listed for lisinopril also apply for losartan:

- GFR: A decline in GFR which is 30% or more below the baseline GFR and ≤ 100 ml/min/1.73m² which is repeated and confirmed in a well-hydrated participant requires modification.
- 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.
- BP: Symptoms of orthostatic hypotension.
- Cough: Persistent cough unrelated to other causes.
- Angioedema: Lisinopril or losartan should be discontinued and a Serious Adverse Event Form (Form # 61) and a Study Medication Termination Form (Form # 45) should be completed. The Core Coordinating Center should be notified.

Dosage Modifications for Losartan Toxicity:

If a, b, or c (above) pertain, the dose of losartan should be reduced to 67% of the original dose for 2 weeks. If the indication for dosage modification persists, the dose should be reduced to 33% of the original dose for 2 weeks. If the abnormality persists, the medication should be discontinued. If item d (above) pertains, then losartan should be discontinued. A Study Medication Termination Form (Form # 45) should be completed and the Core Coordinating Center notified. If a, or b occur, the losartan dosage should be reduced before making any change in the cyclosporine dosage.

Subsequent Dosing:

The dose of losartan at which the toxicity is corrected should be maintained for the remainder of the 18-month treatment period, unless a new toxicity occurs.

If the losartan has to be discontinued to achieve resolution of toxicity after week 10, then the drug should not be restarted.

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8.4.7. Summary Instructions for Reinitiation of Study Medications

The following table summarizes the instructions given above (Section 8.4.) that indicate which medications should be reinstituted following temporary discontinuation if symptoms have resolved.

MEDICATION	REINSTITUTE (Y/N)		COMMENTS
<i>Cyclosporine (8.4.1)</i>			
Declining GFR	N		
Hyperkalemia	N		
Significant side effects	Y		Seizures are only significant side effect for which drug is not reinstituted Target original dose
<i>MMF (8.4.2)</i>			
GI	Y		Reinstitute in reverse order, target full dose
Leukopenia	Y		Same as GI
Anemia	Y		Same as GI
<i>Dexamethasone (8.4.3)</i>			
Hyperglycemia	Wk 1-8: Y	Wk ≥ 10 : N	Reinstitute after completion of first 8 wk, in reverse order, target full dose
Neuropsychiatric	Wk 1-8: Y	Wk ≥ 10 : N	Same as hyperglycemia
Miscellaneous	Wk 1-8: Y	Wk ≥ 10 : N	Same as hyperglycemia
<i>Prednisone (8.4.4)</i>			
Hyperglycemia	N		D/C in 1 step
<i>Lisinopril (8.4.5)</i>			
GFR	N		
Hyperkalemia	N		
BP	N		
Cough	N		D/C in 1 step Replace with ARB, losartan
Angioedema	N		
<i>Losartan (8.4.6)</i>			
GFR	N		
Hyperkalemia	N		
BP	N		
Cough	N		D/C in 1 step
Angioedema	N		

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.4.8. 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 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.

Note

If prednisone is given for the treatment of a relapse, it will not be provided as part of the study medication protocol. It must be prescribed locally. It is recommended that the participants be prescribed prednisone, 5mg tablets, or prednisolone liquid preparation (Orapred) to maintain consistency with the formulations provided as part of the trial. No other immunosuppressive medications can be prescribed for the treatment of a relapse.

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. Local standards should be followed for the symptomatic treatment of these participants with drugs such as diuretics.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.5. Flow Charts of Dose Modification Algorithms

This section provides flow charts detailing the sequence of steps of the dose modification algorithms for each study drug. The flow charts are as follows:

CSA1: CSA Dose Adjustments Based on Trough CSA Level

Describes protocol for dose adjustments based on the CSA trough level. CSA dose is increased by 1 mg/kg/day if trough CSA < 100 ng/mL, and decreased by 1 mg/kg/day if trough CSA is between 251 and 400 ng/mL. Trough CSA levels greater than 400 ng/mL are treated as a toxicity, with dose reductions to 67% and then to 33% of the original dose (see CSA 2).

CSA2: CSA Dose Reduction Protocol

Describes general protocol for CSA dose adjustments due to toxicities. This protocol should be implemented directly for toxic trough CSA levels and significant side effects listed as toxicities (c) and (d) in Section 8.4.1. However, CSA dose reductions should be implemented in response to toxicities a) declining GFR or b) hyperkalemia *only* after reducing the dose of ACEi or ARB as described in the flow chart HYP below.

Remember

The CSA dose reduction protocol should be implemented for declining GFR even if within safe range (100 – 250) or for hyperkalemia **ONLY AFTER** implementing the dose reduction protocols for ACEi or ARB therapy described in the flow charts CSA3, HYP, and A2 below.

The flow chart indicates that there should be no attempt to re-escalate the CSA dose following resolution of any of the toxicities a) declining GFR, b) hyperkalemia, c) toxic trough blood CSA level, or other CSA-related serious adverse events. However, if possible, CSA dose should be re-escalated (or re-instituted if CSA was discontinued) in the indicated stepwise fashion following resolution of other side effects (designed as (d) of section 8.4.1) not designated as SAE.

CSA3: CSA Dose Adjustment Due to Estimated GFR Decline > 30% to $\text{GFR} \leq 100 \text{ ml/min/1.73m}^2$

Describes the steps to be taken for a participant randomized to the CSA group following a decline of greater than 30% in estimated GFR based on application of the Schwartz or Cockcroft-Gault formulas to a centrally determined serum creatinine. The CSA dose reduction protocol (Node 9) is implemented only if a) a decline in GFR which is 30% or more below the baseline GFR and $\leq 100 \text{ ml/min/1.73m}^2$ is confirmed in a well-hydrated participant, and b) implementation of the ACEi or ARB dose reduction protocol described in the flow chart A2 did not resolve the > 30% GFR decline / $\text{GFR} \leq 100 \text{ ml/min/1.73m}^2$.

HYP: Dose Adjustment Protocol for Hyperkalemia (Serum K > 5.5)

Describes procedure for dealing with hyperkalemia. If the elevated serum K is confirmed, and the blood trough CSA level is $\leq 250 \text{ ng/mL}$, then the steps outlined below for either Nodes **A**, **B**, or **C** should be implemented depending on the level of the second serum K measurement. The CSA dose reduction protocol (Node A13 or C4) is implemented only if the implementation of the ACEi/ARB dose reduction protocol described in A2 did not resolve the elevated serum K.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

Due to space constraints, additional nodes beyond C7 and C10 are not included on the flow chart. In both cases, serum K should be repeated within 2 weeks. For Node C7, if the repeat serum K exceeds 5.5 mmol/L then initiate the CSA dose reduction protocol described in the flow chart CSA2. For Node C10, if the repeat serum K exceeds 5.5 mmol/L then terminate ACEi or ARB therapy, and repeat serum K within 2 weeks. If the repeat serum K continues to exceed 5.5 mmol/L, then initiate the CSA dose reduction protocol described in the flow chart CSA2.

Information related to the use of the low potassium diet indicated in Nodes A1, B1, and C1 is provided in Section 8.6.1.

MMF1: Toxicities to MMF

Describes response to the three categories of toxicities for MMF described in Section 8.4.2. The stepwise MMF dose reduction protocol described in MMF2 is implemented if ANC 1000-1500 or HCT < 25%, but MMF is discontinued in 1 step if ANC < 1000.

MMF2: MMF Dose Reduction Protocol

Describes dose reduction algorithm for MMF. The dose reduction steps following the basic 67%, 33% sequence for implementing dose reductions for toxicity subject to the rounding required by the 250 mg capsules or 0.2mg (40 mg) suspension.

DEX1: Toxicities to Dexamethasone

Describes response to toxicities from dexamethasone. Information related to implementing a low-sugar diet is provided in Section 8.6.2.

DEX 2: Dexamethasone Dose Reduction Protocol

Describes dose reduction algorithm for dexamethasone. The Dexamethasone dosing schedule has a natural taper when progressing from weekly dosing before week 8. After week 8, Dexamethasone dosing occurs 2 days every other week and then 2 days monthly. Due to the taper, it is expected that Dexamethasone related toxicities will abate at the later phases of the protocol and provide the potential to resume the original Dexamethasone daily dose. The Dexamethasone dose should be increased in the same 33% increments in a stepwise fashion until the full dose is resumed or recurrent toxicity prevents this dose escalation.

P1: Hyperglycemia Toxicity Indication for Prednisone

Describes dose reduction algorithm for prednisone. Instructions for dietary modification to correct hyperglycemia are provided in Section 8.6.2.

A1: Toxicities for ACEi (lisinopril) or ARB (losartan)

Describes response to toxicities for lisinopril and losartan.

A2: ACEi/ARB Dose Reduction Protocol

Describes the dose-reduction protocol for lisinopril and losartan.

CSA1: CSA Dose Adjustments Based on Trough CSA Level

Step 1

1. DCC reports central blood CSA level with
Dose Modification Report if necessary

Step 2

2. If CSA < 100 ng/mL
Increase dose by
1 mg/kg/day

3. If CSA 100-250 ng/mL
Dose unchanged

4. If CSA 251 - 400 ng/mL
Reduce dose by
1 mg/kg/day

5. If CSA > 400 ng/mL
Reduce CSA to 67% of
original dose

Step 3

6. Repeat blood CSA
in 1-2 weeks
GO TO **Step 2**

7. Repeat blood CSA at
next protocol CSA
measurement
GO TO **Step 2**

8. Repeat blood CSA
in 1-2 weeks
GO TO **Step 2**

9. Repeat blood CSA
in 1-2 weeks

10. Is repeat CSA ≤
400 ng/mL?

11. If YES, GO
TO **Step 2**

12. If NO, Reduce CSA to
33% of original dose

13. Repeat blood CSA
in 1-2 weeks

14. Is repeat CSA ≤ 400 ng/mL?

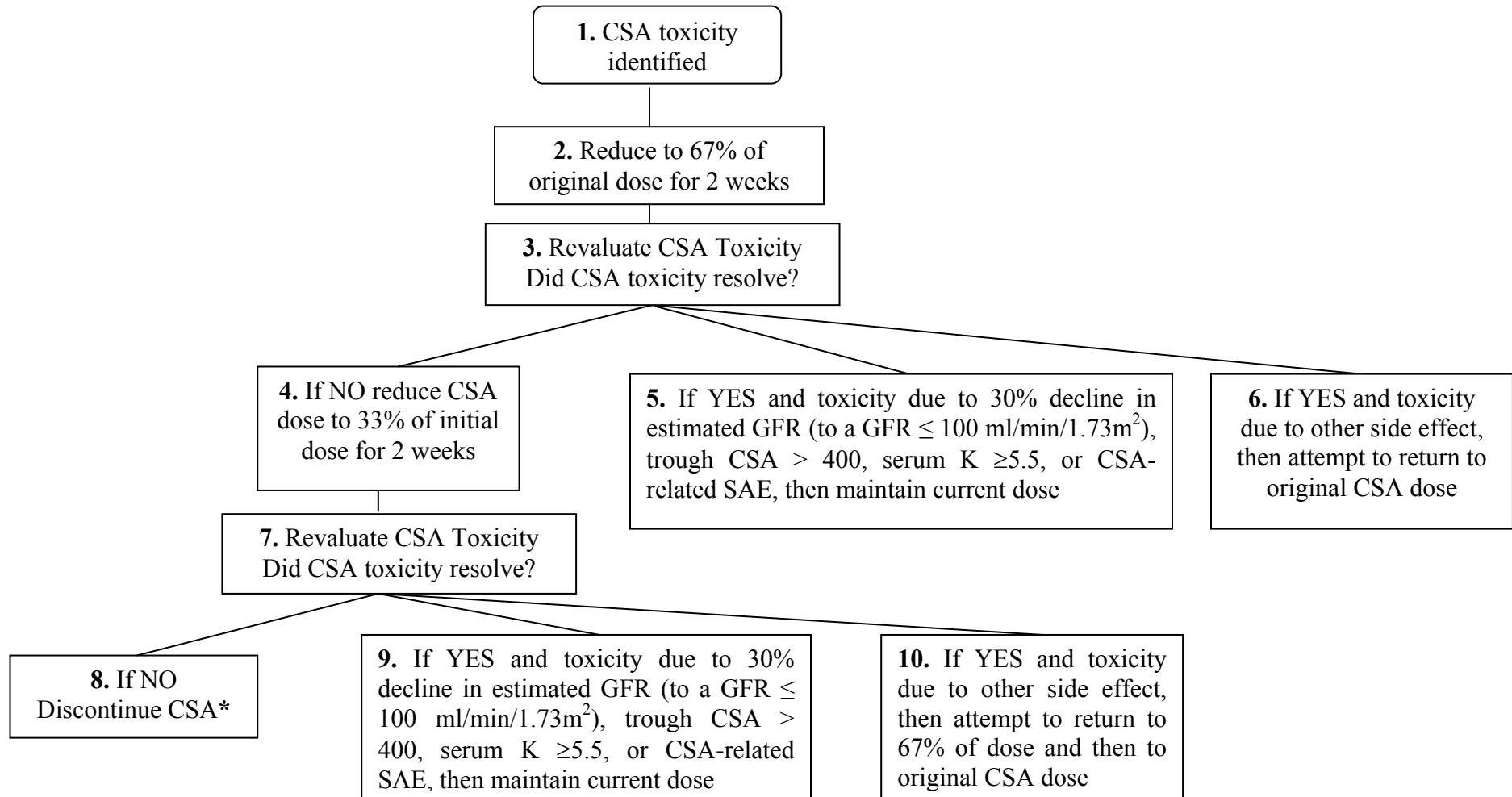
15. If YES, GO
TO **Step 2**

16. If NO, Discontinue
CSA

Note:

- All CSA blood measurements must be properly drawn trough values, obtained at 12 hours (window 10 - 14 hours) after the preceding CSA dose.
- Any CSA blood measurement drawn outside the 10-14 hour window must be repeated.
- PS = Participating Site
- CSA = Cyclosporine

CSA2: CSA Dose Reduction Protocol

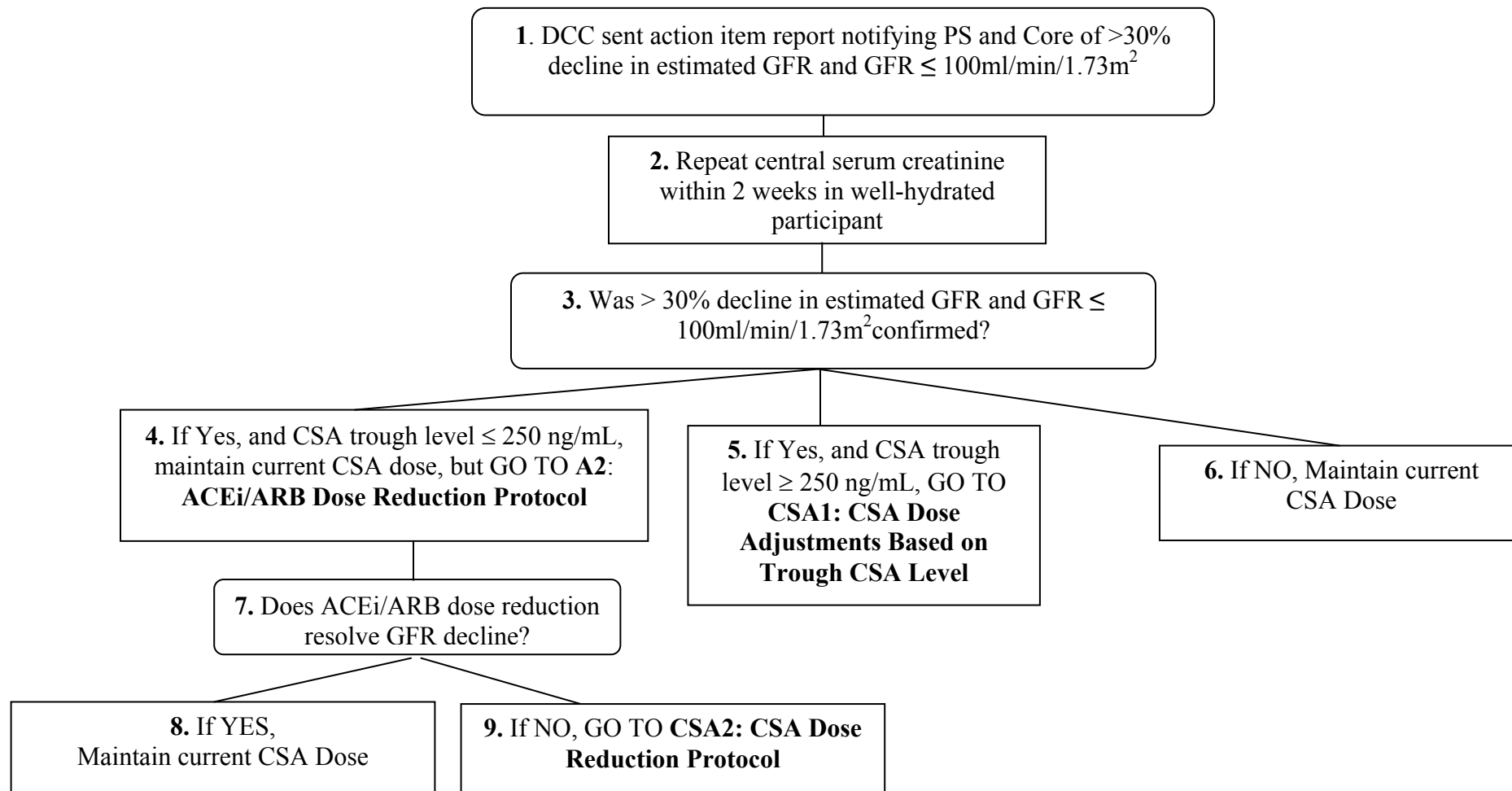


Note:

- Serum Potassium expressed as mmol/L
- CSA = Cyclosporine

* **Node 8.** If toxicity resolves following discontinuation of CSA, AND toxicity was due to another side effect not listed in node 9, then attempt to reinstitute CSA in stepwise fashion

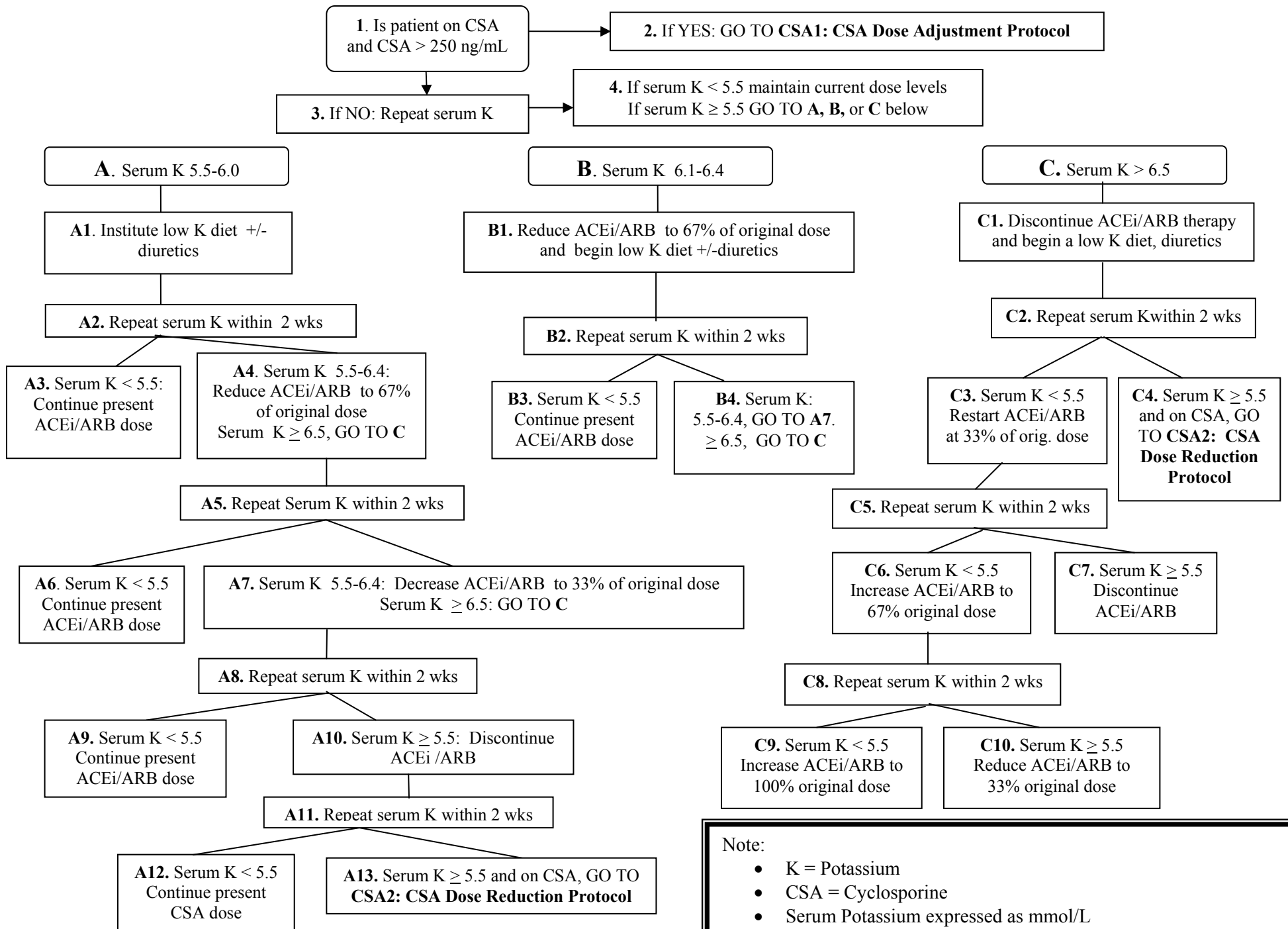
CSA3: CSA Dose Adjustment Due to Estimated GFR Decline $> 30\%$ and $\leq 100\text{ml/min/1.73m}^2$



Note:

- PS = Participating Site
- CSA = Cyclosporine

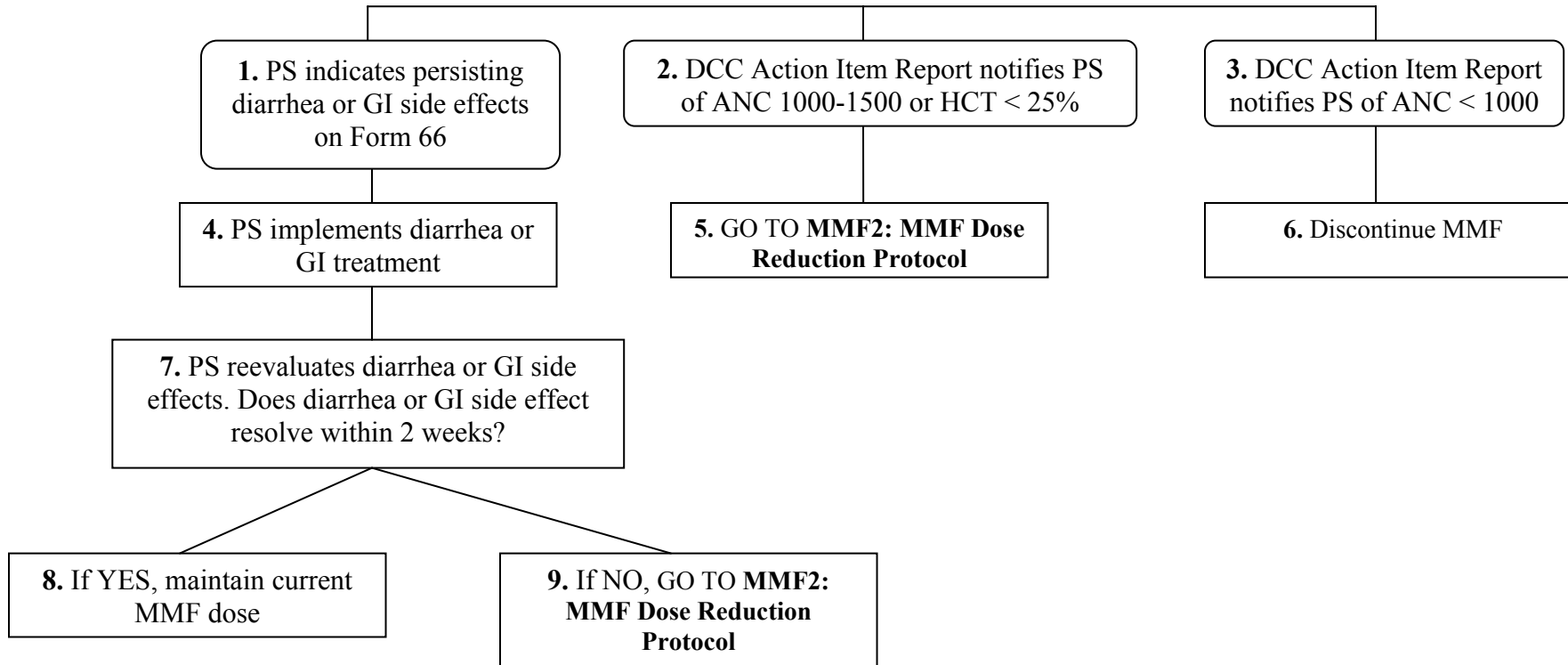
HYP: Dose Adjustment Protocol for Hyperkalemia (Serum K \geq 5.5)



Note:

- K = Potassium
- CSA = Cyclosporine
- Serum Potassium expressed as mmol/L
- Pts on ACEi reaching a Discontinue ACEi node should initiate ARB (see text instructions – Sections 8.4.5., 8.4.6.)

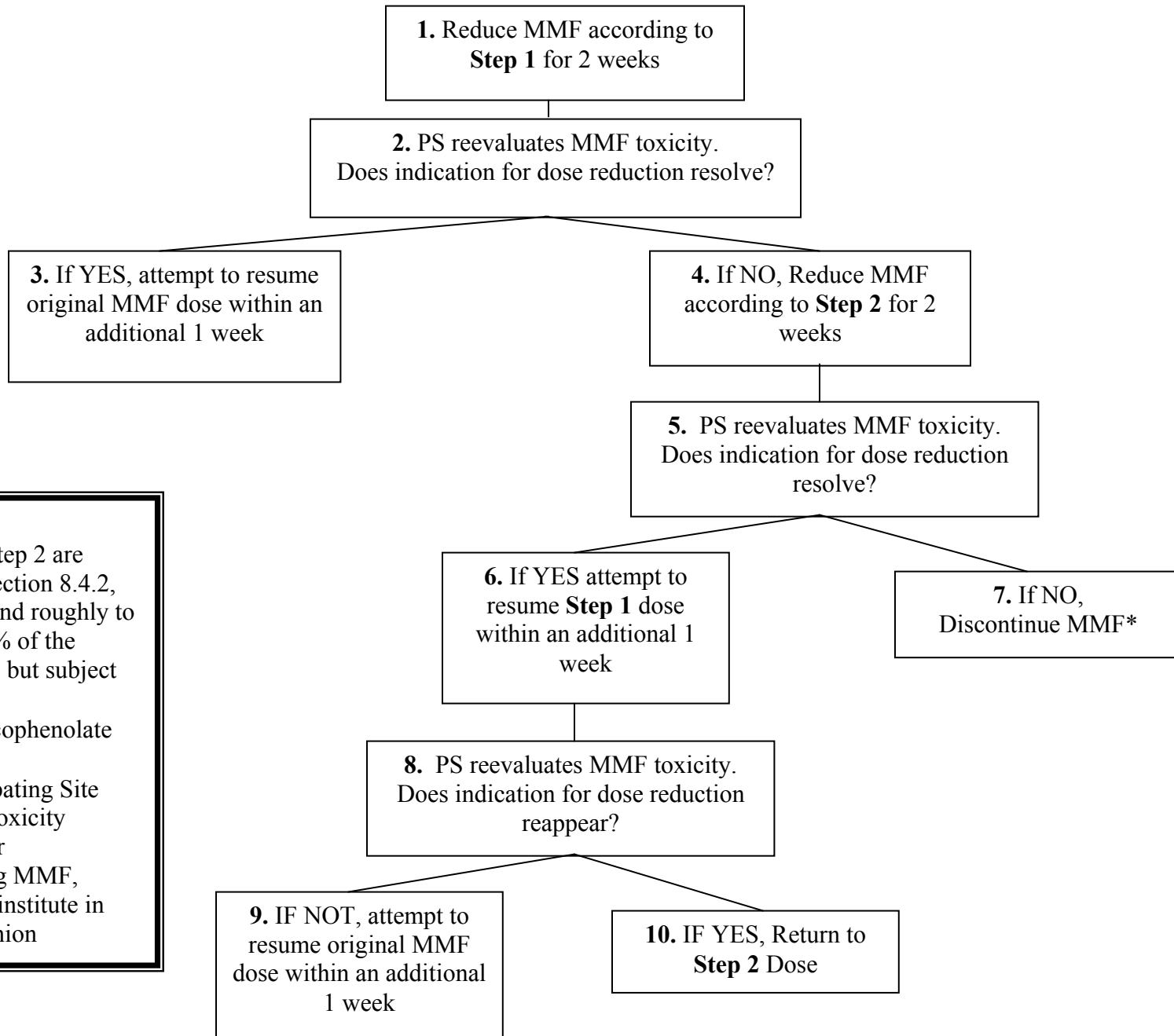
MMF1: Toxicities to MMF



Note:

- MMF = Mycophenolate Mofetil
- PS = Participating Site
- Form 66 MMF GI Toxicity Form

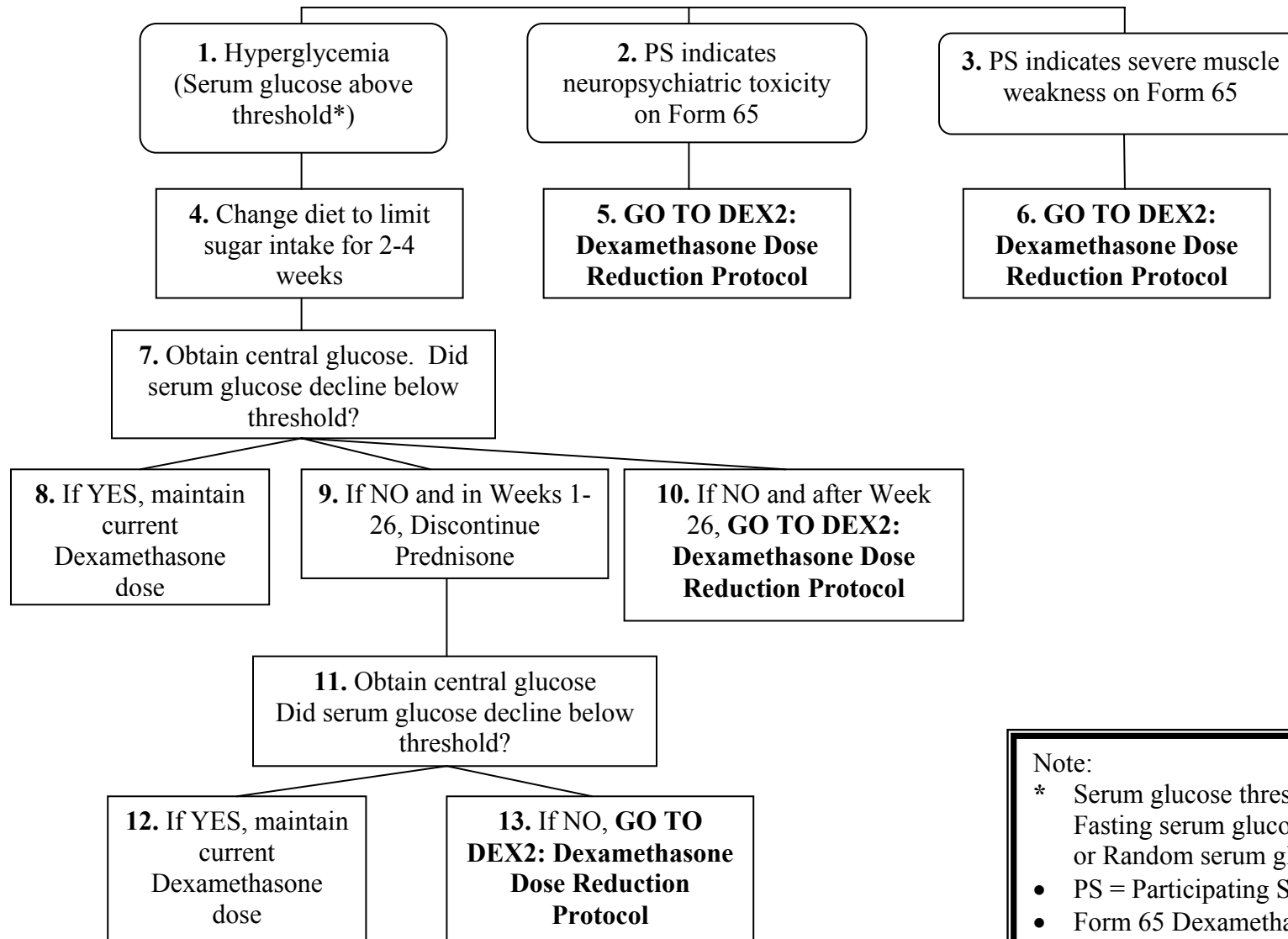
MMF2: MMF Dose Reduction Protocol



Note:

- Step 1 and Step 2 are defined in Section 8.4.2, and correspond roughly to 67% and 33% of the original dose but subject to rounding.
- MMF = Mycophenolate Mofetil
- PS = Participating Site
- * **Node 7:** If toxicity resolves after discontinuing MMF, attempt to reinstitute in stepwise fashion

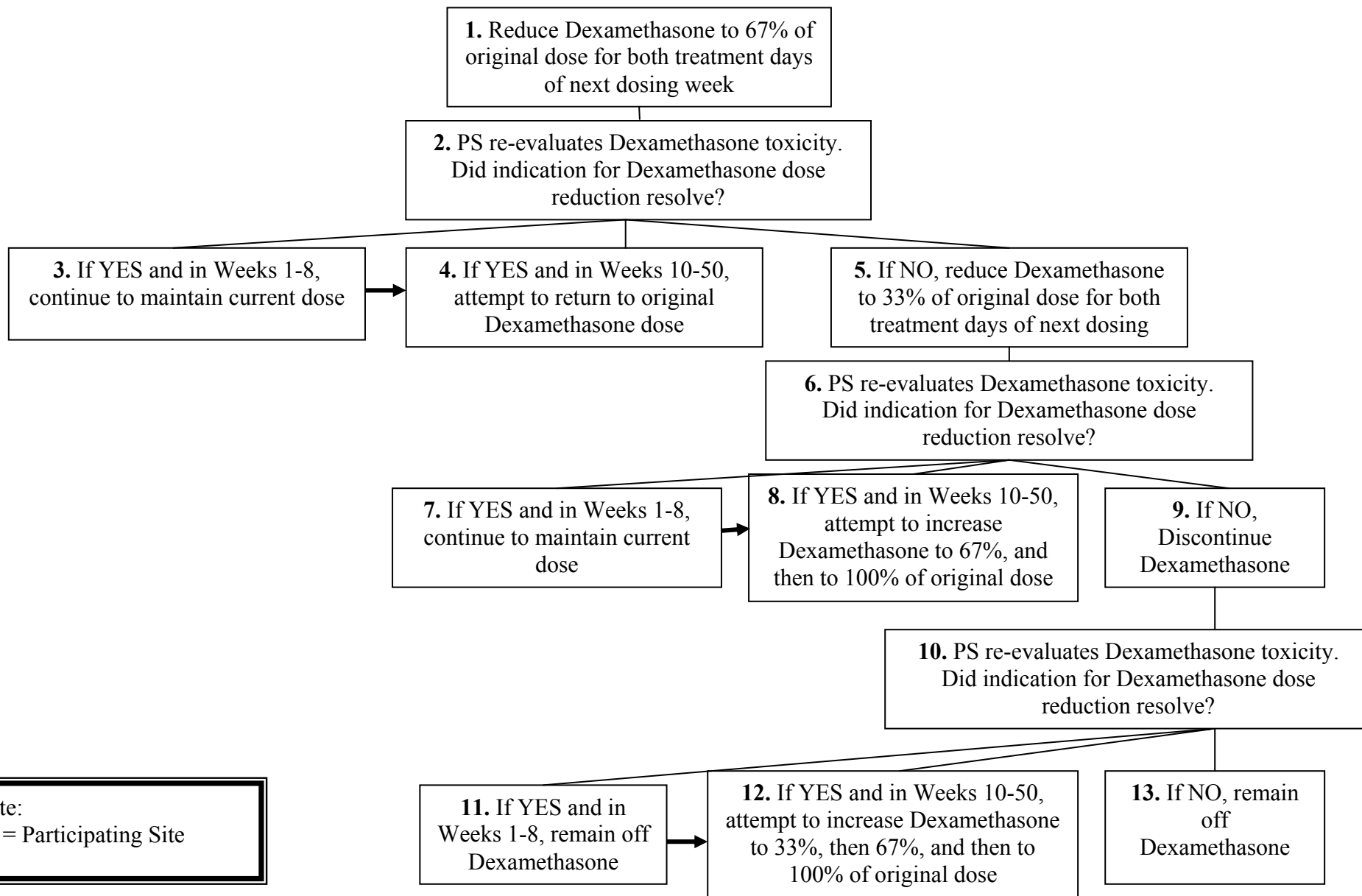
DEX1: Toxicities to Dexamethasone



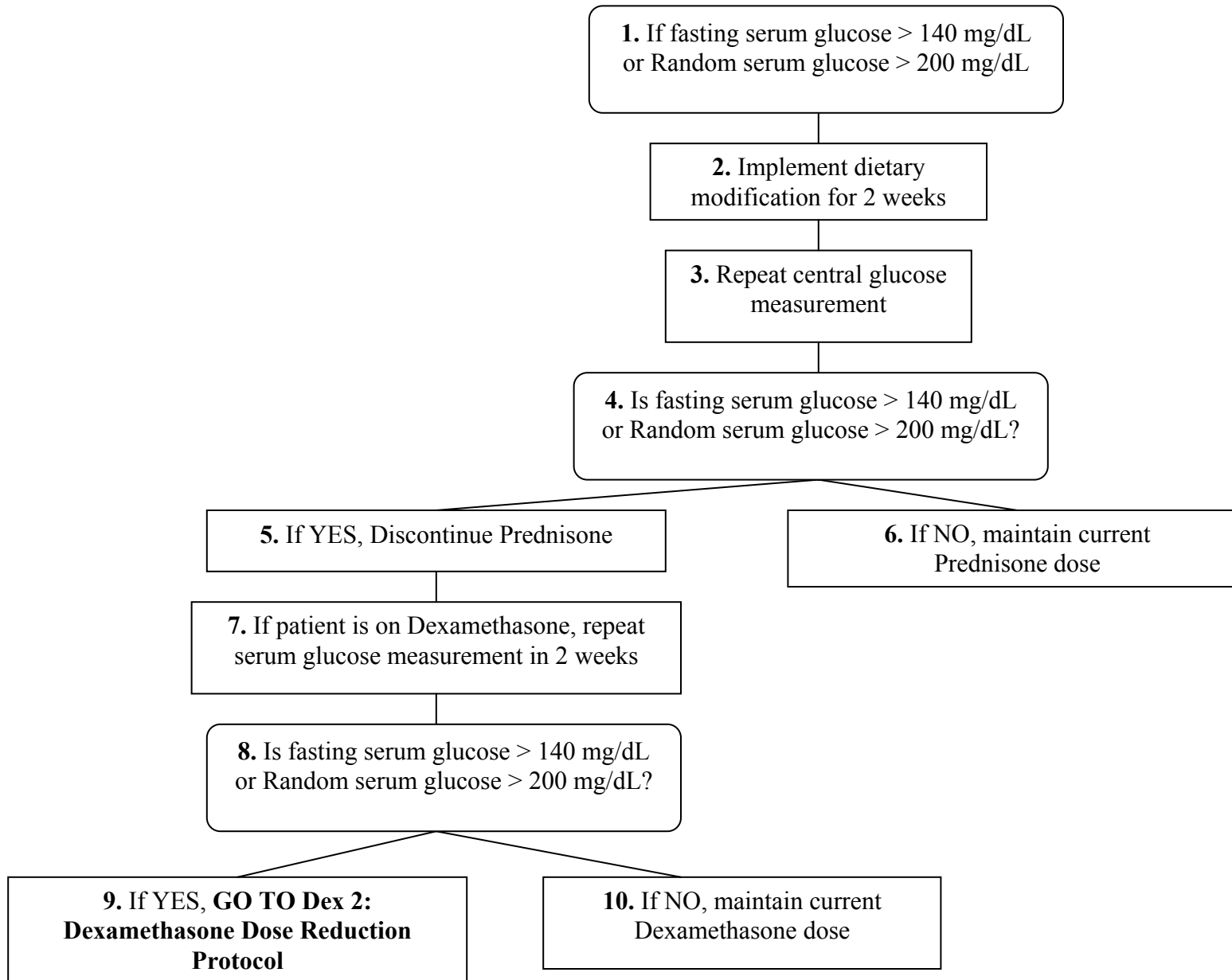
Note:

- * Serum glucose threshold:
Fasting serum glucose > 140 mg/dL
or Random serum glucose > 200 mg/dL
- PS = Participating Site
- Form 65 Dexamethasone Toxicity Form

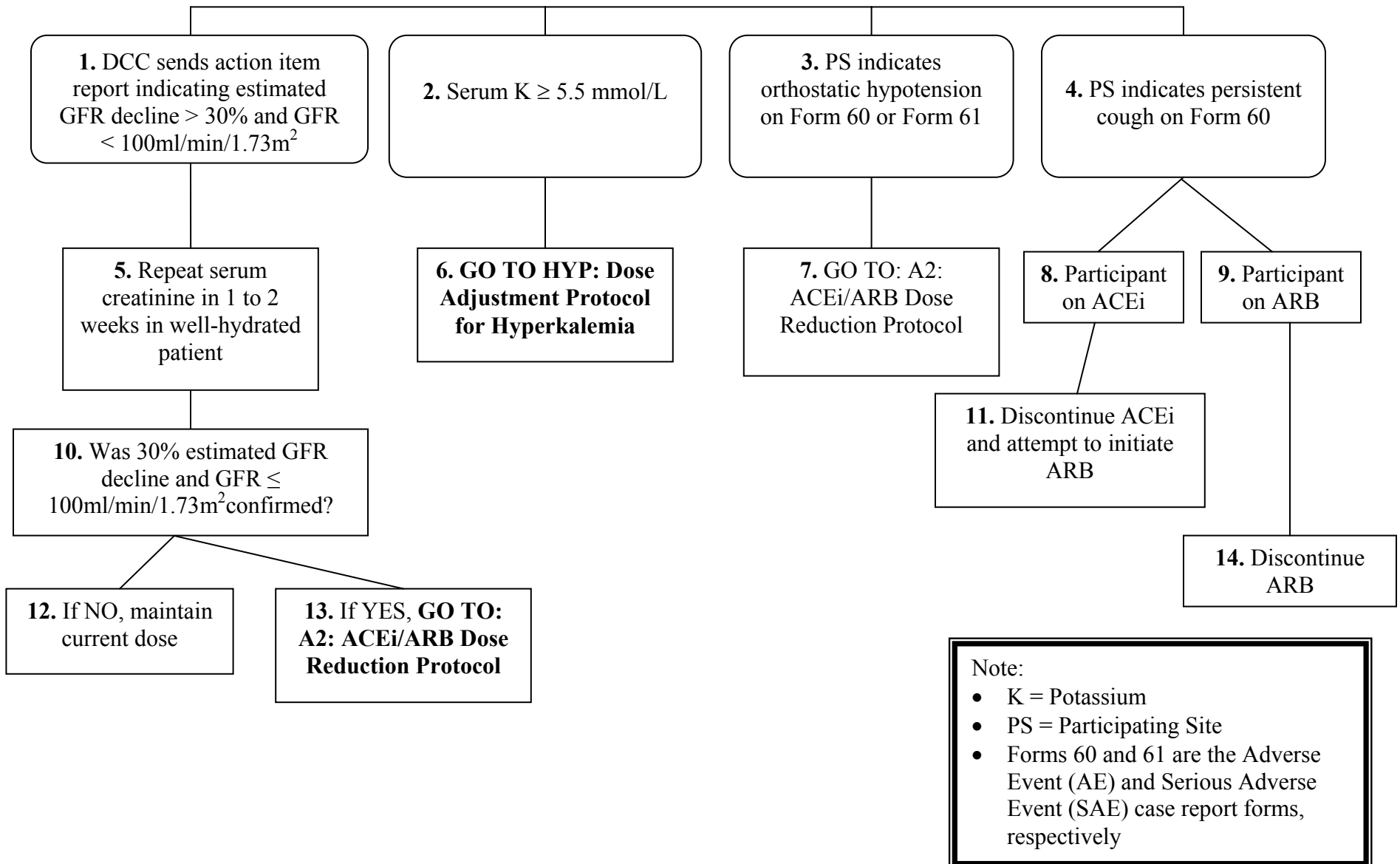
DEX 2: Dexamethasone Dose Reduction Protocol



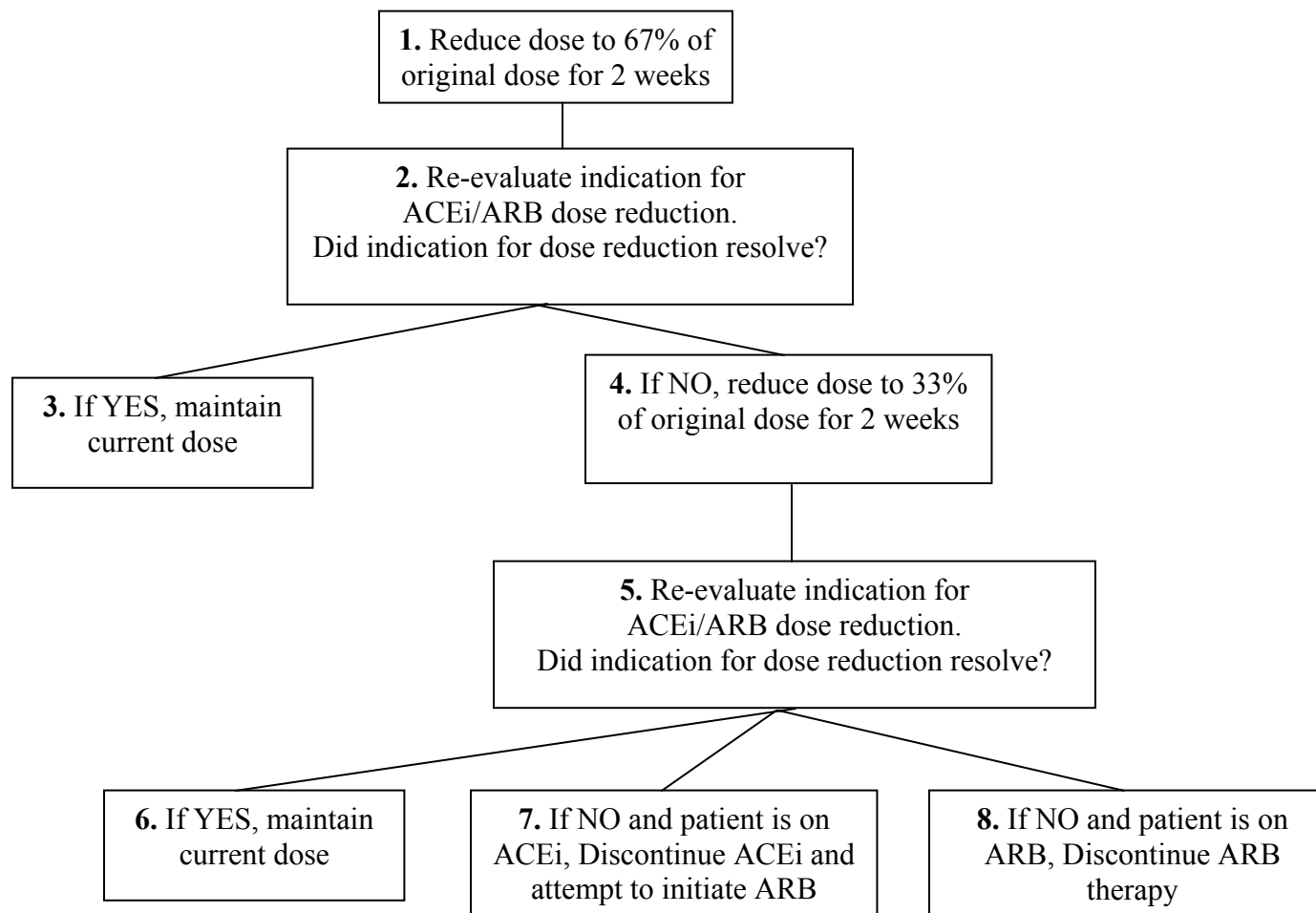
P1: Hyperglycemia Toxicity Indication for Prednisone



A1: Toxicities for ACEi (Lisinopril) or ARB (Losartan)



A2: ACEi (Lisinopril)/ARB (Losartan) Dose Reduction Protocol




8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.6. Dietary Modification


8.6.1. Dietary Modification to Reduce Serum Potassium

Potassium is an electrolyte that helps keep the heartbeat regular and muscles working properly. It is filtered by the kidneys and excreted in the urine. It is the job of the kidneys to keep the right amount of potassium in the body. If high potassium levels become a problem, it is important to avoid potential complications by watching potassium intake and avoiding high potassium foods. The more of these foods that are consumed the higher the risk of complications, so limit the number and quantity of the high potassium foods. If indicated, a dietician can help in formulating a diet.

Here is a list of some foods to avoid that are **HIGH** in potassium to use as a guide to help with potassium control and a list of **Low Potassium** foods to substitute as an alternate food.

	 High Potassium Foods to Avoid	Low Potassium Foods
Fruits	Avocado Banana Coconut Dried Fruits (apricot, date, fig, prune, raisin) Kiwi Melon (cantaloupe, honeydew) Nectarine Orange and Orange Juice Peaches, fresh Prune juice Tangelo	Apples Applesauce Blackberries, Blueberries Boysenberries, canned in syrup Cherries Cranberries, Gooseberries Grapefruit Grapes Loganberries Mandarin Oranges, canned in syrup Pears Pineapple Plums Raspberries Rhubarb, cooked Strawberries Tangerines Watermelon
Vegetables	Artichokes Bamboo Shoot, fresh Beans and peas, dried Broccoli, Brussel Sprouts Greens (collard, dandelion, mustard, swiss chard) Kale Lentils Legumes Lima beans Mushrooms Potato (regular, French fried, sweet) Pumpkin	Alfalfa sprouts Asparagus Bamboo Shoot, canned Beans, green or wax Bean spouts Beets Cabbage Carrots Cauliflower Corn Cucumber Eggplant Lettuce

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	 High Potassium Foods to Avoid	Low Potassium Foods
	Tomato (raw or canned) Vegetable Juice Yam Winter squash (acorn, butternut, hubbaard, spaghetti)	Mixed vegetables Okra Onions Parsley Peas, green or sweet Radish Rutabagas Squash (summer, zucchini)
Other	Bran and Bran products Chocolate Coffee (limit to 2 cups/day) Granola Ice Cream (limit to 1 cup/day) Milk (limit to 1 cup/day) Molasses Orange flavored pop Nuts and Seeds Salt Substitutes Snuff/chewing tobacco Tea (limit 2 cups/day)	Rice Noodles Bread and Bread products Cereals Cake Cookies Pies (however NO chocolate or high-potassium fruit pies!)

8.6.2. Dietary Modification to Reduce Serum Glucose

Specific toxicities have been defined by the trial protocol to require dose modification. Hyperglycemia above the WHO criteria for diabetes (Fasting >140 mg/dL or Random > 200 mg/dL) should precipitate diet instruction to limit concentrated sweets. Avoiding concentrated carbohydrates can help achieve and maintain near normal glucose levels. The “No Concentrated Sweets” diet typically consists of eating three small meals and 2 – 3 snacks a day. It is important to read food labels to avoid foods with sugar, honey, sucrose, dextrose, fructose, maltose, molasses or corn syrup listed as the first or second ingredient. Foods that should be avoided include: cakes, pies, cookies, ice cream, pastries, jelly, regular sweetened beverages, candy and fruit in syrup.

The diet should focus on high fiber, complex carbohydrates such as vegetables, beans, whole grain breads and cereals. Reaching and maintaining a healthy weight is also critical with controlling hyperglycemia.

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8.7. Rounding Following Dose Adjustments

Table 8.7.1.
CSA Dose Adjustments Based on CSA Level
Absolute Rounded Dose Changes
Corresponding to 1 mg/kg/day Increase or 1 mg/kg/day Decrease

Body Weight Range (Kg)	Absolute Change in Dose (mg)
10	10*
11	10*
12	10*
13	10*
14	10*
15	20*
16	20*
17	20*
18	20*
19	20*
20 – 37.9	25
38 – 62.9	50
63 – 87.9	75
88 – 112.9	100
113 – 137.9	125
138 – 162	150

* Participants under 20 kg assumed to be on liquid formulation.

For participants weighing more than 50 kg the CSA dose increases should not exceed 50 mg increments.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

Table 8.7.2.

Total Daily CSA
Dose Levels Table for Toxicity-Related Dose Modification
For Participants Taking Capsules

Initial Dose mg/day	67% of Initial Dose mg/day	33% of Initial Dose mg/day
50*	25.00	Discontinue
75*	50.00	25.00
100*	75.00	25.00
125	75.00	50.00
150	100.00	50.00
175	125.00	50.00
200	125.00	75.00
225	150.00	75.00
250	175.00	75.00
275	175.00	100.00
300	200.00	100.00
325	225.00	100.00
350	225.00	125.00
375	250.00	125.00
400	275.00	125.00
425	275.00	150.00
450	300.00	150.00
475	325.00	150.00
500	325.00	175.00
525	350.00	175.00
550	375.00	175.00
575	375.00	200.00
600	400.00	200.00
625	425.00	200.00
650	425.00	225.00
675	450.00	225.00
700	475.00	225.00
725	475.00	250.00
750	500.00	250.00
775	525.00	250.00
800	525.00	275.00

* Consider switching to liquid medication to achieve dose reductions when dose is below 50 mg/day.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.8. Allocation of FSGS-Study Drugs

At the time a participant is randomized, the DCC will send Drug Allocation Reports to Fisher BioServices, the Core Coordinating Center and the Participating Site designating quantity of medications to be sent to the Participating Site based on:

1. The participant's randomized treatment assignment
2. The Participating Site's designation of liquid vs. pill formulation, and
3. The participant's weight

A sample Drug Allocation Report is provided on the following page.

In normal circumstances, Fisher will ship the drugs by Federal Express the same day (for next day delivery) if they receive requests by 12 noon.

Fisher will always ship by the following business day for delivery no more than 2 days after receipt of the request.

The Participating Site will receive the participant's first shipment within 2 days of randomization.

There will be a total of 3 shipments for each participant who remains in the study and on study drug through the Week 72 visit:

1. At randomization to last until Week 32
2. After the primary outcome status of the Week 26 visit is determined, to last through the Week 52 visit
3. At Week 52, to last through Week 78 (lisinopril or losartan only)

The DCC will monitor the dose levels and expected supply of drug for each participant, and if the supply reaches a threshold level, will send extra Drug Allocation Reports to Fisher, the Core Coordinating Center and the Participating Site for extra shipments.

In rare instances, Participating Sites may need additional drug beyond that available at their site. In these cases, the participating site will notify the DCC (fsgs_dcc@bio.ri.ccf.org) with the amounts of the additional drug required. A Drug Allocation Report will be generated and Fisher will ship the required drug by the following business day.

Monitoring:

The Participating Sites will fax packing slips provided by Fisher to confirm receipt of medications.

Labeling:

All bottles (or blister packs) labeled with:

1. The commercial label for the product
2. A study label indicating that the drug is to be used only for the FSGS study
3. A participant-specific label indicating the participant's FSGS Study ID and Alpha-Code

**Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial
Drug Allocation Report**

Generated: 18-NOV-2004 09:30 AM

Participant ID: 123456
Alpha Code: JM
Site: 505 CHILDREN'S HOSPITAL SEATTLE
Principal Investigator: Sandra Watkins
Participant Weight at Baseline: 25.5 kg
Medication Type: Cyclosporine: Liquid
Lisinopril: Liquid
Prednisolone: Liquid
Drug Allocation Type: Supply for Months 0-6
Expected Receipt Date: 19-NOV-2004
Receipt Address: Wade Benton
Children's Hospital & Regional Medical Center;
Pharmacy
4800 Sand Pont Way NE, 3C-2
Seattle, WA 98105-0371

Quantities of Study Drug to be Received:

Cyclosporine:

11 bottles (50 ml/bottle) of 100 mg/ml liquid
(Lot 609H3629; MBS code CVFS30; expires 31-Oct-2006)

Lisinopril:

4 bottles (90 capsules/bottle) of 10 mg capsules
(Lot N3910; MBS code CVFS22; expires 30-Sep-2006)

Prednisolone:

3 bottles (237 ml/bottle) of 3 mg/ml liquid
(Lot RM0334; MBS code CVFS23; expires 30-Nov-2005)

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.9. Implementing and Monitoring Dose Adjustments

Initial Prescription at Randomization:

The central database will determine the participant's initial prescription based on the participant's weight and other information in the database at randomization (including; participant's preference for study medication formulation, any known allergies to study medications, and participant's randomization assignment). The DCC will electronically transmit an Initial Prescription Report to the CCC and the Participating Site. A sample Initial Prescription Report is provided in Section 8.10.1.

Changes in Prescriptions:

Changes in prescriptions may be required based on two sources:

1. Core Lab measurements -

The Core Lab will electronically transfer lab results to the DCC nightly. If these results lead to a dose change by the protocol, the DCC will send a note indicating that the dose of a study drug needs to be changed, and instruct the Participating Site to modify the dose in accordance with the FSGS-CT protocol. The Participating Site should contact its associated Core Coordinating Center if it has any questions regarding the appropriate dose modification.. Dose levels will not be modified in response to weight changes. The Participating Site indicates implementation of dose changes on the Medication Form (Form # 44).

2. Adverse Events (AEs) or Serious Adverse Events (SAEs) documented by the Participating Site -

If the participant develops an AE or SAE that necessitates a dose change based on the study's dose adjustment protocol (see Sections 8.4-8.5 of the MOP), the Participating Site should document the event leading to the dose change on the Adverse Event Form (Form # 60) or the Serious Adverse Event Form (Form # 61), and then record the dose change on the Medication Form (Form # 44). Note that in some cases persisting side effects that may not normally be classified as adverse events may lead to dose modifications. However, even in these cases, if the side effect leads to a dose modification, it should be documented as an adverse event so that the dose modification process can be monitored. The tables provided in Section 8.7 may be used as an aid in determining how to round dose levels in accordance with the available doses of study medications following when implementing dose adjustments.

Once the dose adjustment is documented in the database by Form 44 in conjunction with either Forms 60 or 61, the DCC will send a Site-Initiated Dose Adjustment Report to the Core Principal Investigator, who should review the appropriateness of the dose adjustment. A sample Site-Initiated Drug Dose Adjustment Report is provided in Section 8.10.3.

Informing Participants of Dose Modifications:

Prescriptions may be modified at or between participant visits. When prescriptions are modified between visits, it is expected that Participating Sites will notify participants by telephone of prescription changes. Postcards will be distributed to the Participating Sites to provide written

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

dosage information. These postcards can be mailed to the participants by the Participating Sites to confirm dose adjustments, which have been made by telephone.

Clinical Management Committee

The Clinical Management Committee will review questions and problems with the drug regimens and monitor data summaries of adherence to the study dose regimens on an ongoing basis. Any clinical management question(s) can be referred to the Clinical Management Committee through email: fsgs_clinquestions@bio.ri.ccf.org.

8.10. Sample Reports

8.10.1. FSGS Study Drug Initial Prescription Report

This report is transmitted at the time the participant is randomized, and describes the participant's initial prescription for the study drug. Information provided in this report includes:

Randomized Group: Designates the randomized treatment assignment (CSA or MMF/DEX) the participant was randomized to. Depending on the randomized groups, the initial prescription report will designate either the drugs for the CSA group: CSA, Prednisone, and either lisinopril or losartan, or the drugs for the MMF/DEX group: MMF, Dexamethasone, Prednisone, and either lisinopril or losartan.

Medication Type: Designates the type of formulation (capsules, tablets, or liquid preparation) for each study drug. This information is obtained by the database from the Baseline Visit Form (Form # 11).

Initial medication dose levels: Designates initial dose levels for each study drug corresponding to the participant's randomized group and body weight.

Notes: Notes at the bottom of the report will provide a reminder to perform upward titration in dose for the following drugs (provided they are included in the participants initial prescription): MMF, lisinopril, and losartan.

Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial

Initial Prescription Report

Generated: 22-NOV-2004 03:49 PM

Participant ID: 123456
Alpha Code: JM
Site: CHILDREN'S HOSPITAL SEATTLE

Weight at Baseline: 25.5 kg
Randomized Group: CSA
Medication Type: Cyclosporine: Liquid
Lisinopril: Liquid
Prednisolone: Liquid

Initial Medication Doses:

Cyclosporine:	140 mg/day	5.1 mg/kg/day
	Divided into two 70 mg doses	
Lisinopril:	2.5 mg/day	0.1 mg/kg/day
Prednisolone:	8.1 mg/every other day	0.3 mg/kg/every other day

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.10.2. FSGS Study Site-Initiated Drug Dose Adjustment Report

Page 1 of 2:

Randomized Group: Designates the treatment group (CSA or MMF/DEX) the participant was randomized to. Depending on the randomized groups, the initial prescription report will designate either the drugs for the CSA group: CSA, Prednisone, and either lisinopril or losartan, or the drugs for the MMF/DEX group: MMF, Dexamethasone, Prednisone, and either lisinopril or losartan.

Medication Type: Designates the type of formulation (capsules, tablets, or liquid preparation) for each study drug. This information is obtained by the database from the most recent New Study Medication Prescription and Dispensing information table in the Medication Form (Form # 44).

Prior medication dose levels: Indicates the participant's prior dose levels according to the New Study Medication Prescription and Dispensing information table in the latest Medication Form (Form # 44) entered prior to the event requiring the current dose change.

Dose Modification: Indicates dose modification implemented by the Participating Site on the Medication Form (Form # 44).

Page 2 of 2:

New medication dose levels: Summarizes new prescribed dose levels for all study drugs indicated in the New Study Medication Prescription and Dispensing information table in the Medication Form 44.

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

FSGS Study Site-Initiated Drug Dose Adjustment Report Page 1 of 2
Summary of Current Dose Levels Date of Report: 8/1/04
Visit W20

Participant ID #: 123456
Site: Winston-Salem Nephrology Associates

Participant Baseline Weight: 38 kg

Randomized Group: CSA

Medication Type: CSA: Capsule Prednisone: Tablet Lisinopril: Capsule

Prior **medication** dose levels (based on previous dose adjustment on 6/15/04):

CSA: 200 mg/day 5.3 mg/kg/day
 (Divided into 2 daily doses)

Prednisone: 10 mg/every other day 0.26 mg/kg/every other day

Lisinopril: 20 mg/day 0.52 mg/kg/day

Dose Modification:

CSA Dose reduced to 125 mg/day 3.3 mg/kg/day
(Divide into 75 mg and 50 mg doses)

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

FSGS Study Site-Initiated Drug Dose Adjustment Report
Summary of New Dose Levels

Page 2 of 2
Date of Report: 8/1/04
Visit W20

Participant ID #: 123456
Site: Winston-Salem Nephrology Associates

Participant Baseline Weight: 38 kg

Randomized Group: CSA

Medication Type: CSA: Capsule Prednisone: Tablet Lisinopril: Capsule

New **medication** dose levels (based on site-initiated dose adjustment on 8/1/04):

CSA:	125 mg/day (Divide into 75 mg and 50 mg doses)	3.3 mg/kg/day
Prednisone:	10 mg/dose	0.26 mg/kg/QOD
Lisinopril:	20 mg/dose	0.52 mg/kg/day

New dose status:

CSA:	Toxicity Dose Adjustment
Prednisone:	Maintenance
Lisinopril:	Maintenance

8. STUDY MEDICATIONS AND DOSAGE ADJUSTMENT PROTOCOLS

8.11. Local Distribution of Drugs

Drugs will be shipped to and distributed from each Participating Site following their own approved local procedures. The study allows drugs to be shipped to and distributed from a pharmacy or from the clinical offices of the Participating Site. Participating Sites should use their own approved local procedures to track receipt, distribution, return, and disposal of any study medications.

New drug should be given to a participant when the participant needs it, either because the participant is running out or because the old drug is no longer usable.

If a Participating Site is working with its local pharmacy, the Participating Site should notify the pharmacy when a participant has been randomized so the pharmacy will know that the drug will arrive in one or two business days.

The Participating Site will acknowledge receipt back to Fisher, using a form provided by Fisher and enclosed in the drug shipment box.

More information pertaining to drug distribution and the Central Pharmacy is provided in Section 12.

9. ADVERSE EVENTS AND DEVIATIONS FROM ASSIGNED RX

9.1. Serious Adverse Events

All serious adverse events (SAE) will be documented on the Serious Adverse Event Report Form (Form # 61). Form # 61 will request that the participating site note whether or not the SAE was related to the study medication.

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

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

If an SAE or unanticipated adverse effect occurs during the study or in a post-study period of reasonable duration, you are required to inform the PI of the CCC by telephone and an official at your local IRB within 2 business days (or within 72 hours if a weekend intervenes) of occurrence or knowledge of the event. 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.

After this initial notification, the Serious Adverse Event Report Form (Form # 61) should be completed and FAXed to the CCC. The PI at the CCC will report the SAE to the Steering Committee and the DCC, which will inform all participating sites of the occurrence. In addition, if it is necessary to inform officials from the NIDDK or FDA, the PI at the CCC will do this.

Telephone and FAX numbers and e-mail addresses for key personnel involved in the SAE notification process are listed in the FSGS Study Address Directory.

9.1.1. Other Adverse Events

These events will be recorded at each follow-up visit on the Adverse Event Report Form (Form # 60). These events will be reviewed by the Clinical Management Committee and summarized on an annual basis for the Data Safety Monitoring Board (DSMB).

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

9. ADVERSE EVENTS AND DEVIATIONS FROM ASSIGNED RX

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

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, MMF, or dexamethasone). Visits and data collection continue after medication 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 if at all possible. If possible, the participant will resume the intervention at a later time.

The Participating Site will complete a Study Medication Termination Form (Form # 45). The DCC and Clinical Management Committee reviewers will jointly complete a Study Medication Termination Confirmation Form.

General Stop Points:

1. Pregnancy
2. Decline in GFR: $\geq 50\%$ decline from baseline in estimated GFR to $\text{GFR} \leq 75 \text{ ml/min/1.73m}^2$
3. Maintenance dialysis
4. Study Medication related toxicity (see Section 8)

If any of these events occur, the Participating Site PI will complete the Study Medication Termination Form (Form #45) and return it to the CCC or enter the information into the database within 10 working days.

NOTE: If a study participant becomes pregnant during the course of the clinical trial, then she must be followed until the time of delivery (premature or full-term) to determine the outcome of the pregnancy and if there are any birth defects in the infant.

Measurements at the Time of a Stop Point

When the Clinical Management Committee Review has confirmed a Stop Point, extra measurements of serum creatinine, cyclosporine level, CBC, lipids, and Up/c will be obtained.

Follow-Up After Stop Point

If some or all study medications are stopped, but the primary and main secondary outcomes are not determined, then all study visits should be completed on schedule.

10. LABORATORY SECTION

The Core Lab for the FSGS-CT Study is Spectra East

Prior to the first individual participants' shipment of specimens (blood and/or urine) to Spectra (the Core Lab), a Form 10 (Preliminary Screening Form) must be entered into the Oracle database. A hard copy of page 1 of Form 10 must be included inside the shipping container (along with the appropriate Mailing Form). This step is for each first shipment (per participant) to Spectra.

HIV testing

Rhode Island state regulation of HIV testing only allows testing at the Rhode Island State Department of Health. For Participating Sites in Rhode Island, the HIV sample must be sent to the Rhode Island Department of Health and the results should be sent to the DCC on Form # 77.

For participants in the state of New York, Spectra must have the LAB CORP HIV requisition in order to send the sample for testing. A LAB CORP HIV Requisition form is located on the FSGS-CT web site under Study Documents → MOP.

10. LABORATORY SECTION

10.1. Lab Ranges

Laboratory results will be forwarded electronically to the DCC and a hard copy will be faxed to the PI at the Participating Site. The results should be reviewed for accuracy and abnormal values should be acknowledged. The following Table summarizes the reference range, alert value, and panic value for each of the tests that will be performed by the Core Lab.

T.C.	TEST NAME	REF RANGE		UNITS	ALERT	PANIC
115	Albumin	3.8 - 5.2		g/dL	<3.5 >8.0	<1.0
109	Alkaline Phosphatase	35 - 104	>17 yrs F	U/L	>700	>1000
		40 - 129	>17 yrs M	U/L	>700	>1000
111	ALT/GPT	7 - 52		U/L	>75	**
110	AST/GOT	13 - 39		U/L	>75	**
106	Bicarbonate	22 - 29		mEq/L	**	<12 >40
107	Calcium, Total	8.4 -10.2		mg/dL	>11.0	<6.0 >12.0
105	Chloride	96 - 108		mEq/L	**	<85 >120
116	Glucose, Serum	70 - 105		mg/dL	>250	<50 >500
301	Hepatitis B surface Antigen	Negative		**		1st time Positive
200D	HCT	37.0 - 47.0	F	%	<24	<18 >52
		42.0 - 52.0	M	%	<24	<18 >52
200C	HGB	12.0 - 16.0	F	g/dL	**	<8.0 >18.0
		14.0 - 18.0	M	g/dL	**	<8.0 >18.0
108	Phosphorus	2.6 - 4.5		mg/dL	>6.0	< 2.0 >12.0
201	Platelets	130 - 400		1000/mcL	<130 >500	<50 >1000
103	Potassium, Serum	3.3 - 5.1		mEq/L	<3.2 >6.3	<3.0 >6.5
104	Sodium	133 - 145		mEq/L	**	<120 >150
117	Uric Acid	2.4 - 5.7	F	mg/dL	**	<2.0 >15.0
204	WBC	4.80 - 10.80		1000/mcL	**	<2.00 >20.00
216A	Absolute Neutrophils	1.9 – 8.0		1000 cells/mcL		<1.0
425	Cyclosporine	100 - 250		ng/mL		>400

10.2. Characteristics of Blood and Urine Collections

For those participants who consent to provide biological samples for the biorepositories, urine, serum, and plasma specimens will be shipped to the NIDDK Biosample Repository at Fisher Clinical Services 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. Refer to Section 13 of the MOP for Repository details.

10. LABORATORY SECTION












<u>Visit Number</u>	<u>Week</u>	<u>Type of Kit</u>	<u>Tubes Filled</u>		<u>Total Blood Volume</u>		<u>Number of Urine Samples</u>
			<u>MMF Arm</u>	<u>CSA Arm</u>	<u>MMF Arm</u>	<u>CSA Arm</u>	
B1	- 1 or - 2	Screening	1 - 8.5 mL SST 1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 8.5 mL SST 1 - 3.5 mL SST 1 - 2 mL Lav. Top	14 mL	14 mL	2
W0	0	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1
W2	2	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W4	4	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W6	6	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W8	8	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W14	14	Visit	1 3.5 mL SST 1 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W20	20	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	1
W26	26	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	2
W32	32	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1
W38	38	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	1
W44	44	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1
W52	52	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	5.5 mL	7.5 mL	2
W65	65	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	5.5 mL	3.5 mL	1
W78	78	Visit	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 1 - 2 mL Lav. Top	5.5 mL	5.5 mL	2

10. LABORATORY SECTION

Note:

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

Labels are tube specific

SST GEL PT.  13000000Q	REQUISITION PT.  000000Q
GOLD POST PT.  23000000Q	LAVENDER PT.  12000000Q
URINE CHEMISTRIES PT.  54000000Q	LIGHT BLUE / COAG PT.  15000000Q
URINALYSIS PT.  36000000Q	MISCELLANEOUS PT.  11000000Q
MISCELLANEOUS PT.  11000000Q	MISCELLANEOUS PT.  11000000Q
000000Q SITE USE ONLY	000000Q SITE USE ONLY
000000Q SITE USE ONLY	000000Q SITE USE ONLY
Urine Vol.: _____	Pt. Ht.: _____
Total Hrs.: _____	Pt. Wt.: _____
PLEASE USE PATIENT DATA STICKERS ABOVE! Catalog No. 88-3331-6 (6/08)  spectra clinical research Rockleigh, NJ 07647	

This barcode label is for the requisition form only

10.2.1. Supplies

Supplies for the FSGS Clinical Trial will be provided by Spectra East. Start up supplies will be sent to your site prior to the start of your site in this clinical trial. Visit specific study kits will be labeled **FSGS B1 KIT** for Baseline visit and **FSGS VISIT KIT** for all subsequent visits. An FSGS Shipping Kit, and an individual urine collection kit will also be available should additional testing be necessary. Should you need additional supplies at any point during this clinical trial please call the Spectra East Customer Service Representative. See Section 10.4. for the FSGS

10. LABORATORY SECTION

Study Supply Order Form. Contact information for Spectra can be found in the FSGS-CT Address Directory.

After each visit make sure that your Participating Site has lab supplies needed for the participant's next visit for specimen collection for the Core Lab and, if applicable, for the Repository. Double check the expiration dates on the shipment containers.

10.2.2. Description of Blood and Urine Sample Kits

The Core Lab will provide all the following sample kits.

- A. Blood Sample Kit for Screening Visit
 - 1 – 8.5 mL Serum separator tube (SST)
 - 1 – 3.5 mL SST
 - 1 – 2 mL lavender top tube
 - 2 – Urine Collection kits
- B. Blood Sample Kit for All Follow-up Visits
 - 1 – 3.5 mL SST
 - 2 – 2 mL lavender top tubes
 - 1 – Urine Collection kit

Extra Urine Collection Kits required at visits W26, W52, and W78 will be provided separately.

All kits contain 23G butterfly needles, mailing labels, barcode stickers and shipping supplies.

Barcode labels are provided for each specimen collection. Each sheet of barcodes has a unique barcode number with corresponding accession numbers. Use a different sheet for each specimen to be shipped to Spectra - one barcode sheet for Blood/Serum, one barcode sheet for first urine specimen, one (different from first urine) barcode sheet for second urine specimen at visits B1, W26, and W78. See “Note” on page 4 for instructions on barcode use.

When key entering a bar code for a serum or urine mailing form into the database, you should expect to enter digits, not alphabet characters. Bar codes will begin with a letter (typically Q) followed by a series of numbers. The Core Lab has indicated that the letter "o" and "i" will never appear, so assume characters that look like an O or and I are zero and one.

1. Affix the barcode label to the Blood and Serum Mailing Form (Form #83). Affix the corresponding accession numbered labels to each test tube. *See “Note” on page 4 for instructions on barcode use.*
2. Affix the barcode label to the Urine Mailing Form (Form # 80) of the first urine specimen. Affix the corresponding accession numbered label to the Spectra provided urine tube. *See “Note” on page 4 for instructions on barcode use.*
3. For the B1, W26, W52, and W78 visits, using a different sheet of barcode labels, affix the barcode label to the Urine Mailing Form (Form # 80) of the second urine specimen.

10. LABORATORY SECTION

Affix the corresponding accession numbered label to the Spectra provided urine tube.
See “Note” on page 4 for instructions on barcode use.

DO NOT reuse barcode labels. Throw unused accession numbered labels out.

The Core Lab operates on Tuesday through Saturday. Therefore, specimens may be shipped from Monday through Friday. Because samples shipped on Friday may occasionally arrive in the Core Lab on Monday due to shipping problems, it is advised that samples not be mailed out on Friday. However, if it is necessary to ship samples on Friday make certain to attach several Saturday labels on the air bill and the sample box.

ALL SHIPPING COSTS INCURRED IN THE STUDY WILL BE COVERED BY THE DCC AND THE CORE LAB. THESE EXPENSES WILL NOT BE CHARGED TO THE CCC OR THE PARTICIPATING SITE.

10.2.3. Blood Collection, Processing and LifePak™ Packaging Procedure

 **Freeze ice packs the day before Blood Draw**

Prior to Blood Draw

1. Call FedEx to schedule a pickup.
2. Complete Blood and Serum Mailing Form (Form # 83) and/or the Urine Mailing Form (Form # 80) for each participant. At B1, W26, W52, and W78 two urine collections should be shipped to Spectra. Both urine samples will need individual Urine Mailing Forms (Form # 80).
3. Using barcode sheet provided in the sample collection kit for the Blood/Serum:
 - a. Affix the barcode label to the Blood and Serum Mailing Form (Form #83).
 - b. Affix the corresponding accession numbered labels to each test tube.

DO NOT reuse barcode labels. Throw unused accession numbered labels out.

Blood Drawing

Blood should be drawn using a 23G needle and tubing supplied in the blood sampling kit. All serum separator tubes (SST) of blood should be filled to the top. Lavender top tubes should be allowed to fill as much as the vacuum permits. Do not overfill the lavender top tubes.

10. LABORATORY SECTION

10.2.4. Collection Procedure for Whole Blood Specimens

1. Using venipuncture, collect specimen in the appropriate tube, namely the lavender top tubes. For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above “Exp” in the lower right corner of the BD label is equal to or later than the current month.
2. Allow tubes to fill completely to ensure proper mix of anticoagulant to blood. Tubes are vacuum tubes and will fill to the correct amount once tube top is punctured.
3. Invert tube 5-10 times gently, to mix.
4. Label tube with corresponding bar coded accession label.
5. Refrigerate specimen in LifePak™ tray.

10.2.5. Collection Procedures for Serum Specimens

1. Using venipuncture, collect specimen in the Serum Separator tube (SST). For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above “Exp” in the lower right corner of the BD label is equal to or later than the current month.
2. Fill tube(s) completely. Tubes are vacuum tubes and will fill to the correct amount, once the tube top is punctured.
3. Invert tube 5-10 times gently to mix.
4. Stand tubes upright to allow the specimens to clot at room temperature for 20 to 30 minutes, but no longer than 60 minutes.
5. Centrifuge SST (within 60 minutes of collection) for at least 15 minutes at 3000rpm, to separate the cells from the serum.
6. Refrigerate specimen in LifePak™ tray until shipped.

Blood samples for hematology (CBC) must be received within 48 hours of collection. Serum samples for chemistry tests (electrolytes, etc.) must be received within 72 hours of collection.

As explained above, tubes should be labeled with the barcode stickers provided in the sample collection kit. One label should be placed on the Blood and Serum Mailing Form (Form # 83) and matching labels (accession numbered labels) should be placed on all sample tubes that will be shipped.

NEVER REUSE THE BARCODE SLIPS

The barcode sticker should be placed lengthwise along the tube to enable reading of the code by the apparatus at the Core Lab.

Packaging

1. Pack specimen tray into the small poly bag. Place the poly bag into the LAB LOC BAG.
2. Place completed forms in back flap of LAB LOC BAG, place in box.
3. See Packaging and Transport of Specimens for detailed instructions (Section 10.2.7.).

10. LABORATORY SECTION

GOOD SAMPLE PREPARATION MEANS ACCURATE RESULTS USE THE INSIST METHOD



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



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

10. LABORATORY SECTION



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



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

10. LABORATORY SECTION

10.2.6. Collection procedure for Urine Sample

Urine sampling

Any clean container can be used to collect urine at home. The sample should be transferred to the urine tube provided by Spectra. If the urine collection container provided by Spectra is used for collection of urine samples at home, then the urine should be transferred to the urine tube by peeling the label from the top inserting the tube into the slot and allowing the urine to enter the tube by suction. **It is necessary to provide a minimum of 1 mL of urine for each specimen to insure accurate results.**

1. Give the urine container to the participant with instructions for collecting a first morning void. If the participant will be returning with 2 urine samples, ask them to mark the body of the containers (not the tops) in a way that allows you to distinguish the 2 samples. Refrigerate urine specimens until they are brought to the study visit.
2. When the participant returns to the clinic with the urine container, remove yellow label.
3. Invert tube over cannula.
4. Press down on tube to puncture rubber stopper.
5. Allow to fill.
6. For B1, W26, W52, and W78 two Urine collections are required. Barcode labels are provided for each specimen collection. Each sheet of barcodes has a unique barcode number with corresponding accession numbers. Use a different sheet for each specimen to be shipped to Spectra. One barcode sheet for the first urine specimen, one (different from first Urine) barcode sheet for the second urine specimen.
 - a. Affix the barcode label to the Urine Mailing Form (Form # 80) of the first urine specimen. Affix the corresponding accession numbered label to the Spectra provided urine tube.
 - c. For B1, W26, W52, and W78 using a different sheet of barcode labels, affix the barcode label to the Urine Mailing Form (Form # 80) of the second urine specimen. Affix the corresponding accession numbered label to the Spectra provided urine tube.

DO NOT reuse barcode labels. Throw unused accession numbered labels out.

7. Place tube in LifePak™ tray.
8. Send only the tube to Spectra. **DO NOT SEND URINE CUP.**
9. Discard urine cup appropriately.

Urine specimens may be received up to ten days from collection but must have been stored under refrigeration after collection.



Freeze ice packs the day before shipping blood to Spectra East

10. LABORATORY SECTION

10.2.7. Packaging and Transport of Specimens

When ready to ship specimens call Federal Express to schedule a pickup

1. Place tubes in specimen trays.
2. Place the tray(s) in the plastic, poly bag provided.
3. Place the poly bag in the LAB-LOC SPECIMEN BAG, seal bag.
4. Place appropriate mailing form(s) in back flap of the specimen bag.
5. Place LAB-LOC specimen bag in box, making sure forms are in the bag.
6. Fold box divider over and place ice pack in box.
7. Before closing the box, review checklist that was included in kit (refer to sample checklist below) to make sure all items are accounted for.
8. Close the box and seal with tape.
9. Affix an airbill pouch to the box.
10. Complete the airbill and insert in the pouch. A total weight of 2 lbs should be marked in the appropriate box on the airbill.
11. If a Friday shipment for Saturday delivery, attach Saturday label appropriately.

10. LABORATORY SECTION

10.2.8. Checklist Sample (Before You Close This Box)

**THIS IS A SAMPLE OF THE CHECKLIST THAT WILL BE INCLUDED
IN EACH SHIPPING KIT SHIPPED AS OF 22/JUL/05**

BEFORE YOU CLOSE THIS BOX

REVIEW

- Review Section 10 of the Manual of Operations

BARCODES

- One sheet of barcodes per Mailing Form (note: 2 urine samples require 2 separate Form 80 Urine Mailing Forms; each Form 80 and its urine specimen requires a separate sheet of barcodes). Discard unused barcodes

FORMS

- Make sure the Mailing Forms (80 and 83) are completed properly
- Make photocopy of Mailing Forms to retain at site. Place original forms with affixed barcode into outer pocket of LAB-LOC bag
- *Baseline Visit only** – also place copy of Form #10 (Page 1 only) into outer pocket of LAB-LOC bag

SHIPPING

- If shipping FRIDAY:
 - Check SATURDAY Delivery
 - Affix Saturday Delivery sticker to top of box

10. LABORATORY SECTION

10.3. General Information

10.3.1. Reference Ranges

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

10.3.2. Alert/Panic Values

Alert and Panic values are meant to flag important deviations from the normal range. These values appear on the Alert and Panic Report.

Panic values require immediate attention and are returned to the site via fax as soon as they are available in the laboratory. A follow-up telephone call is made to confirm receipt of the fax during business hours, namely 7 AM to 10 PM, Eastern Standard Time.

10.3.3. Reports

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

- Cover page
- Alert/Panic Report
- Participant report(s)
- Report Summary

10.3.4. Turn-Around-Time

Routine chemistry and hematology tests are performed within 24 hours of Spectra's receipt of a specimen. Serology results (HCV, Hep B) may be delayed for necessary repeats. HIV tests will have a turn-around-time of 7-10 days. The HIV results will be sent via Express mail to the PI at the Participating Site. HIV results may be faxed from Spectra to the Participating Site.

Rhode Island state regulation of HIV testing only allows testing at the Rhode Island State Department of Health. For Participating Sites in Rhode Island, the HIV sample must be sent to the Rhode Island Department of Health and the results should be sent to the DCC on Form # 77.

For participants in all other states, HIV testing will be performed at Spectra. The results will be faxed directly to the PI at the participating sites.

10. LABORATORY SECTION

10.3.5. Test Repeats and Cancellation

If a specimen is hemolyzed and the potassium value would lead to a dose modification, the blood collection should be repeated and a new specimen sent to Spectra.

Tests will be cancelled by Spectra when specimens are received in a condition that does not allow accurate testing in the same timeframe as reporting the results, which is within one business day. Reasons for test cancellations will include the following:

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

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

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

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

10.3.6. Tubes to be Used for Repeat Testing

1. If a cyclosporine (CSA) level or a CBC needs to be repeated, then the blood sample should be drawn into a lavender top tube.
2. If a serum potassium or creatinine concentration needs to be repeated, then the blood sample should be drawn in a small SST.
3. If a urine for protein:creatinine (Up/c) ratio needs to be repeated, use the urine collection kit but send only a single tube of urine (do not send the urine cup).

10.3.7. Ordering Extra Tubes or Kits

If repeat tests are necessary, the Site Investigator should use tubes and supplies from kits already available at the Site. Note that the smallest tube in the kit is for HIV sample only. If additional supplies are needed to handle repeat testing, then the Site Investigator should contact Spectra to request a shipment of the required number of tubes or replacement mailing boxes. See Section 10.4. for the supply order form.

10. LABORATORY SECTION

10.4. FSGS Study Supply Order Form

FSGS STUDY SUPPLY ORDER

STUDY COORDINATOR _____

SITE # _____

DATE: _____

PHONE: _____

ITEM	UNITS		QUANTITY
FSGS SCREENING KIT	EA		
FSGS VISIT KIT	EA		
FISHER REPOSITORY KIT	EA		
23G BUTTERFLY NEEDLES	EA		
LAV TOP TUBES (5tubes)	5tubes		
3.5ml SST (TIGER TOP TUBE) (5 tubes)	5tubes		
8.5ml SST (TIGER TOP TUBE) (5 tubes)	5tubes		
URINE COLLECTION KIT	each		
FSGS SHIPPING BOX	each		
STUDY BARCODES	each		

PLEASE FAX SUPPLY ORDER TO:
KELLY CONNELL @ 201-767-7358

PLEASE ALLOW 10 BUSINESS DAYS FOR DELIVERY

11. PATHOLOGY SECTION

In order to confirm participant eligibility for the trial, a pathologist at the CCC will review the renal biopsy performed at the Participating Site.

Renal biopsy

The following materials should be sent to the Core Pathologist:

1. Representative light microscopy slides containing a minimum of 1 glomerulus demonstrating segmental sclerosis on light microscopy will be required to confirm the diagnosis. A minimum of one slide showing the FSGS lesion is required. If available, a full set of slides should be sent that includes:
 - a. 1 Hematoxylin & eosin (H&E) slide
 - b. 1 Periodic acid-Schiff (PAS) slide
 - c. 1 Silver stain slide
 - d. 1 unstained slide
2. A copy of the immunofluorescence and electron microscopy reports (describing the staining pattern and appearance of at least 1 glomerulus)
3. Representative photomicrographs (1-5 per participant) of the electron microscopy containing at least 1 glomerulus and demonstrating the FSGS lesion)

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

All study materials should be addressed to the Core Pathologist. The mailing label should clearly identify the sample as FSGS-CT biopsy material.

The shipping addresses for the five Core Pathologists are listed in the Address Directory.

The Core Pathologist will review all biopsy specimens within 2 business days of receipt. The review will be communicated to the local site pathologist. Reports of the Core Pathologist review will be completed and returned to the Participating Site's PI, Study Coordinator, and the CCC.

12. CENTRAL PHARMACY

The Central Pharmacy (aka Drug Distribution Center) for the FSGS-CT is Fisher Clinical Services. The contact information for the Central Pharmacy is listed in the Address Directory. The Distribution Project Manager for the FSGS-CT Study, Dave Zimmerman, can be contacted by e-mail at david.zimmerman@fishersci.com. Any questions pertaining to a study drug shipment can be made through the Fisher helpdesk at 610-871-0150.

The drug formulations, which are provided by the Central Pharmacy, are described in Table 8.1 of Section 8.

List of medications provided through the Central Pharmacy:

- Prednisone
- Dexamethasone
- Mycophenolate mofetil
- Cyclosporine
- Lisinopril
- Losartan
- Flavorex™

All study drug received from the Central Pharmacy will be commercially labeled. On each commercially labeled package there will be an auxiliary label linking the package to the FSGS Study. Each auxiliary study label will contain the hand written Participant Number the drug was requested for.

Local Distribution of Drugs

Drugs will be shipped to and distributed from each Participating Site following their own approved local procedures. The study allows drugs to be shipped to and distributed from a pharmacy or from the clinical offices of the Participating Site. Participating Sites should use their own approved local procedures to track receipt, distribution, return, and disposal of any study medications.

New drug should be given to a participant when the participant needs it, either because the participant is running out or because the old drug is no longer usable.

If a Participating Site is working with its local pharmacy, the Participating Site should notify the pharmacy when a participant has been randomized so the pharmacy will know that the drug will arrive in one or two business days.

The Participating Site will acknowledge receipt back to Fisher, using a form provided by Fisher and enclosed in the drug shipment box.

Shipment requests

At the time a participant is randomized, the DCC will send a Drug Allocation Report to Fisher Clinical Services, the Core Coordinating Center and the Participating Site designating quantity of medications to be sent to the Participating Site based on:

1. The participant's randomized treatment assignment
2. The Participating Site's designation of liquid vs. pill formulation, and

12. CENTRAL PHARMACY

3. The participant's weight

In normal circumstances, Fisher will ship the drugs by Federal Express, the Drug Allocation Report received on day one, drug requested filled and shipped on day two for expected receipt on day three.

The Participating Site will receive the participant's first shipment within 3 days of randomization.

There will be a total of 3 shipments for each participant who remains in the study and on study drug through the Week 72 visit:

1. At randomization to last until Week 26
2. After the primary outcome status of the Week 26 visit is determined, to last through the Week 52 visit
3. At Week 52, to last through Week 78 (lisinopril or losartan only)

The DCC will monitor the dose levels and expected supply of drug for each participant, and if the supply reaches a threshold level, will send a extra Drug Allocation Report to Fisher, the Core Coordinating Center and the Participating Site for an extra shipment.

In rare instances, Participating Sites may need additional drug beyond that available at their site. In these cases, the Participating Site will notify the Data Coordinating Center by e-mail (fsgs_dcc@bio.ri.ccf.org) with the amounts of the additional drug required. The DCC will prepare an additional Drug Allocation Report and e-mail it to Fisher, the Participating Site, and the Core Coordinating Center. A shipment request should contain the drug requirement for only one participant (in the e-mail request in addition to specifying the study medication, reference the PID # and alphacode). Shipments of Study Drug will include a packing slip and receipt confirmation form. The receipt confirmation form should be completed by the Participating Site and faxed to Fisher Clinical Services shipping department (610 871-8590).

Drug Returns

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

Study Drug shipped by Fisher Clinical Services can be returned to Fisher by completing a Product Return Form (see below) and including it with the shipment of Study Drug to:

Cleveland Clinic (FSGS-CT)
C/O Fisher Clinical Services
6575 Snowdrift Road
Allentown, PA 18106
Attn: Fisher Return Drug

12. CENTRAL PHARMACY

The following information is required on each Product Return Form (below).

Participating Site #

Participating Site Name

Participating Site Address

PI's Name

Product Name

Product Strength and Dosage Form

Product Lot #

Product Quantity

Contact Name and Phone Number

12. CENTRAL PHARMACY

CLEVELAND CLINIC (FSGS) - PRODUCT RETURN FORM

RETURN ONLY PRODUCTS SUPPLIED BY FISHER. THE PRODUCTS LISTED BELOW WERE RETURNED BY:

Site Number: _____

Site Name _____

Address: _____

Protocol/Study Number: _____

Investigator: _____

INSTRUCTIONS FOR INVESTIGATOR

1. Type or print clearly all information – one item per line. Fill in all sections.
2. DO NOT mark in the shaded areas.
3. Sign and date list.
4. Pack the products well to minimize breakage and leakage.
5. Enclose the completed list with the products and return to:
Cleveland Clinic - FSGS
c/o Fisher Clinical Services
6575 Snowdrift Road
Allentown, PA 18106
Attn: Fisher Return Drug

<i>Product Name</i>	Strength & Dosage Form	Lot # / I.D.#	Unused Quantity (Specify unit)	Used Quantity (Specify Unit)	FOR FISHER USE ONLY	
					Project:	
					Was this form initiated by Fisher	Yes or No
					Fisher Stock Code	Receipt Date:
						Shipped via:
						Rec'd (circle one)
						RT FB CB DI
						Inspected by/ Date:

To be completed by site (Individual preparing this list)

Name: _____

Title: _____

Signature/ Date: _____

Telephone Number: _____

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13. REPOSITORIES

13.1. Background

Participants who are enrolled in the FSGS-CT will be invited to volunteer to provide biological samples to be stored for use in future studies of the pathobiology of FSGS. A separate materials informed consent will be required (note: NIH approval is required for Repository Consents before specimens can be taken out of the Repository). A template materials consent form is provided at the end of this Section. 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 Fisher 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.

Contact information for both repositories can be found in the FSGS Address Directory.

13.2. Volumes of Samples

The amounts of blood to be drawn for storage in the repositories depends on the participant's age, and is summarized in the following table:

Volume of Blood Samples Collected for NIH Repositories

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

Type of Blood Sample	Study Visits Sample Collected	Age (Years)		
		Age 2 - 6	Age 7-12	Age ≥ 13
Whole blood for DNA (mL)	Week 0	7	10.5	17
Serum (mL)	Weeks 0, 26, 52, and 78	4	8	16
Plasma (mL)	Weeks 0, 26, 52, and 78	4.5	9	18
Total amount of blood required for repositories (mL)	Week 0	15.5	27.5	51
	Weeks 26, 52, and 78	8.5	17	34
Maximum total amount of blood required for both repositories and main FSGS trial (mL)	Week 0	21.0	33.0	56.5
	Weeks 26, 52, and 78	16.0	24.5	41.5

13. REPOSITORIES

13.3. Logistics for Biosample Repositories

The two biorepositories will provide sample collection kits including the necessary blood collection tubes, urine collection containers, packing and shipping materials, and Federal Express labels for collection and shipping of the samples. The sample collection kits provided by Rutgers will be shipped directly to the Participating Sites. Where as, the sample collection kits provided by Fisher will be provided first to the FSGS Core Lab (Spectra East), which will be responsible for shipping the kits to the Participating Sites. The tube labels to be used with all repository specimens will be supplied to the Participating Sites by the DCC. The tube labels will include pre-printed 9-digit identification numbers, in which the first 3 digits designate the NIDDK Repository Site Identification code and the final 6 digits designate the participant's FSGS Participant ID. The labels will also include two spaces in which the Participating Site should mark the participant's FSGS alpha code, which will be used as an alternative ID by the Biosample Repositories.

For consenting participants age 13 or greater, at the Study Week 0 visit Participating Sites will fill four 4 mL (SST) tubes, followed by four 4.5 mL plasma separator (PST) tubes, and then two 8.5 mL yellow top (ACD) tubes. Note that the 10 tubes for the repositories should be filled after first filling one or two tubes (depending on the participants randomized treatment arm) required by the Core Lab for the clinical trial protocol, so that a total of either 11 or 12 blood tubes will be filled at the Week 0 visit. The Participating Sites should also obtain a urine specimen (10 to 90 mL) to be shipped in the 90 mL urine collection containers provided by the Fisher Biosample Repository. The urine specimen is collected fresh during the participant's visit and should not be confused with the separate first morning urine collection which is obtained for the Core Lab.

The ACD tubes are filled only at the Week 0 visit; the remaining repository samples (e.g., four 4 mL SST tubes, four 4.5 mL PST tubes, and the urine collection container) are obtained again at the study visits at weeks 26, 52, and 78.

For participants age 7 to 12, Participating Sites will fill two 4 mL SST tubes and two 4.5 mL PST tube at study weeks 0, 26, 52, and 78, plus three 3.5 mL ACD tubes at study week 0. For participants age 6 or less, the Participating Sites will fill one 4 mL SST tube and one 4.5 mL PST tube at study weeks 0, 26, 52, and 78, plus two 3.5 mL ACD tubes at study week 0. This information is provided in tabular form in the table on the following page.

The serum (SST tubes), plasma (PST tubes), and urine containers should be shipped refrigerated to Fisher using the shipping kits and packing materials provided by the Fisher Biorepository. After adding the participant's alpha code, the tube labels provided by the DCC should be placed on each tube prior to shipment. A completed paper copy of the Biological Specimen Repository Mailing Form (Form # 95) should be included in the kit shipped to Fisher. The information on the form must also be entered in the database. On arrival, Fisher will divide the serum, plasma and urine into aliquots (5 mL aliquots for urine, and twenty 0.2 mL aliquots for the first 4 mL of both serum and plasma, and 0.5 mL aliquots for the remainder) and then freeze the aliquots for storage.

The ADT tubes should be shipped at ambient temperature to the Rutgers Cell and DNA Repository using the provided shipping kits and packing materials. After adding the participant's alpha code, the tube labels provided by the DCC should be placed on each tube prior to

13. REPOSITORIES

shipment. A completed paper copy of the (DNA) NIDDK Genetics Initiative Phlebotomy Mailing Form (Form # 96) should be included in the kit shipped to the Rutgers Cell and DNA Repository (Rutgers). The information on the form must also be entered in the database. The repository will immortalize cells from the blood samples on arrival. DNA will be harvested after approximately 60 days from approximately 50% of the cells. The remaining cells will be frozen for future use. The DNA will be stored in 1-microgram aliquots.

Although the kits for the Fisher repository specimens will be provided by Fisher, for logistical purposes the kits will be distributed to the Participating Sites by the Core Lab (Spectra East) along with the standard kits for the blood and urine specimens required by the study protocol. Rutgers will be sending Participating Sites their specimen supply kits directly. After the initial baseline Preliminary Screening Form (Form # 10) is entered into the database, Spectra and Rutgers both receives an electronic Enrollment Report (a report specifying how many Preliminary Screening Forms - # 10 were entered that day) from the DCC. Upon receipt of the Enrollment Report(s) Spectra and Rutgers will send the repository kit(s) required for the W0 visit to the Participating Site by Federal Express. Each kit from the Fisher repository will contain four 4 mL SST tubes and four 4.5 mL PST tubes. The Participating Site personnel should fill the required number of these tubes based on the participant's age in accordance with the table below and may return the remaining tubes with the shipment to the repository. Two types of kits will be used for the Rutgers repository: for participants age 12 and under, the kit will contain three 3.5 mL ACD tubes, while for participants age 13 or greater the kit will contain two 8.5 mL ACD tubes. As described in the table and its footnotes, two of the 3.5 mL tubes should be filled for participants age 6 years or less, all three of the 3.5 mL tubes should be filled for participants age 7 – 12. Both 8.5 mL tubes should be filled for participants age 13 years or greater.

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FSGS Trial and Repository Samples at Study Weeks 0, 26, 52, and 78*

<u>Study Week</u>	<u>Destination</u>	<u>Tubes Filled</u>		<u># of Urine Samples</u>
		<u>MMF Arm</u>	<u>CSA Arm</u>	
0	Spectra (for Clinical Trial Protocol)	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST	1
	Fisher Biosample Repository*	4 - 4 mL SST 4 - 4.5 mL PST	4 - 4 mL SST 4 - 4.5 mL PST	1
	Rutgers Cell and DNA Repository*	2 - 8.5 mL ACD	2 - 8.5 mL ACD	none
26, 52, and 78	Spectra (for Clinical Trial Protocol)	1 - 3.5 mL SST 1 - 2 mL Lav. Top	1 - 3.5 mL SST 2 - 2 mL Lav. Top	2
	Fisher Biosample Repository*	4 - 4 mL SST 4 - 4.5 mL PST	4 - 4 mL SST 4 - 4.5 mL PST	1
	Rutgers Cell and DNA Repository*	none	none	none

* Indicated are quantities for participants age 13 years or greater.

For participants age 7-12 years, repository amounts are as follows:

Fisher: 2 – 4.0 mL SST tubes, 2 – 4.5 mL PST tubes;

Rutgers: 3 - 3.5 mL ACD tubes.

For participants age 6 years or less, repository amounts are as follows:

Fisher: 1 – 4.0 mL SST tubes, 1 – 4.5 mL PST tubes;

Rutgers: 2 - 3.5 mL ACD tubes.

Note: Always collect the specimens required by the FSGS-CT protocol first, and then collect the specimens for the repositories.

13. REPOSITORIES

13.4. Fisher Biosample Repository Procedure Instructions

1. Complete and attach the participant I.D. labels provided by the DCC to the blood tubes and the urine container. Use the labels provided and place them lengthwise on the tubes. Be careful not to cover up the ID when they are wrapped around the tubes. DO NOT write the participant's name or any other personal identification information (e.g. SS#, DOB) on the tubes.
2. For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above "Exp" in the lower right corner of the BD label is equal to or later than the current month.
3. Collect the specimen in the appropriate container.
4. Follow the appropriate order of draw for blood collection in accordance with the FSGS protocol. Specifically, collect the blood specimen in the SST serum separator (gold top) tube after obtaining the blood specimens for the trial protocol (to be shipped to Spectra) and before the draw for the PST tubes.
5. After filling, invert each SST tube gently at least 5 times and the PST tube 8-10 times to mix the blood with the additives. Let the SST tubes stand in a rack at room temperature for at least 30 minutes or until the blood is separated, but not longer than 60 minutes prior to centrifuging (the PST tubes can be centrifuged immediately). Centrifuge the PST and SST tubes for at least 10 minutes at 1300 g. (Blood containing anti-coagulants such as heparin or warfarin may take longer to clot in SSTs.) Then move the tubes to the refrigerator until the shipper is ready to go.
6. For urine collection, after the container is filled according to the laboratory procedure, tighten the cap on the container. Move the container to a refrigerator until the shipper is ready to go.
7. Double check the subject ID, and verify that ID information on the container matches that on the NIDDK Specimen Shipment Form # 95.
8. Date and identify person completing the NIDDK Biological Specimen Repository Mailing Form (Form # 95). Make a copy of each form; keep the copy and send the original with the shipment.
9. Prepare shipments for FedEx pickup on Monday through Thursday. *No Friday shipments, please.* The facility is not scheduled to be open on Saturday and Sunday when the package would be delivered. If there must be an exception, please coordinate with the Biosample Repository (see Section 13.6) before close of business on Thursday.
10. Assemble the package according to the instructions for the refrigerated shipment.
11. Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number (in Section 7 - Payment) of the pre-printed FedEx Air bill, and your pickup address. FedEx will dispatch a courier to pick up the package.

13. REPOSITORIES

12. Notify Rich Frome or Heather Higgins at the NIDDK Biosample Repository by email or fax when you have scheduled the pickup and provide them the Federal Express tracking number(s). Use the contact information in the FSGS Address Directory.

Assembling the FSGS Refrigerated Laboratory Shipper

1. Insert each type of Vacutainer into a separate bubble wrap pouch. Verify that the lid on the urine container is secured tightly.
2. Place the pouches and urine container, with a white absorbent strip, each inside a leak proof, zip-lock bag. Squeeze out the air and seal the bags.
3. Place a frozen ice pack in the bottom of the foam cooler. Put a piece of bubble wrap on top of the ice pack to separate it from the zip-lock bags.
4. Place the zip-lock bags containing the Vacutainers and urine specimen on top of the bubble wrap. Make sure the urine container is in an upright position. If necessary, add additional packing to prevent contents from shifting.
5. Place the lid on the foam cooler. Place the completed shipping document (Mailing Form #95) on top of the cooler.
6. Close and tape the outer cardboard box.
7. Stick the label “UN3373 DIAGNOSTIC SPECIMENS” on the top of the box in the upper left corner.
8. Place the repository address label on the top of the box on the upper right corner.
9. Use the pre-printed Fed Ex air bill to ship the specimens to the repository. Fill in the date, your return address, and phone number in Section 1. Leave “Sender’s FedEx Account Number” blank.
10. If the package is sent on Friday for Saturday delivery, cross out the Recipient’s Address line in Section 3 and neatly enter the following on the blank address line in Section 3: 7331 Calhoun Place. Change the city to Rockville, leave the state as is, and change the zip code to 20855. In Section 6, Special Handling, check the block for “HOLD Saturday at FedEx location”. Notify the repository no later than 3 pm on Friday.
11. In Section 6, check the “No” block indicating no dangerous goods are contained in the shipment.
12. In Section 7, enter “1” under “Total Packages”, and a total weight of 2 lbs. Follow the peel and stick instructions on the back of the air bill. Attach the airbill to the side of the box, opposite “Rush!! Perishable Shipment”.
13. **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339).** Give them the account number in Section 7, Payment, of the pre-printed FedEx Air bill, and your pickup address. FedEx will dispatch a courier to pick up your package.



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13.5. Rutgers Cell and DNA Biorepository Procedure Instructions

Flow Sheet for Blood Sample Collection

YELLOW TOP TUBES FOR NIDDK GENETICS INITIATIVE at RUTGERS UNIVERSITY

1. Complete and attach I.D. labels to the tubes. **DO NOT write the participant's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**
2. Collect adult blood specimen in the two 8.5 mL yellow top (ACD) tubes. In pediatric case use two or three pediatric 3.5 mL ACD tubes, depending on the participant's weight. For blood collection, ensure the (vacutainer) tubes have not expired. Check that the date shown above "Exp" in the lower right corner of the BD label is equal to or later than the current month. **Be sure to invert each tube gently 6 times to mix blood with additives and keep them at room temperature. DO NOT CENTRIFUGE THE SAMPLES GOING TO RUTGERS.**
3. Double check NIDDK ID #, verify that ID information on tube matches that on the enclosed NIDDK Phlebotomy Collection Form (Form # 96).
4. Date and identify the person (same as their username for the database) completing the NIDDK Phlebotomy Collection Form (Form # 96).
5. Package the blood tubes in the safety mailer following the enclosed instructions. When using tape to secure tubes in the container, make sure that you do not tape over the affixed label on the tube. Be sure to seal the Styrofoam container with the red tape (water resistant).
6. Place the collection form (NIDDK Phlebotomy Collection Form # 96) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete. Be sure not to tape over any part of the box label.
7. Use the enclosed Federal Express shipping label to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.
8. For routine shipments make sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650."
9. **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339), and a courier will be dispatched to pick up the samples. Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination.**
10. **Notify Dana Witt and Elva Peralta at the Rutgers University Cell and DNA Repository** that blood is being shipped and provide the Federal Express tracking number _____ and NIDDK ID # _____.
This can be done by email (witt@biology.rutgers.edu; peralta@biology.rutgers.edu), fax (1-732-445-1149), or phone (1-732-445-1498).

Assembly instructions for one Polyfoam Packers Model 472 Thermo~~Safe~~® Safety Mailer System

Read all instructions thoroughly before starting assembly.

Required Components:

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

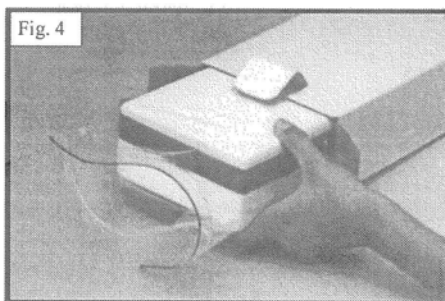
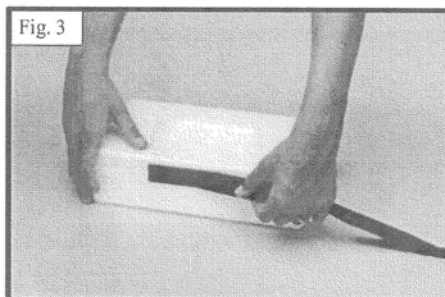
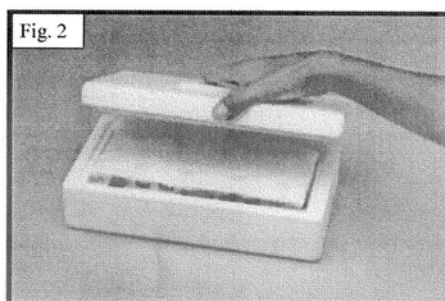
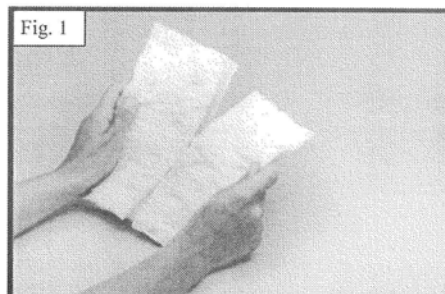
Assembly Procedure:

- 1) Place tubes and other diagnostic test components in body of the Safety Mailer, as usual.
- 2) Tear off one section of absorbent material along the perforations (Fig. 1) and place it so it exactly covers the cavity of the Safety Mailer, including all diagnostic test components (Fig. 2).
- 3) Place the lid of the Safety Mailer over the body and absorbent material (Fig. 2), and press down firmly until the sides of the lid meet the sides of the body.
NOTE: If absorbent material is pinched between the lid and the body, the lid will not close properly. In this case, reposition absorbent material and then refit the Safety Mailer lid.
- 4) Cut two 18" long pieces of red, waterproof tape. Peel the backing from one piece of tape and begin sealing the Safety Mailer lid to the body (Fig. 3). Then peel the backing from the second piece of tape and continue sealing the mailer, overlapping the first piece of tape about two inches on both ends.
- 5) Place the sealed Safety Mailer into the press-lock plastic bag. **DO NOT SEAL THE BAG YET** (air trapped in the sealed bag will prevent it from fitting into the corrugated shipping carton).
- 6) Slide the Safety Mailer and open press-lock bag into the corrugated carton (Fig. 4). Then seal the press-lock bag, close the carton using the locking tabs, and place sealing tape (not included) over them.

POLYFOAM Packers

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13.6. Access to Data and Privacy

Each of the NIDDK Central Repositories will be under the supervision of an Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations at 45 CFR 46 (The Common Rule). This research material may only be utilized in accordance with the conditions stipulated by the Repository IRB.

During the course of the FSGS Clinical Trial and for a period of 2 to 4 years following the completion of the trial, all studies employing biosamples from FSGS participants stored in either the Fisher or the Rutgers repositories must receive approval from the FSGS Clinical Trial Ancillary Studies Committee and from the FSGS Steering Committee. The process for submission of ancillary studies is described in Section 14 of the MOP. Section 14 also provides guidelines for conduct and publication, which must be adhered to by all ancillary studies making use of the FSGS specimens.

The FSGS Steering Committee will relinquish its authority over the FSGS Clinical Trial specimens residing in the biorepositories after 2 to 4 years following the completion of the FSGS Clinical Trial. Subsequent to this time, an appropriate external panel appointed by NIH will review all requests to use Repository samples. That panel will include a bioethicist and other individuals with expertise in one or more areas including human genetics, clinical research, epidemiology, physiology, and genetics of complex traits, statistical analysis, and molecular genetics research. NIH Program and Review staff is excluded from membership on this panel, but can provide appropriate guidance, background information, and technical assistance.

Requests will be reviewed based on:

1. Consistency with the terms of the informed consent under which the sample was submitted
2. The experience and qualifications of the applicant principal investigator and co-investigators to store and handle the requested materials safely and carry out the study
3. The adequacy of research environment to ensure safe handling of the requested materials and to carry out the study
4. Ethical considerations
5. The significance of the proposed research project
6. The adequacy of proposed research design
7. The adequacy of the applicant principal investigator's funding resources to support the proposed study
8. The balance between potential exhaustion of a limited set of samples versus the relative importance of the research question

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13.7. Usage agreement

Every recipient investigator will be obligated to sign a Usage Agreement that stipulates the following conditions:

1. The project has the written approval, and continuing supervision, from an IRB that has executed an applicable Assurance with the Office for Human Research Protections for each research project that proposes to use human biological material acquired from the repository.
2. Recipient investigators shall conduct only research that is encompassed within the scope of the associated Informed Consent Document, as applicable.
3. Recipient investigators shall not attempt to ascertain personally identifiable information about the sample sources.
4. Recipients shall return all new data derived from the samples and/or data received within one year after receipt of samples and/or data, or upon publication of research in which the new data were presented, whichever comes first, and annually thereafter. This will continue until the Research Project is completed.
5. Recipient investigators shall not provide human biological material acquired from the repository to any other investigator, unless directed to do so by the NIDDK. Unused samples should be returned to the repository. All data must be destroyed or returned to the repository after the approved period of use.

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13.8. Template Materials Consent for Provision of Biorepository Samples

This template can be downloaded from the FSGS-CT web page. Note: NIH approval is required for Repository Consents before specimens can be taken out of the Repository.

CONSENT FORM FOCAL SEGMENTAL GLOMERULOSCLEROSIS TRIAL STORED MATERIALS/NIDDK CENTRAL REPOSITORIES

1. Introduction

You are being invited to participate in this research study of participants with FSGS. This part of the study involves collection and storage of blood and urine that will be stored at **NIDDK CENTRAL REPOSITORIES** for future research. Before you can decide whether or not to volunteer for this study, you should understand the purpose of the research, any risks to you, what is expected of you, and the absence of any direct benefit for you. This process is called informed consent.

You do not have to participate in this study. You may stop your participation in this study at any time without changing your current or future relationship with “X” medical center or its doctors.

If you decide to participate in this study you will be told about any new information learned during the course of the study that might cause you to change your mind about staying in the study. You are being asked to participate in this study because you have focal segmental glomerulosclerosis. You may be asked to participate because you are also taking part in a study to compare two treatment methods for focal segmental sclerosis. You can participate in the treatment study of FSGS and decide not to participate in this study.

2. Why is this study being done?

The purpose of this study is to learn more about FSGS so that we might be able to better help participants in the future. To do that, we plan to study blood, urine, and DNA from participants with FSGS. We are asking you [or your child] to provide a sample of blood and urine, which will be sent to the NIDDK Central Repositories, a research resource supported by the National Institutes of Health. The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research for the study of focal segmental glomerulosclerosis to advance our understanding of the pathobiology of this condition including but not limited to its diagnosis, response to therapy, prognosis and risk of complications of therapy. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. These samples may be used for genetic tests, looking for causes of FSGS or to increase our understanding of why some participants respond to therapy and others do not. In addition, the kidney biopsy material used to confirm the diagnosis

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of FSGS, may be available for future examination by experts in the field. The biopsy materials will be kept at the Core Pathologist sites for possible subsequent review.

3. How many people will take part in this study?

Five hundred adults and children will be asked to participate in this study. The study will take place in five coordinating centers across the country, which will collaborate with smaller centers so that a wide representation of adults and children from 200 centers across the United States will take part in the study. A total number of 500 people will be asked to participate in this study. “X” number will be asked to participate from “Y” University.

4. What is involved in the study?

When blood or urine is being obtained for clinical or research purposes, any blood or urine that is remaining and is not used for research purposes or for clinical purposes will be saved and sent to a central storage bank at the **NIDDK CENTRAL REPOSITORIES**. Thus, there will be no extra sticks to obtain blood and there will be no more frequent visits to obtain blood or urine specimens. All samples for the repositories will be collected on scheduled visit dates at weeks 0, 6, 12 and 18 months.

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

These biomaterials will be kept in the **NIDDK CENTRAL REPOSITORIES** and the renal biopsies will be maintained at the Core Pathologist’s Sites for use in research at a later time.

____ My samples and associated data may be used for any scientific purposes involving this or any other projects. Do not contact me again for permission.

____ My samples and associated data may be used for this project only. Do not use them for any other project. Do not contact me again for permission.

If you choose either of the two options, it is unlikely, but possible that in the future a genetic test could be developed that would give a result that could be important to your personal health. Such information could have risks. For example it could make you anxious, or possibly make it more difficult to get insurance or a job. Please choose and initial one of the options below to tell us what you would like us to do with the information.

If you are over 18 years old, please check one of the following two choices. (If your child is under 18 and is part of this study, we will ask him/her to decide when he/she becomes 18 whether he/she wants to receive information about genetic tests).

____ Please try to contact me if information is discovered in future studies of my genetic material that would be important to my personal health.

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____ Don't contact me with any information obtained from future studies of my genetic material.

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

5. What happens if I discontinue or withdraw from the study?

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

6. What are the risks of this study?

Your participation in this study does not involve any physical risks to you. Genetic tests, if they became known, could affect your ability to get insurance or a job. Some people become anxious or upset when they find out they have an abnormal genetic test.

7. Are there benefits in taking part of this study?

Participation in this research study will not benefit you directly. We hope that by using your blood and urine for future studies other participants with focal segmental sclerosis may benefit.

8. What are other options?

The only other option is to not participate in this study.

9. What are the costs?

There will be no cost to you by participating in this study.

10. What happens if I am injured while I am participating in this study?

We do not anticipate any injuries from this study. If there were an injury, medical care including hospitalization is available. This medical care is not free. You will be responsible for the cost. You may call the director of Risk Management if you have questions about the cost of treatment or if you have any questions about research related injuries.

11. Will I be paid for participating in this study?

You will not be paid or compensated for participation in this study.

12. How will confidentiality be protected?

We will make every effort to keep your research records private, but confidentiality cannot be guaranteed. Records that identify you and this consent form may be looked at by a regulatory

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agency such as the Food and Drug Administration, the Department of Health and Human Service Agency, Institutional Review Board and the National Committee for Quality Assurance. If results of this study are published or presented in public your name will not be used. Your blood and urine collected for this study will be identified by a code number. This code number could be used to identify you, but the list identifying your name and code number will be kept in a secure place, separate from the specimens.

The Core Pathology sites and the Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before the researchers in this study send samples to the Repository, each sample will be given a code number. Your name, or your child's name, and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you or your child, to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, race, and outcomes of the initial study.

13. What are my rights as a study participant?

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

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

If you are an employee or student, whether or not you take part in this study will not affect your job, current or future medical care or studies.

14. Whom do I call if I have questions or problems?

If you have questions about any part of the study now or in the future, you should contact _____, who can be reached at _____. If you experience side effects or injuries while participating in this study, please contact _____, who may be reached at _____. For after hours, weekends, or holidays call _____. If you have questions about your rights as a research participant contact the Institutional Review Board (which is a group of people who review the research to protect your rights) at _____.

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Participant/Subject Acknowledgement

The procedures, purposes, known discomforts and risks, possible benefits to be and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I understand it. I agree to participate in this study. I have been given a copy of this consent form.

Participant/Subject Signature

Date

Signature of Person Obtaining
Informed Consent

Date

Optional:

Signature of Principal Investigator
or Designate

Date

The procedures, purposes, known discomforts and risks, possible benefits to my child and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I understand it. I agree to allow my child to participate in this study. I have been given a copy of this consent form.

Subject Assents by Signature,
when applicable

Date

Subject Age

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Parent/Guardian Signature

Date

Parent/Guardian Signature

Date

Signature of Person Obtaining
Informed Consent

Date

Both parents need to sign for children to participate in a research study. If only one parent can sign this consent, indicate the reason that applies to the other parent.

____ deceased

____ unknown

____ legally incompetent

____ no legal responsibility for the care and custody of the child

____ not reasonably available – indicate why _____

[Acceptable reasons for this category must not be based on convenience]

Optional:

Signature of Principal Investigator
or Designate

Date

[Affirming eligibility for the study and that informed consent has been obtained]

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If child cannot reasonable assent or if well being of child is directly benefited by participation without assent, please explain.

Signature of Principal Investigator
or his/her authorized agent

14. ANCILLARY STUDIES

14.1. General Policy

FSGS-CT publications:

The Steering committee will serve as the Publication Committee.

The Steering Committee will strive to cast as wide a net as possible to allow active participants in the study [those sites and PIs who enrolled patients] to engage in publication writing with attention paid to including junior members of the FSGS-CT community in manuscript development.

Ancillary study publications will be encouraged to take a similar approach to manuscript development as the FSGS-CT writing committees.

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
- Investigators who are not part of the FSGS-CT but have an FSGS-CT liaison investigator from a CCC

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 CCC 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

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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

1. The proposed study must meet requirements of the highest scientific merit.
2. Relevance to FSGS.
3. Opportunity for acquisition of new scientific knowledge.
4. Adequacy of experimental design, methodology and data analysis.
5. Adequacy of the investigator and research environment.
6. Participant (enrolled participants and participating site providers) burden.
7. The proposed study must be acceptable to the participants (e.g. time, discomfort, privacy).
8. The proposed study must not interfere with other parts of the main FSGS-CT.
9. The proposed study must not hamper continued participation in the main Clinical Trial.
10. The proposed study must put minimal demand on scarce FSGS-CT resources such as blood samples.
11. The proposed study must require the unique characteristics of the FSGS-CT cohort to accomplish its goals.
12. The investigators must have adequate resources to effectively complete the project, including both financial support and personnel.

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13. The ancillary study investigators must agree to return the complete ancillary data set back to the DCC, if requested.
14. The proposed study must not interfere with or impede the completion of the primary or secondary objectives of FSGS-CT.
15. The proposed study must not adversely affect participant cooperation or compliance with FSGS-CT protocols.
16. 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, CCC or DCC.

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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.

14.3.4.1. Ancillary Study Proposal Format

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 -70⁰F
 - 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

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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.

14.3.5. 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.

14.3.6. 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:

1. Statistical and data management staff for coordinating the additional data management and analyses with the DCC.
2. Expenses involved in modifying identifying data to protect subject confidentiality and maintain HIPPA compliance.
3. Costs for notification of alert values.
4. Costs incurred by Participating Sites including space, personnel, equipment, and IRB approval.
5. Costs relative to visits or examinations outside of the primary study protocol.

14.4. 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.

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

1. Monitoring the study to assure continuing compatibility with FSGS-CT.
2. Maintaining communications with the FSGS liaison investigator.
3. Provide written progress report on the ancillary studies.

14.5. 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 or abstracts resulting from all ancillary studies will be submitted for review to the *Steering Committee and will require approval by the Executive Steering Committee prior to submission for publication or presentation. The text and figures for planned presentations or posters will be submitted for review to the Steering Committee at least three days before the oral or poster 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.

* Members of the Ancillary Studies Committee will often be asked to review manuscripts or abstracts, especially if a committee member(s) had initial involvement in the approval process for that said ancillary study.

14.6. Feedback of Results of Ancillary Studies to Participants

The results of genetic testing will not be disclosed to patients who participate in the FSGS-CT study.

At the end of the study, the External Advisory Committee would be asked to determine if there are findings that might be clinically relevant to participants in the FSGS-CT.

At the end of the study, if any of the genetic tests are determined to be clinically relevant for patient care, this will be reported to all participating physicians as part of a summary of the findings of the study. At that point, if a patient wants to know their individual results for any tests that have been found to be clinically relevant, their attending nephrologists will submit a written request, signed by the patient, to the DCC.

During the study, if the DSMB concludes that there is clear evidence that information from the study should be shared with participants, they will recommend such disclosures to the Steering Committee.

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14.7. 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 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. The FSGS-CT Study Policy on Use of Archived Study Data will govern subsequent access to these data.

15. FORMS COMPLETION INSTRUCTIONS

15.1. General Forms Completion Instructions

The FSGS Clinical Trial Group is structured with 5 CCC and 175 Participating Sites. The Participating Sites will enroll and follow participants. Each CCC is also a Participating Site. Each CCC is responsible for training the staff of the Participating Sites that make up its Core and for the completeness and integrity of the data from each of these Participating Sites.

The current version of each form (Case Report Form – CRF) and individual form instructions (page 0 of each form) is available on the FSGS study's web site. FSGS-CT CRFs include two types, Mailing Forms and Other Forms. Mailing Forms must be completed on paper. After a Mailing Form has been fully completed, the form is photocopied; the original form is sent to the lab with the specimens, the form is key entered, and a photocopy is kept in the participant's study file.

It is recommended that all forms be completed on paper before they are key entered. However, except for the Mailing Forms, other forms may be completed on line, in a paperless fashion, if desired. If a form is completed on line, when it has been saved, the completed data form should be printed out and kept in the participant's study file (refer to Section 16.3.2 on how to print a CRF).

Each Participating Site will have 100 Participant ID numbers available. The ID number will consist of 6 digits. The first 3 digits represent the Participating Site number. The last 3 digits are sequentially numbered, starting from 001 to 100. At the beginning of the study the DCC will set up a list of 10 potential Participant ID numbers from 001 to 010 for each Participating Site. For example, for the Participating Site 501 the numbers 501001 through 501010 will be set up. If a Participating Site has used all the ID numbers that were initially set up by the DCC, e-mail fsgs_dcc@bio.ri.ccf.org and more ID numbers will be set up for your Participating Site. Once an ID number has been assigned to a specific participant, this participant cannot be assigned a different number throughout the study and this number cannot be reused for another participant in the study. Once the Preliminary Screening Form (Form # 10) has been entered (Saved) into the database, a 2 digit alpha-numeric code will be assigned automatically to that participant. The combination of the Participant ID and the alpha-numeric code is used to uniquely identify each participant in the study. The reference to the alpha-numeric code in the MOP and on the forms is "alpha code" for convenience purposes.

Participating Sites may enter their own data or they may submit their completed CRFs (Case Report Forms) to their CCC for data entry. Either way, they must retain the original or a copy of each form they complete. (If they send forms to the CCC via an overnight delivery service, they should make a photocopy of the form for the participant's study file. This will be necessary for reference when data discrepancies are being investigated.)

The date of completion (question 200) and the name of the person completing (question 201) the CRF should be printed (hand written) on each form and entered into the database. The date the form was entered (question 202) and the username of the person entering the form (question 203) will automatically be stored.

15. FORMS COMPLETION INSTRUCTIONS

All of the following Case Report Forms must be completed prior to randomization

Preliminary Screening (Form # 10), Baseline Visit (Form # 11), Disease History (Form # 14), appropriate QOL Questionnaire (Form # 36 – 43), Medication (Form # 44), Physical Exam (Form # 46), Results of Local PCR Testing for Hep C (Form # 75) *if applicable*, Core Lab Urine Mailing (Form # 80 x2), Blood and Serum Mailing (Form # 83), Biopsy Mailing (Form # 86), Biopsy Results (Form # 87), Results of Local Urine HCG Pregnancy Test (Form # 89) *if applicable*, Results of Local Tuberculin Skin Test (Form # 91) *if applicable*

Please note that there will be no need to enter laboratory data in the database. This information will be forwarded from the Core Lab to the Data Coordinating Center (DCC) electronically. A copy of the lab report will be faxed to the local Participating Site for placement in the participant's clinical record. HIV results will be returned ONLY to the Participating Site via express mail.

Refer to Section 7 of the Manual of Operations for specific directions pertinent to each visit.

The paper CRF includes the MedDRA codes for the most important and for the most commonly anticipated symptoms. The person entering the data form will do on-line MedDRA coding of:

1. Additional symptoms on the –
 - a. Baseline Visit Form # 11
 - b. Follow-up Visit Form # 16
2. Current and chronic comorbid conditions on the Disease History Form # 14
3. Termination codes on the Study Medication Termination Form # 45
4. Abnormal physical exam findings on the Physical Exam Form # 46
5. Diagnoses on the Hospitalization Form # 62
6. Adverse events on either the –
 - a. Adverse Event Report Form # 60
 - b. Serious Adverse Event Report Form # 61
7. Cause of death on the Death Notification Form # 63

The study medications (CSA, MMF, Dexamethasone, prednisone, ACEi and ARB) have been coded and are tracked on the Medication Form (Form # 44). The person entering the Medication Form (Form # 44) will do on-line WHODrug coding of other prescription medications, over-the-counter medications, and vitamin, herbal, or other supplements using. (Exact dosage data are only collected for Study Medications.)

Forms that are missing required data are not considered complete. It is strongly recommended that a data entry person not start the data entry process until he or she knows the response to all required fields on a form. If a form is saved into the study database without a value in a required field, a data discrepancy (inquiry) will be generated and the person who entered the data must obtain the response to the missing required field.

When a staff member at a Participating Site has a question about a CRF or has a problem with data entry, he or she will call the Primary Study Coordinator of their Core Coordinating Center. If the answer to the question cannot be found in the study Protocol or Manual of Operations and the question cannot be answered within the Core, the Data Coordinating Center will be

15. FORMS COMPLETION INSTRUCTIONS

contacted. If staff at the Data Coordinating Center cannot answer the question, the Steering Committee will be contacted, the issue resolved, and the Manual of Operations will be revised so that if a similar question arises in the future, the answer is included in the study documentation.

Paper forms should be completed in black ink. If you make a change to an item on a completed form, cross through the original item, write in the new response, and write your initials and the date in the margin of the paper form. Do not use white out to cover the error.

Prompt key-entry of the collected information into the database is critical for the successful conduct of the study. The automated reports produced by the DCC that are geared to help the Participating Sites to follow the study procedures and to be compliant with the study protocol rely on the information that is submitted/entered into the database. The golden standard for the study is the forms to be key-entered within 2 business days of the day a participant is seen.

The DCC and the Quality Control Committee understand that this goal might not be realistic in all the cases. That is why in addition to the recommended time of 2 business days for data entry we agreed on the following terms for data entry:

1. All other baseline forms and the follow-up forms for the visits held through W06 should be entered into the database within 3 business days after the information was collected.
2. All follow-up forms for the rest of the visits (\geq W08) should be entered into the database within 5 business days.

There are circumstances when it is extremely important to get the data entered immediately:

1. Preliminary Screening Form 10 should be entered in the database within 1 business day. This form officially "creates" the participant in the study and the seven day window for randomization starts from the date of entry of Form 10. Remember that in addition to entering the Form 10 a copy of the first page of the completed Form 10 must be included in each first shipment per participant to the Core Lab (Spectra).
2. Lab Mailing Forms 80 (Urine) and 83 (Serum and Blood) must be entered in the database as soon as possible after the shipment. Not having the lab mailing forms into the database will prevent the loading of the lab test results reported from Spectra.
3. Adverse Event Form 60 and Serious Adverse Event 61 must be entered into the database within 2 business days of the knowledge of the event for the events that have to be reported to FDA immediately (see Section 9 of the Manual of Operations).

Data discrepancy inquiries are resolved on line. Follow the procedures described in the computing section of the MOP (Section 17.3.6). Data discrepancies should be resolved within two business days of the day they arise. Data changes initiated by the Participating Site or by a CCC are made on line following the procedures described in the computing section of the Manual of Operations.

Our database will allow a Participating Site to enter their own data (assuming they have a valid password) or submit the CRF (Case Report Forms) to their CCC for data entry. The database will be set up so a Participating Site can fix a data discrepancy (assuming they have a valid password) or so the CCC can fix a data discrepancy that came from one of their Participating Sites. Each Participating Site will be able to see its own data. CCC will be able to see data from all of their Participating Sites.

15. FORMS COMPLETION INSTRUCTIONS

15.2. Screen Failures

If a participant was consented and screened for the FSGS-CT study and is determined ineligible (screen failure), it is required that at least the following forms be entered into the database:

1. Preliminary Screening Form # 10
2. Core Lab Urine Mailing Form # 80 (x2); Core Lab Results will be loaded
3. Core Lab Serum Mailing Form # 82; Core Lab Results will be loaded
4. Biopsy Mailing Form # 86 and Biopsy Results Form # 87 – if biopsy determined ineligibility
5. Study Exit Before Randomization Form # 31

15.3. Form Instructions

Participating Site personnel that need access to the FSGS-CT database should see Section 16 of the Manual of Operations for a Request for an Oracle Pharmaceutical Applications Account form. The top section of this form must be completed and faxed to the DCC prior to an account being set-up. Once this form is processed and your account set-up a DCC's Study Coordinator will contact you with your username and password information.

Section 16 also includes data entry instructions for Form 02 as well as general data entry instructions for use of Oracle Clinical.

Specific and very detailed instructions of each form are located on “page 0” of each CRF. Forms are located on the FSGS-CT study website where the Participating Site may print off copies of each. It is the Participating Site's responsibility to make sure they are using the most current version of the CRF. The revision date for each form is on the upper left hand corner of each page. Make sure that your hardcopy of the CRF matches the screen layout of the form in the database.

15. FORMS COMPLETION INSTRUCTIONS

15.4. Re-Enrollment / Re-Screening

Screening During the Baseline Phase (B01):

All screening lab results must be conducted in the FSGS-CT Study's Core Lab (Spectra). The chemistries, CBC, Up/c, pregnancy test and QOL questionnaire(s) must be completed within *8 weeks of randomization. The PPD must be completed within 12 months of randomization (note: the PPD placed/resulted \leq 3 months at time of entry/enrollment). The HIV, Hepatitis B, Hepatitis C and lipids must be completed within 12 months of randomization (note: Core Lab must confirm results at initial entry/enrollment). Confirmation of FSGS diagnosis by the Core pathologist may occur anytime prior to randomization.

Rescreening:

There are four scenarios in which a participant who is being considered for enrollment in the FSGS-CT may require rescreening or repeat testing of laboratory studies. In three instances, the rescreening must be performed because the results of the initial Baseline assessment indicated that the participant was ineligible for randomization. In the fourth circumstance, rescreening is required because unanticipated logistical issues prolonged the interval between the Baseline Visit demonstrating eligibility and subsequent randomization and initiation of study medications. Causes for delay may include difficulty in retrieving the biopsy specimen and shipping it to the Core Pathologist for review, discrepant results for proteinuria necessitating collection of a third sample, lost or misplaced blood samples, and difficulties scheduling visits for participants who reside at a distance from the Participating Site.

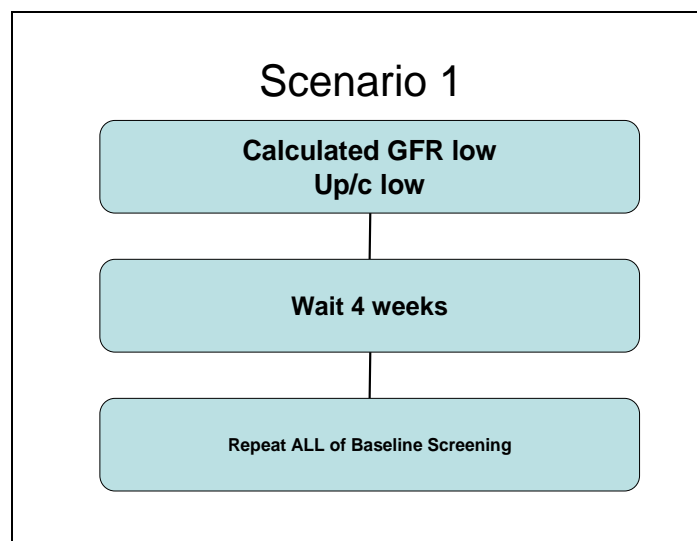
Scenario #:

1. If the **Up/c or serum creatinine** result* does not meet eligibility, the test may only be repeated after a minimum **4 week waiting period (for specific labs that will need to be repeated see Scenario 1 flow chart below). Rescreening may only be attempted once when the ineligibility is based on out-of-range Up/c and/or eGFR with one exception: A third screening may be attempted when the original Baseline and first (failed) Rescreen are at least nine months apart AND at least 4 weeks have past since the failed Rescreen. Refer to section 15.4 of the MOP for rescreening data entry procedures.
2. If the **ANC, HCT or glucose** result does not meet eligibility, the test may be repeated at any time within the **8 week screening period prior to randomization. (See Scenario 2 flow chart below)
3. If the FSGS diagnosis is not confirmed by the Core pathologist, an additional **biopsy** may be performed and submitted for review. (See Scenario 3 flow chart below)
4. If the participant has been randomized and it has been more than **8 weeks without the start of study medications then labs, including blood/serum labs, 2 urine collections, urine pregnancy test (if applicable) and the QOL should be completed. If the time lapse since randomization without administering study medications is greater than 12 months then a repeat of the whole baseline screening should be completed (with the exception of biopsy results). (See Scenario 4 flow chart below)

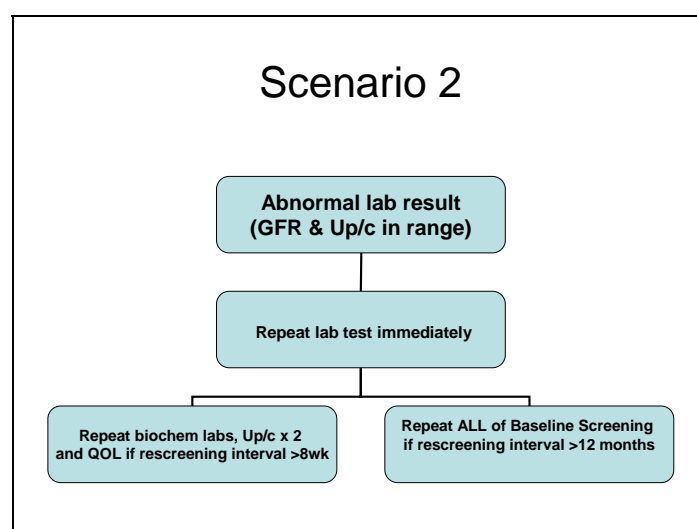
* Latest lab value will be used for accessing eligibility

** Time period based on latest specimen collection date (Baseline Urines and Blood/Serum collection dates)

15. FORMS COMPLETION INSTRUCTIONS



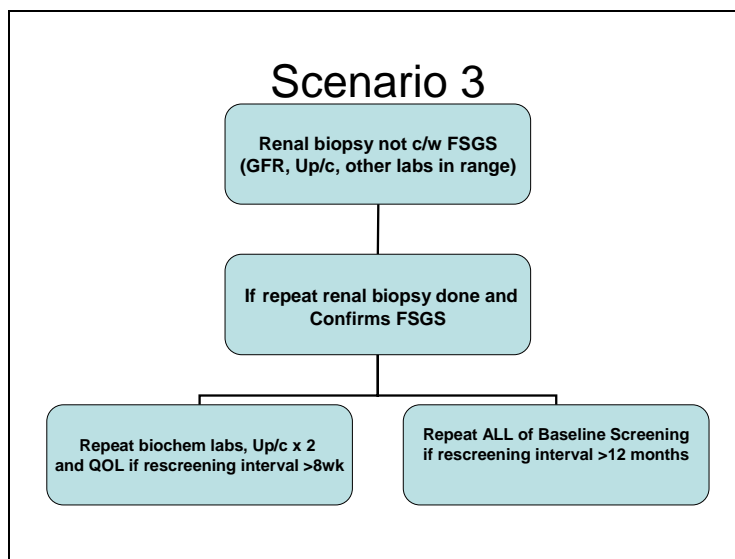
Explanation: Under Scenario 1 circumstances, rescreening can be done after waiting a minimum of 4 weeks from time of last specimen collection. Complete all of the Baseline screening with the exception of the screening viral serology (HIV, Hep B, Hep C) and PPD that would only need to be repeated if the interval between the original and repeat screening exceeds 12 months. Waiting the 4 week interval is necessary to allow adequate time for a participant with a reduced GFR related to an intercurrent illness to recover sufficient kidney function so that it is likely that the participant will be stable enough to be maintained on the study medication for at least 26 weeks. For those participants whose Up/c <1 and, therefore, too low to qualify for the study, it is important for safety reasons to be certain that they qualify for the FSGS-CT before exposing them to the extended course of study medication. At this level of protein excretion, a 4-week observation period should not pose a threat to their general health.



Explanation: In Scenario 2, one of the lab tests besides serum creatinine and Up/c obtained at the Baseline assessment may be abnormal and fall under one of the Exclusion Criteria for FSGS-CT. The possibilities include (but are not limited to) serum glucose concentration, hematocrit, white blood cell count, absolute neutrophil count, or ALT/AST that fall outside the allowable range. Under these circumstances, the rescreening can be done immediately as long as the participant is clinically well and not sick. The rescreening procedure involves only the abnormal

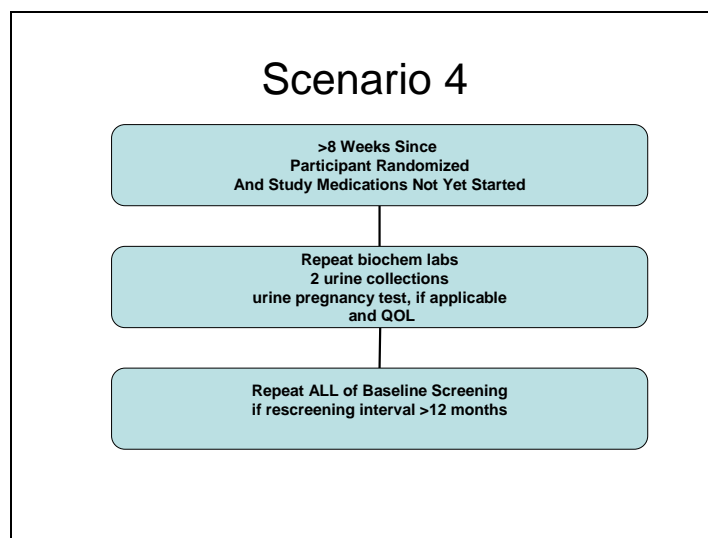
15. FORMS COMPLETION INSTRUCTIONS

laboratory test. This applies as long as the interval between the initial and repeat testing is less than 8 weeks. Otherwise, if the interval exceeds 8 weeks, repeat blood/serum labs, 2 urine collections for Up/c, urine pregnancy test if appropriate, and QOL must also be repeated. *The reason for repeating these tests if the interval exceeds 8 weeks is because they represent the primary outcome and one of the key secondary outcomes.* All of the remaining screening tests including viral serology (HIV, Hep B, Hep C) and PPD need to be repeated only if the interval between the original and repeat screening exceeds 12 months.



Explanation: When the initial renal biopsy was not read as FSGS by the Core pathologist and the participant did not qualify on these grounds for enrollment into the clinical trial, under Scenario 3, if a repeat biopsy is performed that confirms FSGS, then no other tests need to be repeated as long as the interval between the initial and repeat test is less than 8 weeks. Otherwise, just as in Scenario 2, if the interval exceeds 8 weeks, then in addition to the repeat biopsy, blood/serum labs, 2 urine collections for Up/c and QOL must also be repeated. *The reason for repeating these tests if the interval exceeds 8 weeks is because they represent the primary outcome and one of the key secondary outcomes.* All of the remaining screening tests including viral serology (HIV, Hep B, Hep C) and PPD need to be repeated only if the interval between the original and repeat screening exceeds 12 months.

15. FORMS COMPLETION INSTRUCTIONS



Explanation: In Scenario 4, all of the lab tests obtained at the Baseline assessment confirm participant eligibility for FSGS-CT. However, unforeseen circumstances result in a delay of more than 8 weeks between this evaluation and randomization to one of the treatment arms and initiation of study medication. Under these circumstances, because the interval between Baseline and Randomization exceeds 8 weeks, the rescreening procedure involves blood/serum labs, 2 urine collections for Up/c, urine pregnancy test if appropriate, and QOL must also be repeated. *The reason for repeating these tests if the interval exceeds 8 weeks is for safety reasons, namely to verify the need for prolonged therapy with the study medications. Moreover, these tests represent the primary outcome and one of the key secondary outcomes.* All of the remaining screening tests including viral serology (HIV, Hep B, Hep C) and PPD need to be repeated only if the interval between the original and repeat screening exceeds 12 months.

15.4.1. Form Completion Instruction for Re-Screens

If, during baseline, a participant is determined to be ineligible (pertaining to scenario #1 above or if Participating Site will not re-screen based on initial entry criteria), key enter a Form 31 (Study Exit Before Randomization). In questions 5 through 49 indicate the exclusion criteria detected during baseline. If the participant was excluded based on a GFR, enter the date of the associated serum creatinine in item 10.b. If the participant was excluded based ANC, enter the date of blood draw for ANC measurement in item 11.b. If the participant was excluded based on Hematocrit, enter the date of blood draw for Hematocrit measurement in item 12.b. If the participant was excluded based on Serum Potassium, enter the date of blood draw for Serum Potassium measurement in item 13.b. If the participant was excluded based on the Up/c ratio, enter the date of the last urine collection in item 16.b.

Before re-enrolling a previously excluded participant, you must wait at least four weeks from the date entered in item b for questions 10 or 16 (pertaining to GFR and Up/c).

To re-enroll the participant, e-mail the DCC (fsgs_dcc@bio.ri.ccf.org) indicating the intention. The DCC will confirm that enough time has elapsed allowing a re-enrollment.

Then, see the participant for a baseline visit. **The initially assigned ID and alpha code will stay the same.** After the first visit, when you have (as a minimum) the complete new Form 10

15. FORMS COMPLETION INSTRUCTIONS

(Preliminary Screening Form) and the complete new Form 11 (Baseline Visit Form), key enter a Form 32 (Participant Re-Enrollment Form). On the Form 32 (Participant Re-Enrollment Form), it will ask you to restate why the participant was initially excluded (1 = estimated GFR, 2 = ANC, 3 = Hematocrit, 4 = Serum Potassium, 5 = Up/c, or 6 = other, please specify).

A saved Form 32 in the database will indicate to the DCC that your Participating Site is re-enrolling the participant and that you have new baseline data to enter (F10, F11, etc). Once a Form 32 is saved in the database the DCC will move all of the “old” baseline data (**except for Form 86 – Biopsy Mailing Form and Form 87 - Biopsy Results form**) into a storage database. At this time you will be able to enter the new baseline forms.

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16.1. Request for an Oracle Pharmaceutical Applications Account

User Information

First Name: _____	Last Name: _____
Site #: _____	Core Site: Y / N
Circle One: Physician Coordinator Pathologist	Email Address: _____
Pager / Phone _____	

By completing this request, I _____ understand that I must maintain confidentiality of all information, regardless of its form – verbal, written, or computerized pertaining to this clinical research study. Also, I agree to comply with all the requirements governing the access and use of the computing system for the Data Coordinating Center (DCC). Further, I am aware that the privilege of accessing the DCC's computer system will be revoked should I not comply with these policies or fail to use the data for other than its intended purpose(s).

Signature _____ Date: _____

Data Coordinating Center Processing Section

I _____ am verifying that access be granted to the above user for the following applications. Also grant appropriate database privileges since the person will be working in the following roles.

Role (Circle all applicable roles)	
Core Site	Participating Site
Application Specific	Roles
<input type="checkbox"/> Remote Data Capture (RDC)	<input type="checkbox"/> Test Data Entry
<input type="checkbox"/> Thesaurus Management System	<input type="checkbox"/> Browse Access Administrator

Studies: __FSGS_____ Does the user need UNIX account? (circle one) Yes No

User Name: _____ Special Note: _____

DCC PI Signature _____ Date: _____

OPA Manager Signature _____ Date: _____

Administrative Use Only

Person Answering Request: _____ Date: _____

Note:

16. DATABASE AND DATA ENTRY

16.2. Participating Site Information Form # 02

Instructions for Use of the FSGS Clinical Trial Group “Participating Site Information Form” Form # 02

The information on this form is used:

- When creating each study team member’s username (identified on all CRFs)
- When creating study e-mail aliases
- To define if a participating site is ready to start enrolling participant in the FSGS-CT
- To retrieve the contact information needed for drug, labs and repository shipments
- To retrieve the emergency contact information needed for reporting abnormal lab values

It is very important for each participating site to keep their information on this form accurate and up-to-date.

If you are at a Participating Site and have a question about completing the form, contact your CCC. If you are at a CCC and have a question about completing the form, send an email to fsgs_dcc@bio.ri.ccf.org

The form should either be key entered at the Participating Site or faxed to that Participating Site’s CCC for key entry.

16.2.1. Instructions for Data Entry into Oracle Form # 02

Instructions for data entry of the form into an Oracle database at the FSGS DCC in the Cleveland Clinic Department of Biostatistics

1. Get onto a PC that is running any version of Windows and has access to the Internet. Use Internet Explorer to go to the web site <https://clinapps.bio.ri.ccf.org>
Don’t forget the “s” in “https”
2. Under “Tools and Utilities,” select Web Application Utility Downloads.
3. Download [J Initiator 1.3.1.9](#), Java software that allows use of web based Oracle Forms data entry screens. This will only need to be done once on each PC that you are using for FSGS data entry. (Note: this is a different version from the Jinitiator you will install to access the Oracle Clinical Production database, both versions will need to be installed).
4. Click on the .exe file that you downloaded to install J Initiator. If you have trouble installing this software, talk to your local computer support person.
5. Once J Initiator has been installed on your PC, complete the top portion of the request for an Oracle Pharmaceutical Application Account Form (Section 16.1.) and fax it to the DCC (refer to the FSGS-CT Address Directory for most current fax number) to obtain your Oracle username and password. The Department of Biostatistics database administrator will set up a data entry account for you and a DCC staff member will phone you with your

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individual Oracle username and password. (For security reasons, we don't send passwords in email messages.) If we receive the request on a Friday, Saturday, or Sunday, we will get back to you the following Monday.

6. Once you have received your username and password, go back to <https://clinapps.bio.ri.ccf.org>, and select "FSGS Study."
7. At the "FSGS Study" screen, click "Form 2 and Reports (Production)" and then log in with your Oracle username and password.
8. The DCC has initially entered all Participating Site names and assigned each a number. If you do not know your Participating Site number, refer to the FSGS-CT Address Directory or contact your CCC for it. Query up your Participating Site number:
 - Menu bar; Forms → Form 2
 - Menu bar; Query → Enter; type in your Participating Site number. Menu bar; Query → Execute
9. Update your Participating Site's information. When you finish updating data, save the form by clicking on the SAVE icon; the "diskette" on the toolbar, or by choosing Action → Save from the menu bar. If the form has been saved successfully, you will see a message: **FRM-40400: Transaction complete: 1 record applied and saved** at the bottom of the screen. Note: For changes to the Participating Site Number or the Participating Site's Name (items 1 & 2), contact the DCC to implement those updates.
10. When a person from your site is no longer a member of the FSGS-CT study team, change the status of that person on Form 2 in the "Active" field from "Y" to "N". For auditing purposes, **never delete** the name of a study team member from the database.
11. All study e-mail aliases are based on the information provided on Form 2. If a person from your Participating Site is listed on Form 2 but does not need/want to receive study related e-mails, keep their "Status" as Y (active) but delete their e-mail address from Form 2.
12. If you have difficulties entering or changing the form, send an email to fsgs_dcc@bio.ri.ccf.org or call DCC systems personnel. For contact information see the FSGS-CT Address Directory.

Note: DCC personnel are most likely to be available between 7:30 a.m. and 5:00 p.m. Eastern Standard Time, Monday through Friday. The DCC is closed evenings and weekends.

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16.2.2. What to do if you get timed-out of the [Form 2 and Reports \(Production\)](#) database!

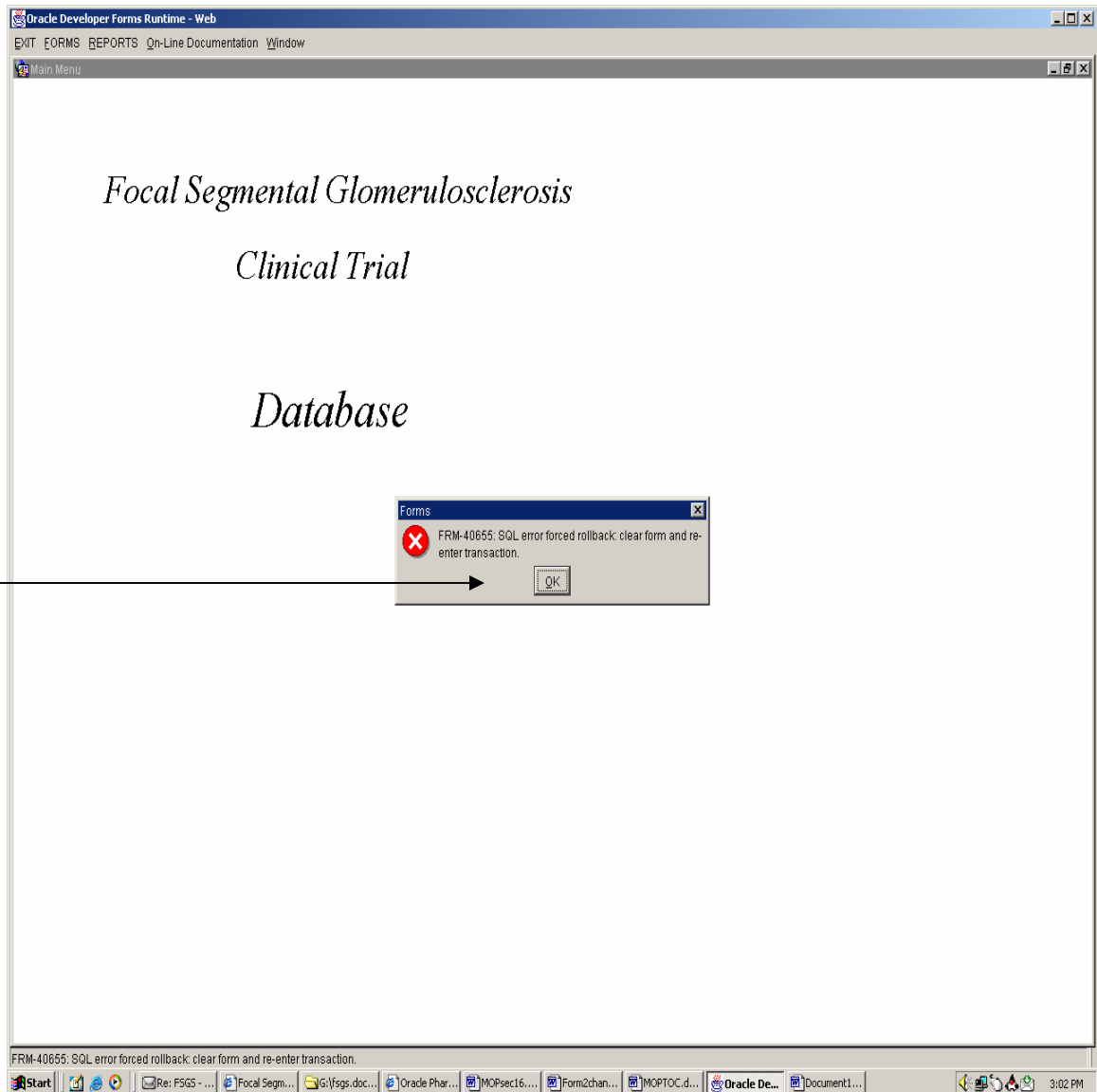
1. The Form 2 database has been setting idle for a while. Not realizing you have been “timed-out”, you try accessing your Site’s information for updating, or you clicked on Exit to get out of the database but instead you get an error message.

The screenshot shows the Oracle Developer Forms Runtime - Web interface. The main window displays the 'FSGS - Form 2' form, which is titled 'FSGS - Participating Site Information (Form 2) - Revision 06/08/2004'. The form is divided into two sections: 'Section 1. Participating Site Identification and Registration...' and 'Section 2. Participating Site Investigators'. Section 1 contains fields for site identification and registration, including 'Participating Site Number', 'Name of Participating Site', and various dates. Section 2 contains fields for site investigators, including 'Site Principal Investigator Name' and a table for 'Repeat this section as needed for Site Investigator(s)'. An error message dialog box is displayed over the form, stating 'FRM-40655: SQL error forced rollback: clear form and re-enter transaction.' The dialog box has an 'OK' button. The form is currently on 'PAGE1' of 'PAGE1', 'PAGE2', and 'PAGE3'. The 'EXIT' button is visible in the top right corner of the form window. The Windows taskbar at the bottom shows several open applications, including 'FSGS - ...', 'Focal Segm...', 'G:\fsgs.doc...', 'Oracle Phar...', 'MOPsec16...', 'Form2chan...', 'MOPTOC.d...', 'Oracle De...', and 'Document1...'.

2. Click **OK**.

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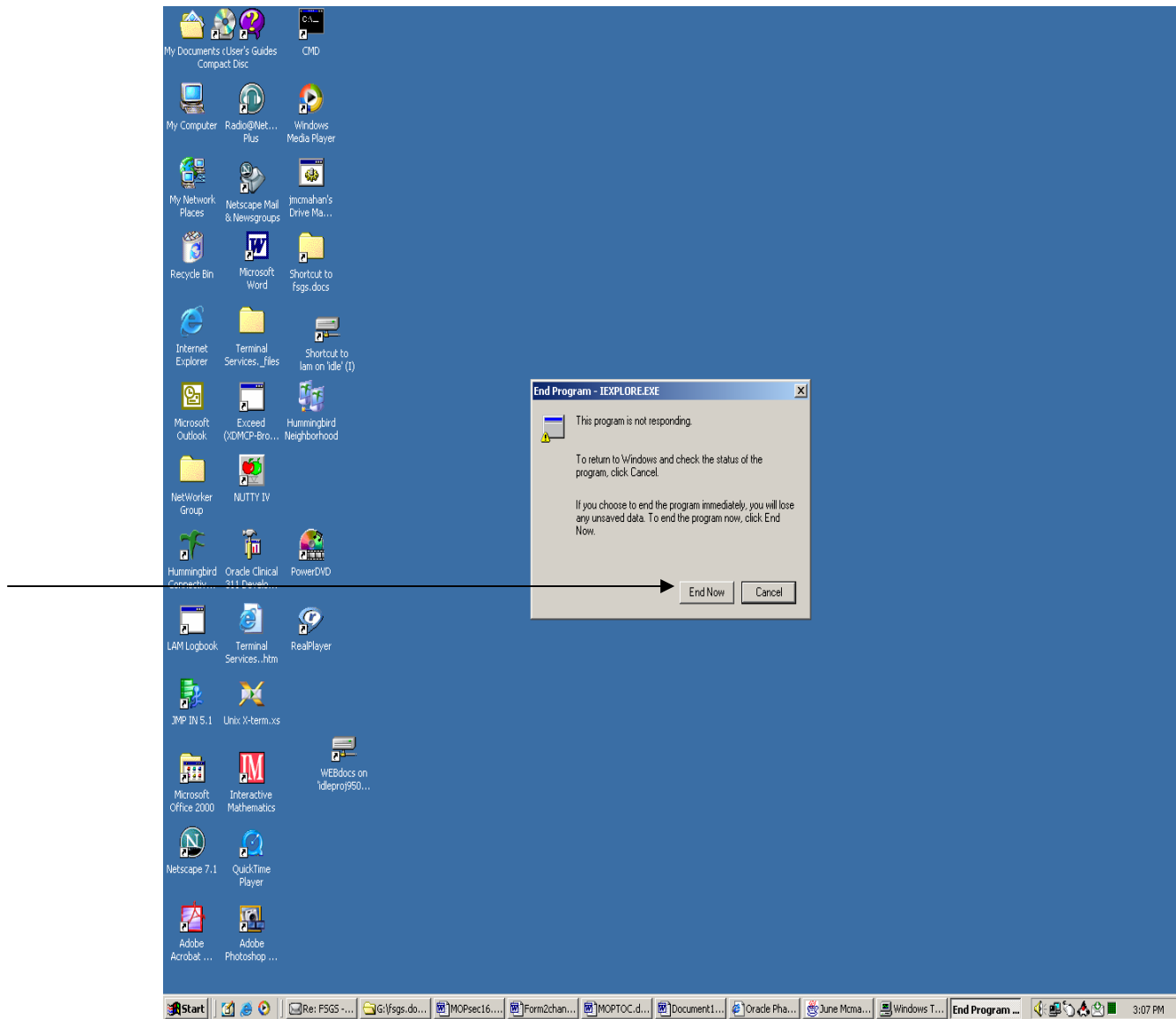
3. The Oracle Developer Forms Runtime window will be displayed with an Error Message. Click **OK**.



4. If you happen to get stuck in a loop of Error Messages, you may want to use your Task Manager to kill the session. **Right click** on your Windows **status bar** (gray in color), located at the bottom of your screen (same "line" as your Start button). **Click** on the **Task Manager** option. **Highlight** (select) the appropriate session to kill (OPP session) and **click** on the **End Task** button.

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5. An End Program pop-up box appears that states the “program is not responding”. Click on the **End Now** button.



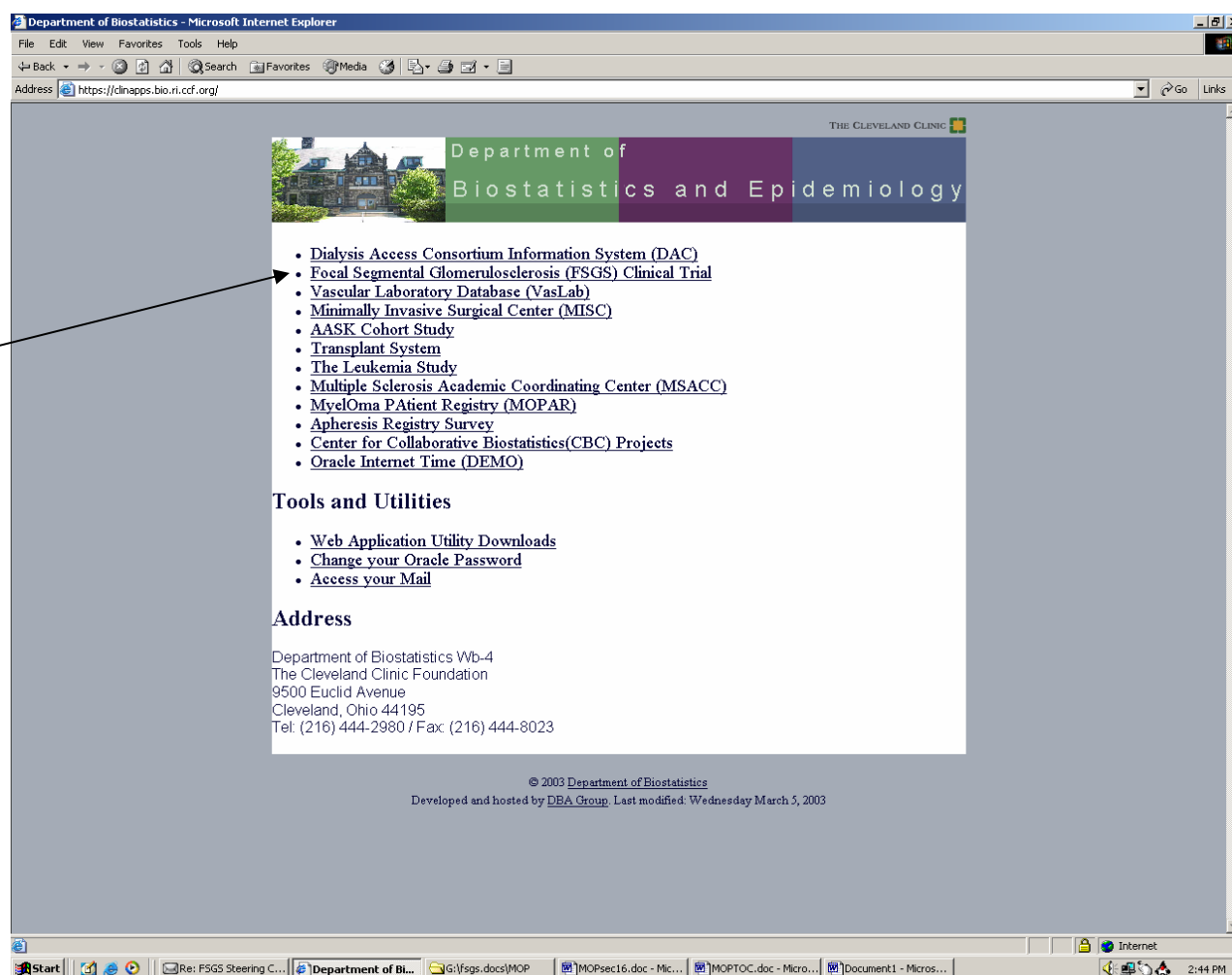
6. You will need to open another session of Oracle Forms to access the Form 2 database.

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16.3. Oracle Clinical Remote Data Capture Production Database

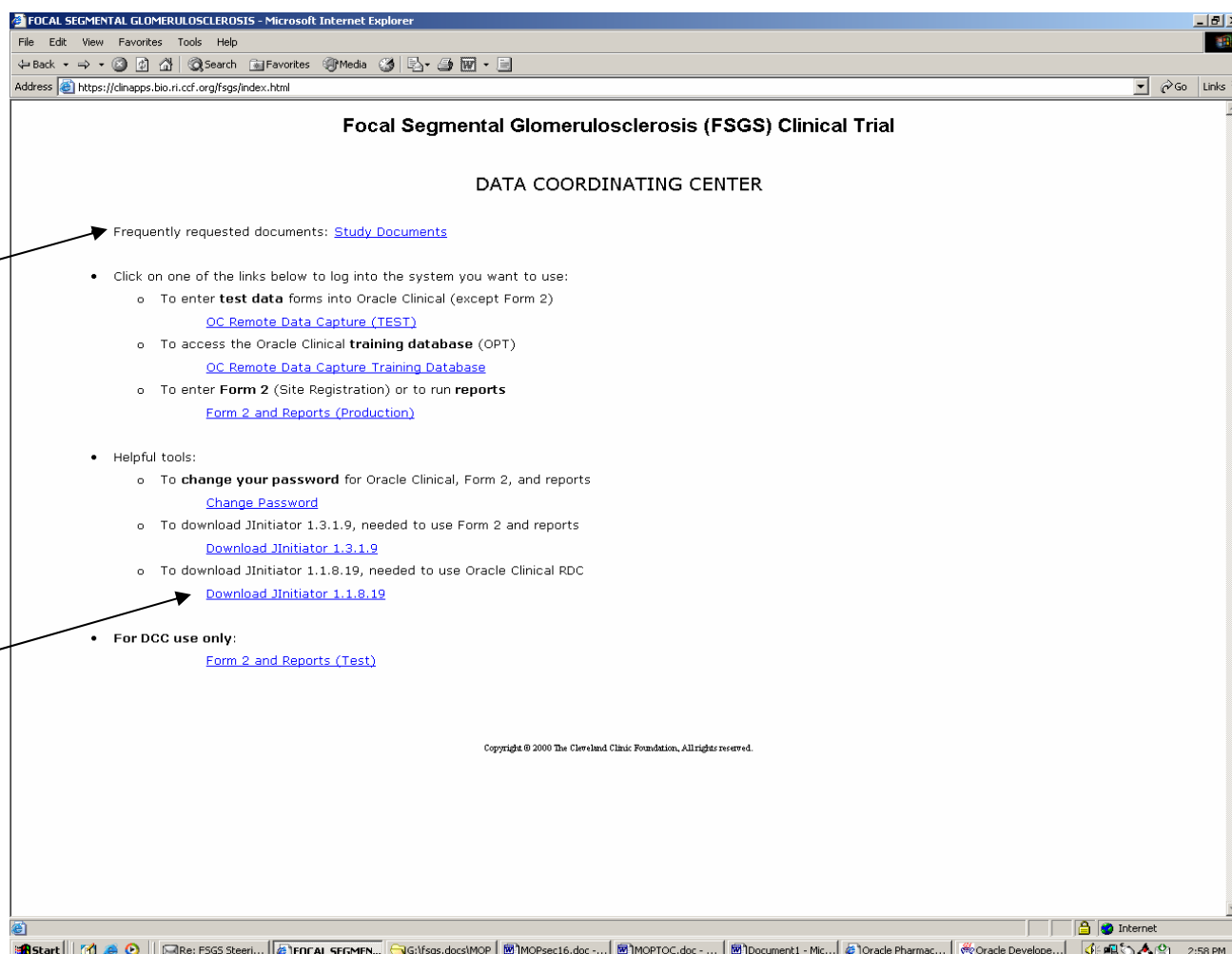
Instructions for Data Entry in Oracle Clinical Remote Data Capture Production Database

1. Go to a PC that is running Microsoft Windows 98 or later, and has access to Internet. Use Internet Explorer (IE) to go to the website **<https://clinapps.bio.ri.ccf.org>**. Notice “https”, not “http”. If you use Windows XP, you need to use IE 6.0.2600 or higher. For the other version of Windows you need to use IE 5.5 or higher.



2. Click on the link **Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial** to access the FSGS web page. This will redirect you to **<https://oc.ccf.org>**. When you get to the web page, you will see the following screen:

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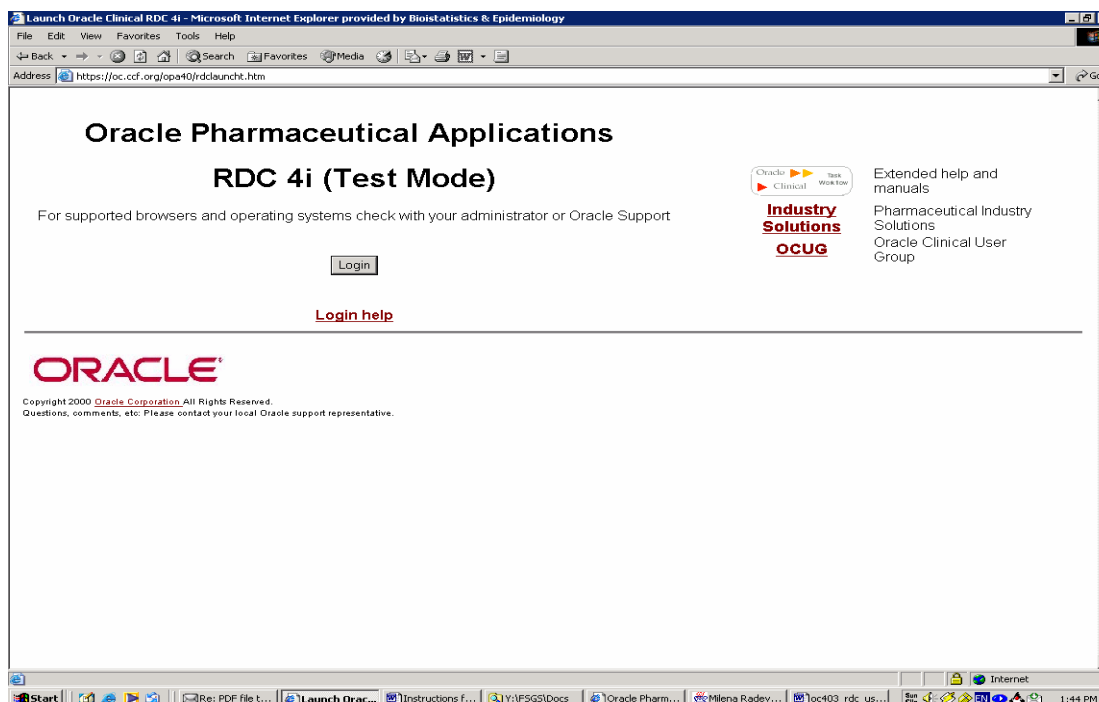


- Before you can access the Production database for the first time, you will need to download and install the Oracle Clinical version of Jinitiator (Note: this is a different version from the Jinitiator you installed to access the Form 2 database, both versions need to be installed). This is software that enables use of the web-based Oracle Clinical data entry screens. Click **Download Jinitiator 1.1.8.19** under **Helpful Tools**. Download Jinitiator to directory C:\TEMP or the location of your choice. Click on the .exe file that you downloaded to install Jinitiator. This will have to be done once on each PC that you are using for FSGS data entry. (You will need to install Jinitiator again only if an updated version is needed.) If you have trouble installing this software, talk to your local desktop computer support person.
- The **Study Documents** option provides you with documents such as the FSGS-CT Protocol, the MOP (as well as Drug Inserts), Forms (CRF), and consent templates. For entering data choose **OC Remote Data Capture Production Database**. To update Form 2 (Site Registration Information) data and to see study reports choose **Form 2 and Reports (Production)**. Note that there is a **Change Password** link under **Helpful Tools**. You should use this link to change the password assigned to you by the DCC as soon as

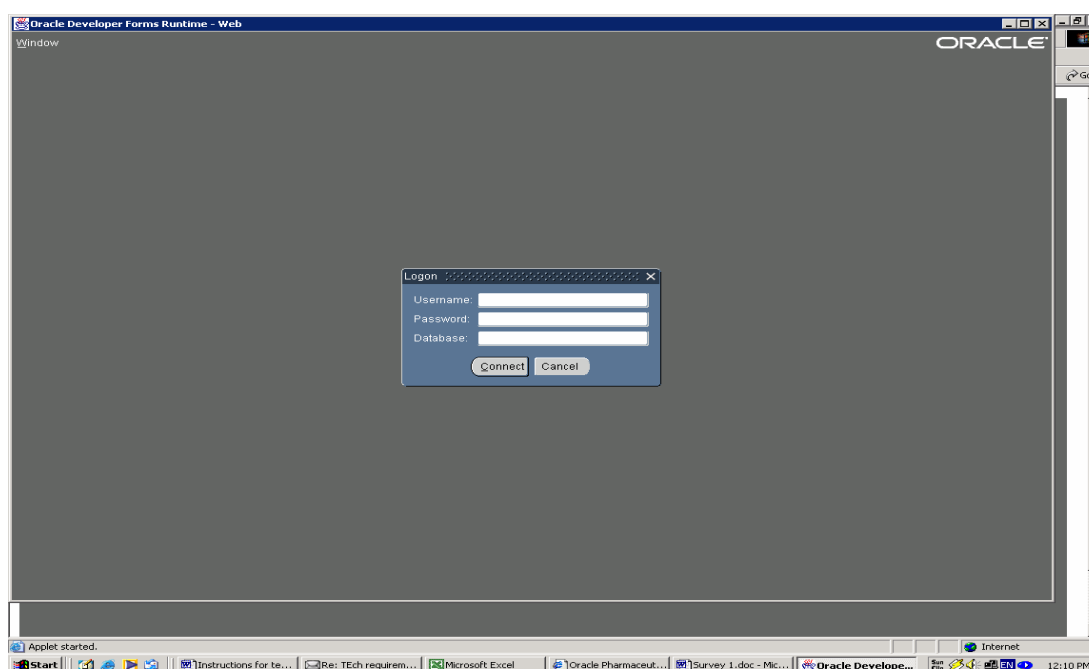
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possible. You will be prompted by the DCC to change your password every 75 days after that.

5. Click on **OC Remote Data Capture Production Database** link. You will see the following screen:



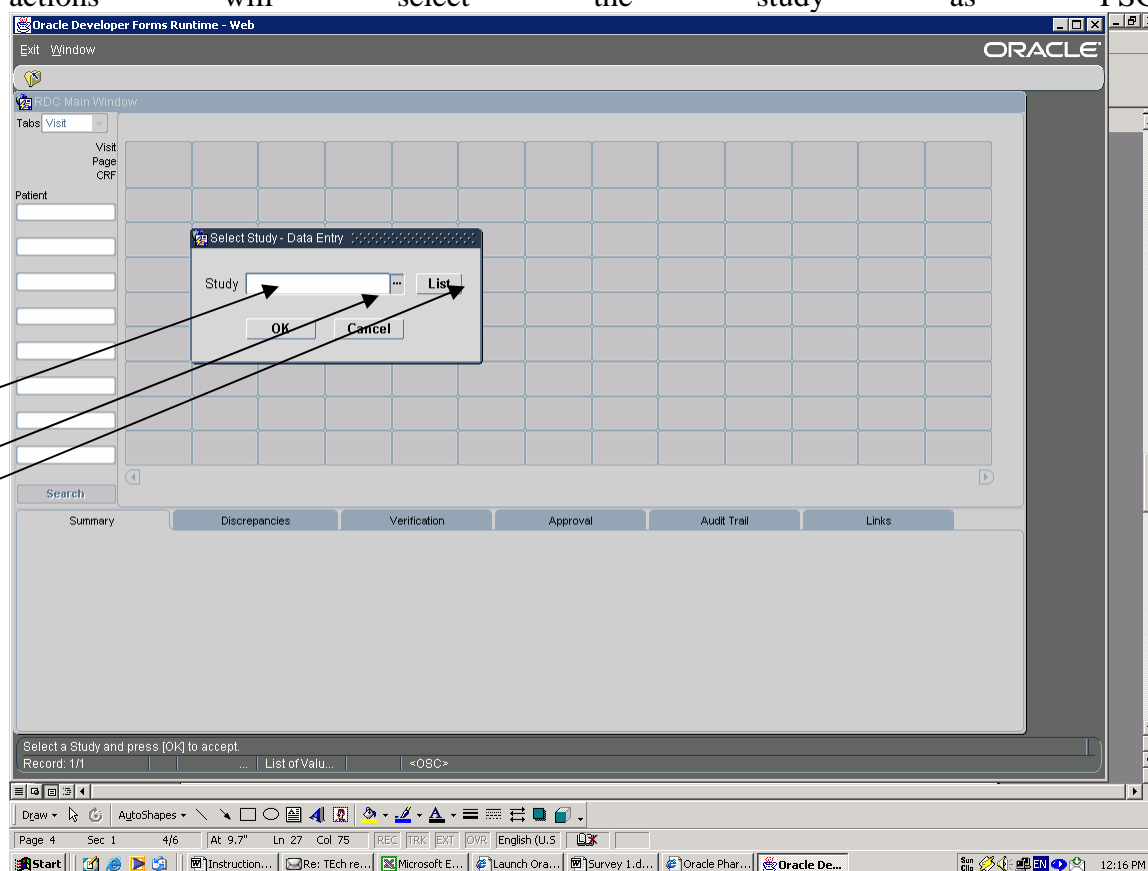
Click the **Login** button. A small pop-up will appear in which you will type your username, password and the database.



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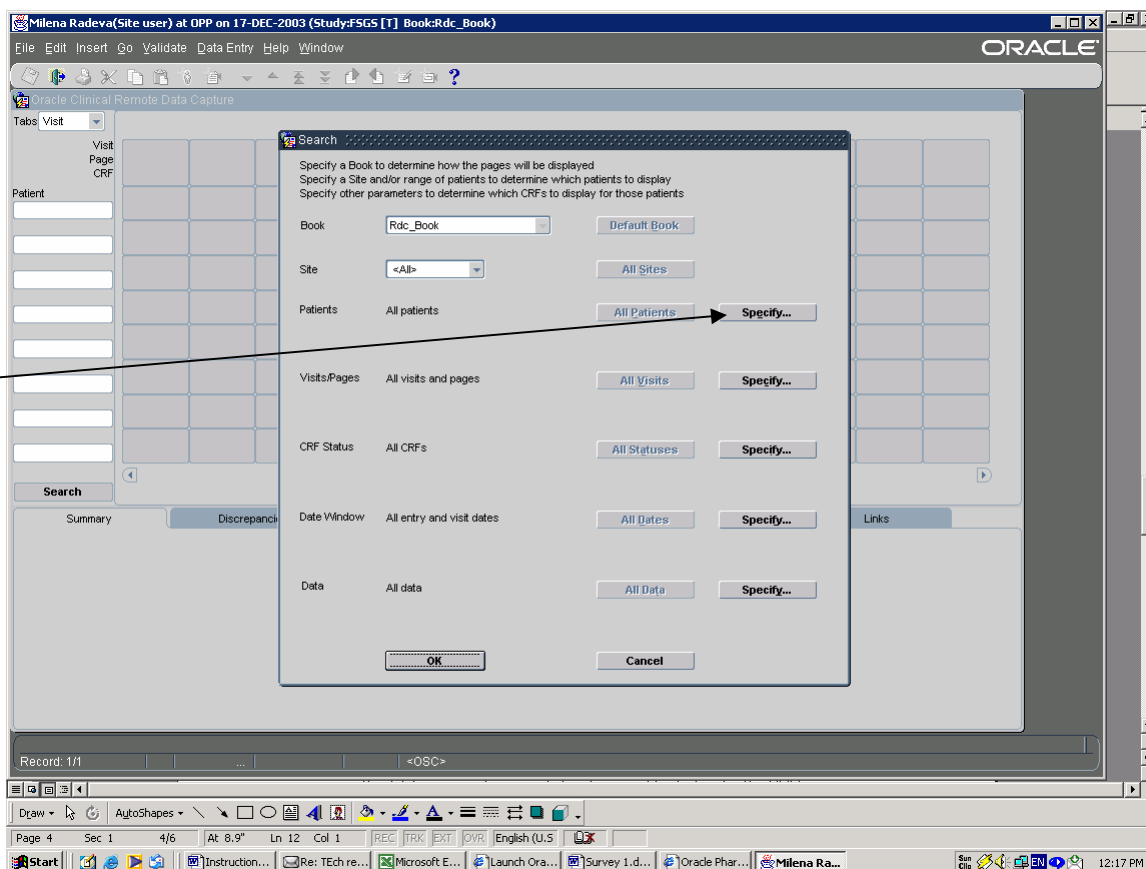
In addition to this screen, a small window will open on your desktop. It will say: **Please do not close this window with a RDC session running. Closing the window will cause the program running to stop working.** It is **very important** not to close this window while you are working in the database.

6. On the login pop-up, enter your username. Your username is assigned by the DCC and is usually the first six characters of your last name followed by the first initial of your first name. For example, for **John Smith** the username will be *smithj*. If this creates a duplicate, a digit will be appended. Use the username assigned to you by the DCC. Once you have entered your username press **Tab** to navigate to the Password field.
7. Enter the password assigned to you by the DCC (or the one you have chosen if you have already changed your password). Press **Tab** to navigate to the Database field.
8. Enter **opp** for the database and click on the **Connect** Button.
9. When the study pop-up box appears, either type “FSGS” and click OK, click on the **List** button, or click on the ellipsis (...), or press the **F9** key on your keyboard. Any of these actions will select the study as FSGS.



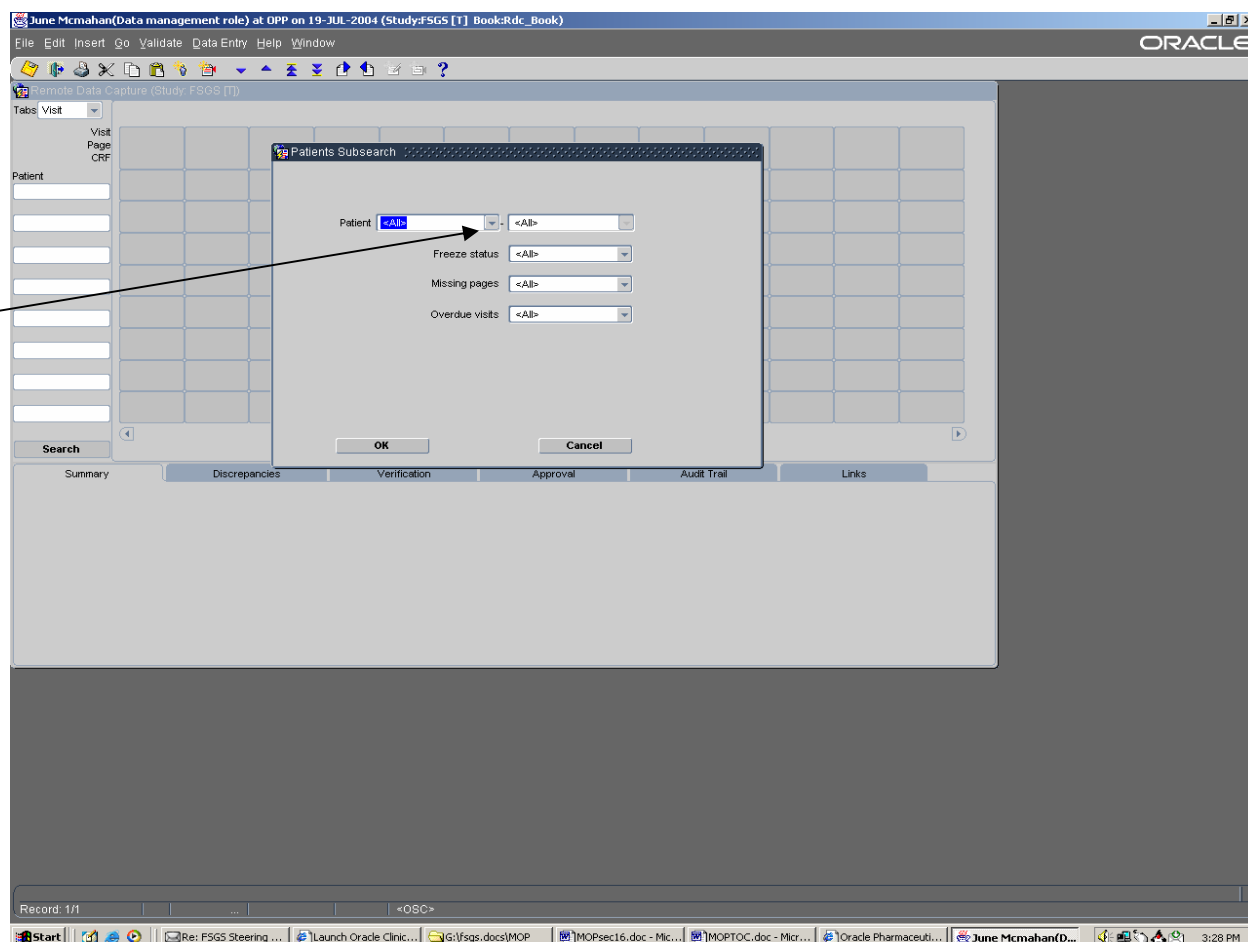
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10. The **Search window** will appear. This window allows you to narrow your view to certain participants, forms, dates, etc. These will be useful for the future as enrollment increases. For your first time accessing the database, a specific “patient” number must be indicated. Click the **Specify** button for Patients.



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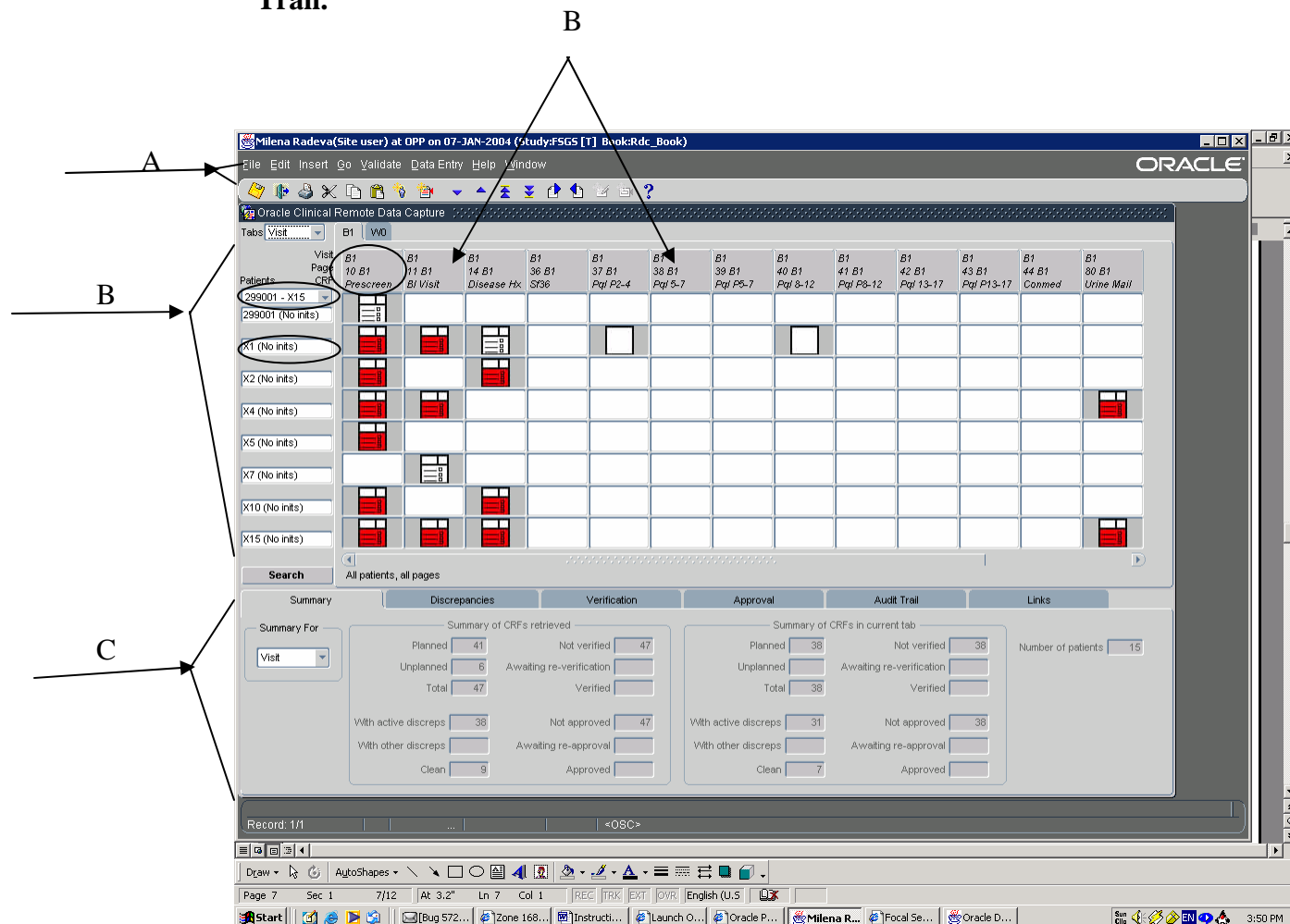
The following screen appears:



11. Click on the Patient **down arrow**. Select the appropriate Participant ID number for your Participating Site. Click **OK**. The search pop-up window appears again. Click **OK**. Note: All Participant ID numbers for the study will be created at the DCC. The Participant ID is a 6-digit number. The first 3 digits represent the Participating Site number. The last 3 digits are sequentially numbered for the Participating Site. The DCC will send you a list of participant numbers assigned specifically for your Participating Site. If you need additional Participant ID numbers created, let us know and we will add more.

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12. You will see a screen that consists of three main parts:
- A. Title bar with commands and toolbar
 - B. Spreadsheet with rows representing participants and columns representing data forms
 - C. Tab area with six tabs: **Summary**, **Discrepancies**, **Verification**, **Approval**, **Audit Trail**, **Trail**.

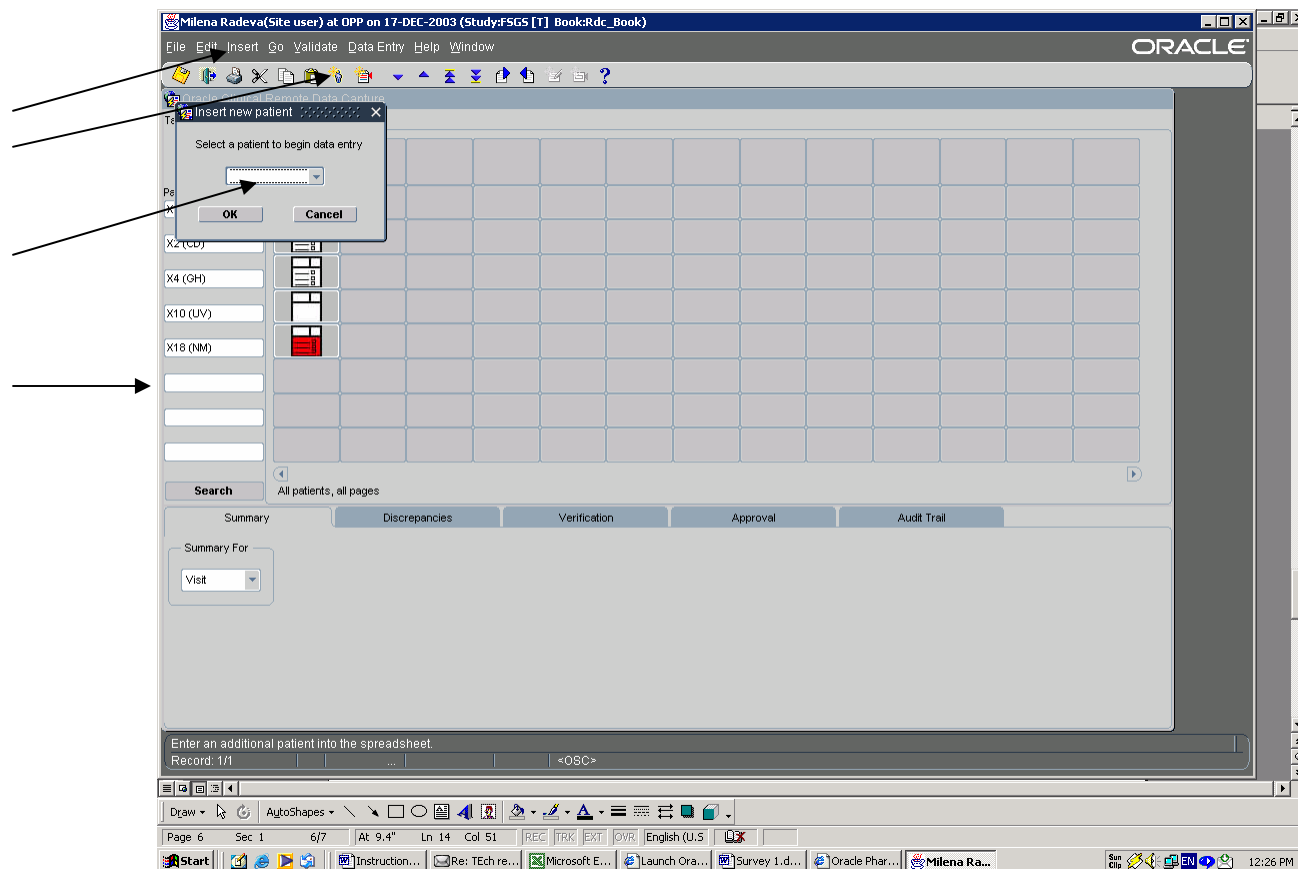


When you rest your cursor on an icon, you will get a brief description. You can also get help on what the different icons and commands mean, etc. by using the Help menu at the top of the screen or the question mark icon. The Summary Tab provides statistics about the item highlighted in the spreadsheet. The Discrepancies Tab is used when queries about participant data need to be answered. The Audit Trail Tab is used to see the history of changes to data. We will not use Verification and Approval in this study, so you may ignore these tabs.

13. For data entry purposes, the format is set-up as a spreadsheet. A cell is the intersection of a row and a column. Each cell represents a specific form (identified in the column title) for a specific participant (identified by the participant ID number shown to the left of the row). Cells contain icons that show the state of data entry (see items 28, 29). Choose the participant and form (CRF) you want to enter by clicking on the appropriate cell on the main table. Note: Make sure that the desired PID and CRF are highlighted before you start entering data.

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14. If data has not yet been entered for the participant, you will need to insert the participant. Click on any empty participant cell, or choose **Insert -> Participant** from the menu bar, or click on the icon on the toolbar that looks like a person. An “Insert new participant” window pops up:



- Click on the down arrow and choose the participant number you are looking for from the list, and then click **OK**.
15. If you are looking for a participant for whom there are some data entered, but that participant's ID number does not show on the screen, click on the down arrow beside the word **Participants** on the screen to display a dropdown. You may select another range of participants to display in the spreadsheet. Participants are always ordered numerically by ID. Also, if you currently have the last displayed participant selected, you may press the down arrow to scroll the participant column to the following participants.
 16. The column tabs (just above the form column headers) can be grouped by study, phase or visit. You can change the current selection by using the down arrow after the **Tabs** button in the upper left corner. The only study that can be chosen is **FSGS**. The phases that are available to choose are **Baseline/Screening** and **Follow-up**. It is recommended that you display the tabs by visit. To go to the forms for a given visit, just click on the appropriate visit tab.
 17. Make sure **Visit** is selected on the **Tabs** options. Then the tabs above the main table will indicate the visit number for which you want to enter data (e.g. B01, W00, etc.). Choose the correct visit tab. Click on the cell where you want to enter or review data (see item 13).

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The current form and participant cell will appear with an aqua background. A data entry window for the form you want to enter will appear.

18. If needed, there are two ways to move or resize the form screen. One option is to right click on the *form's title bar* and choose from the menu. It might take a few iterations before you get to the size and the position of the screen you want. The other option is to left click on the *form's title bar*. This window allows you to move/resize the screen (using your mouse to expand height and width as in using any normal Windows application). Click **Done** once desired size has been obtained. If the form screen "hides" behind the tab/cell screen, just click on the active (aqua colored) cell and the form screen will come forward. The settings for the size of the screen will stay the same for the current session. The screen settings are the default of the program, hence, each time you login you will need to adjust your screen, if you desire.
19. Once you are in the form you want to enter, you will see the following screen:

Click in the **Visit Date** field and hit **Enter** (do not complete this field). The form you selected to enter will appear.

20. You may use the **Enter** or **Tab** key to navigate between fields on a form. The exception is when you are on a repeating group of questions (see item 23). You may also use the mouse to navigate between fields, although it is highly recommended that you complete the questions in the order of the form.
21. Some questions have a finite set of possible valid responses. This is known as a **(LOV) list of values (...)** or **discrete value group**. To pick from the list of values instead of typing, click the LOV icon (...) to the right of the box, which appears in a gray box. Or you may

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press F9 to display the LOV. A pop-up will appear with the valid responses (e.g., 0, 1) and their meaning (e.g., No, Yes). Click on the value you wish to enter, and then click the OK button. The pop-up closes and you are returned to the data entry form, with the selected value in the question field.

22. During entry, univariate data checks are applied to some questions and check for appropriate responses as soon as an entry has been made for that specific question. These are checks for data types, valid values, maximum and minimum, etc. If a pop-up box titled “**Univariate Validation Failure**” appears, this means that a univariate failure has been detected. You may:
 - a. Click **Cancel** and then reenter data for the question, in the event that you mistyped the response, or
 - b. Type a comment (ex. identifying the reason for an “out of range” value) referring to the question’s response, and click **Save** to create a discrepancy.

For detailed navigating instructions and examples refer to Section 17.

23. A **repeating group** is a set of questions that are grouped together for multiple entries for the same question on the same form. Examples are the symptoms/medical history (Forms 11, 14) or medications (Form 44). You may use the **Tab** or **Enter** key to move between questions within a repeating group (one row), and the **Up** and **Down** arrow keys to navigate between the rows of a repeating group. Then you must hit the **Page Down** key to move to the next question, or you may use your mouse to click in the next question after the repeating group.
24. The LOV for MedDRA codes and WHODRUG medication names work differently than other LOVs. This is due to the fact that the system limits a search to no more than 1000 LOVs at a time. The MedDRA and WHODRUG “lookup” contain too large of a quantity to be displayed at once. For this reason the LOV must be limited before being displayed. To do so:
 - a. When in the MedDRA or WHODRUG question and before you display the LOV, type %<TERM>% substituting for <TERM> a word, phrase, or word fragment to limit the search. For example, %HEAD% will cause the MedDRA LOV to display only those terms with HEAD somewhere in the text (e.g., HEADACHE, FUZZY HEAD, HEAD COLD, etc.)
 - b. Click on the ellipses (...) or press F9 to display the codes containing your specified term. You may scroll through the displayed codes to select the one you want.
 - c. When the LOV is displayed, you may further narrow your search by clicking in the “Find” field, enter %<ANTHOTHER TERM>% and pressing **Enter** (for example, by entering %NECK% in the “Find” field will narrow the displayed list to only those terms containing both HEAD and NECK within the text.





For detailed navigating instructions and examples refer to Section 17.

25. When you are done entering the form save it by clicking on the “diskette” icon on the toolbar or by choosing **File-> Save** from the menu bar. A form is also automatically saved once you navigate past the last question on the form (that is you press ENTER at the last field on the form).
26. If you have entered part of a form and you want to “bail out” without saving it, you need to be on page 1 of the form (if you are on a page other than page 1, use the arrow page icon on the toolbar to page up to page 1), and your cursor must be in the Participant ID field. Click




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on the X in the upper right corner of the **form** screen. A pop-up box will prompt you. Choose “**exit without saving**”.

27. If you want to delete a form that has been entered, click in the participant/form cell you want to delete and choose **Edit→Delete Page** from the menu bar. A pop-up box will prompt you. Verify that you do in fact want to delete the page. Note: In this context the CRF is referred to as a PAGE. Be cautious if you decide to use **Edit→Delete Page**. Using this function WILL delete the FORM (CRF), not just the current page within the CRF. Any CRF deletion will be questioned by the DCC.
28. You will notice that the data entry status icon changes to indicate where the form (CRF) is in the data entry process.

Icon	Label	Description
	Blank	The CRF has been marked as blank. See <link to DE Window Header> section for information about blank CRFs.
	Created	The CRF has been opened, but no data has been entered.
	Entry Started	The CRF has been opened and data entry has been initiated, however, not all questions are completed.
	Entry Complete	All questions in the CRF have been completed.

29. If you have entered data on the form that violates the data validity checks that have been programmed, a discrepancy will be created.

	Icon	Label	Description
White		None	There are no discrepancies in the CRF.
Red		Active	There is at least one discrepancy in the CRF that is actionable by you.
Yellow		Other	There is at least one discrepancy that must be addressed by the Investigator and none that are actionable by you.

30. A discrepancy may occur during data entry or may occur after the form has been saved. A pop-up box will prompt you during data entry if you have entered an out of range value, an invalid date, due to other range checks. At this time you will have the option to **cancel** out of the discrepancy window and correct your data entry response in the appropriate field. If your entry is valid and you want this value in the database, type an explanation in the comment section of the pop-up box and click **OK** (an example of why you would want to add a comment, would be a Participating Site filled out the form and the CCC is entering exactly what they have on the hard copy. Further inquiry will be needed for resolution.). After saving, if there is a discrepancy, the form icon will appear red. Click on the discrepancy tab in the lower part of the screen and then click on the form. You need to open the form that contains the discrepancy, go to the field that caused the discrepancy and correct it.

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16.3.1. Resolving Discrepancies

31. Click on the spreadsheet cell for the participant form for which you would like to resolve discrepancies. Recall that a red icon in a cell indicates that the form has unresolved discrepancies.
32. Click on the Discrepancies tab in the tabs pane at the bottom of the RDC window. You may need to move and/or resize the form entry window in order to see the tabs pane.
33. When you first click on the tab, the discrepancies are displayed in summary mode. Each discrepancy occupies one line in the grid. The second column of the grid contains a description of the discrepancy, enabling you to quickly identify each discrepancy. Notice that the sub tab “List” is currently selected.
34. In the left most column of the grid, each discrepancy is numbered starting with 1 and going down the grid. Across the top of the grid, right of the “List” sub tab, are corresponding numbers that detail each “List” discrepancy.
35. To display all the details of a discrepancy, click on the sub tab with the number corresponding to the number of the discrepancy you wish to view. The contents of the discrepancy pane changes to display information for that discrepancy only.
36. For multivariate discrepancies (discrepancies based on a validation check comparing two or more pieces of data), the questions involved in the check will be displayed in a grid under the comments box, with the current value of each displayed to the right. For univariate discrepancies, the value is specified in the description.
37. Review the discrepancy and decide how it should be handled. If a data change is required, for multivariate discrepancies, first click in the **Value column** corresponding to the question you wish to jump to. Now click on the **Action drop down**, and select **Go to Data Field**. The correct form will be displayed in the form entry screen, and the cursor will be placed in the question. Make your data change and save the form. Assuming the new data renders the discrepancy no longer applicable, the discrepancy is automatically marked “Closed.” A pop up box will ask the reason for the change. Select reason for change (i.e., data entry error) and click **OK**.
38. If you need to route the discrepancy to another site or study group, click on the drop down and select the appropriate code: Send to the Participating Site, Send to CCC, or Send to DCC. A pop-up window appears in which you may and should type in the text box an explanation of why you are routing the discrepancy. Click **OK** to save the text. Notice that the Status changes appropriately.

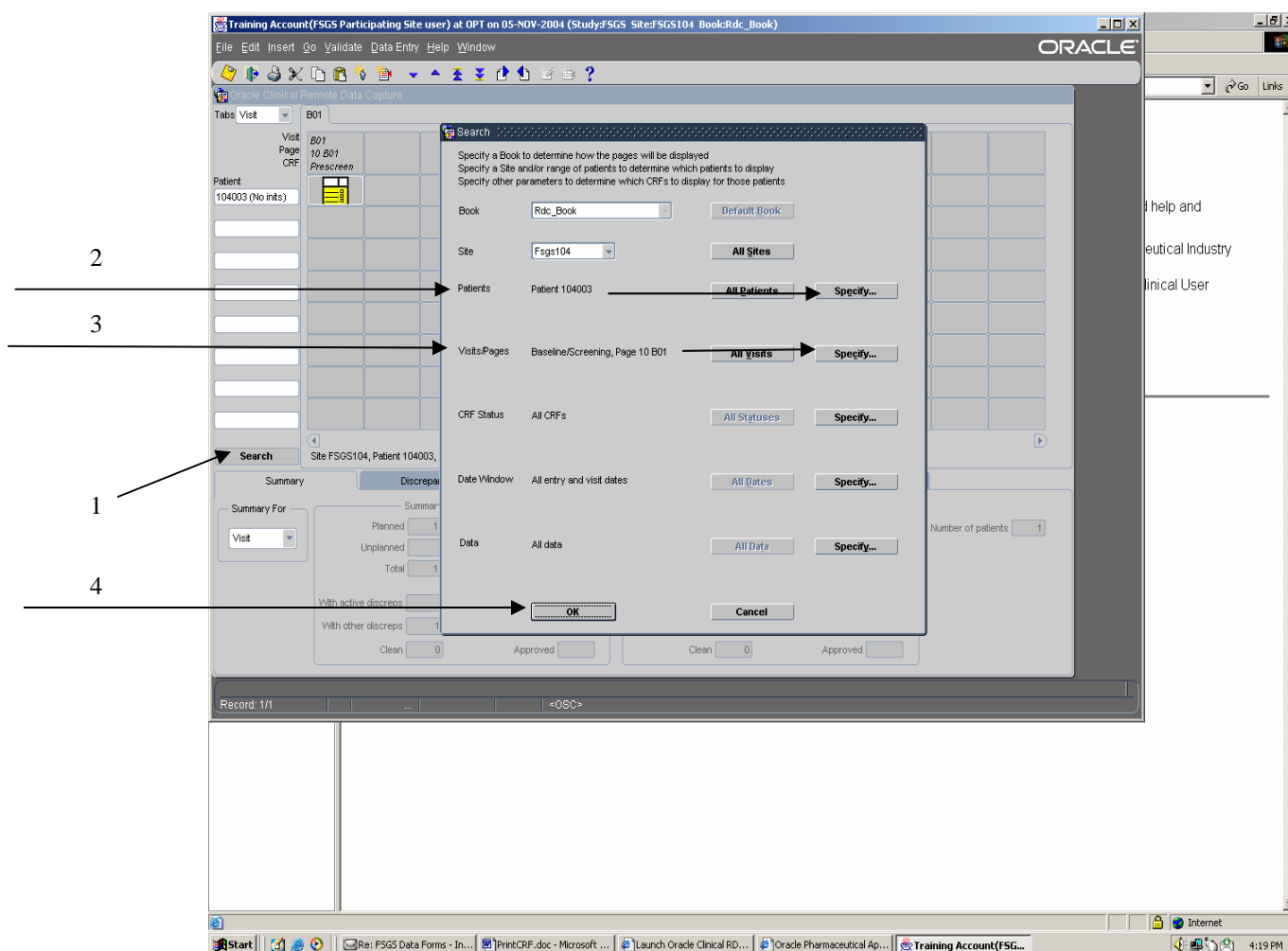
If you need any help, contact your CCC and they will do their best to assist you. The contact information is available in the FSGS-CT Address Directory. If the CCC cannot resolve the problem, the CCC will contact the DCC. DCC personnel are most likely to be available between 7:30 a.m. and 5:00 p.m. Eastern Standard Time, Monday through Friday. The DCC is closed evenings and weekends.

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16.3.2. Instruction on How to Print a CRF From Within the Oracle Clinical RDC Production Database

Printing a Completed CRF (form entered into the database):

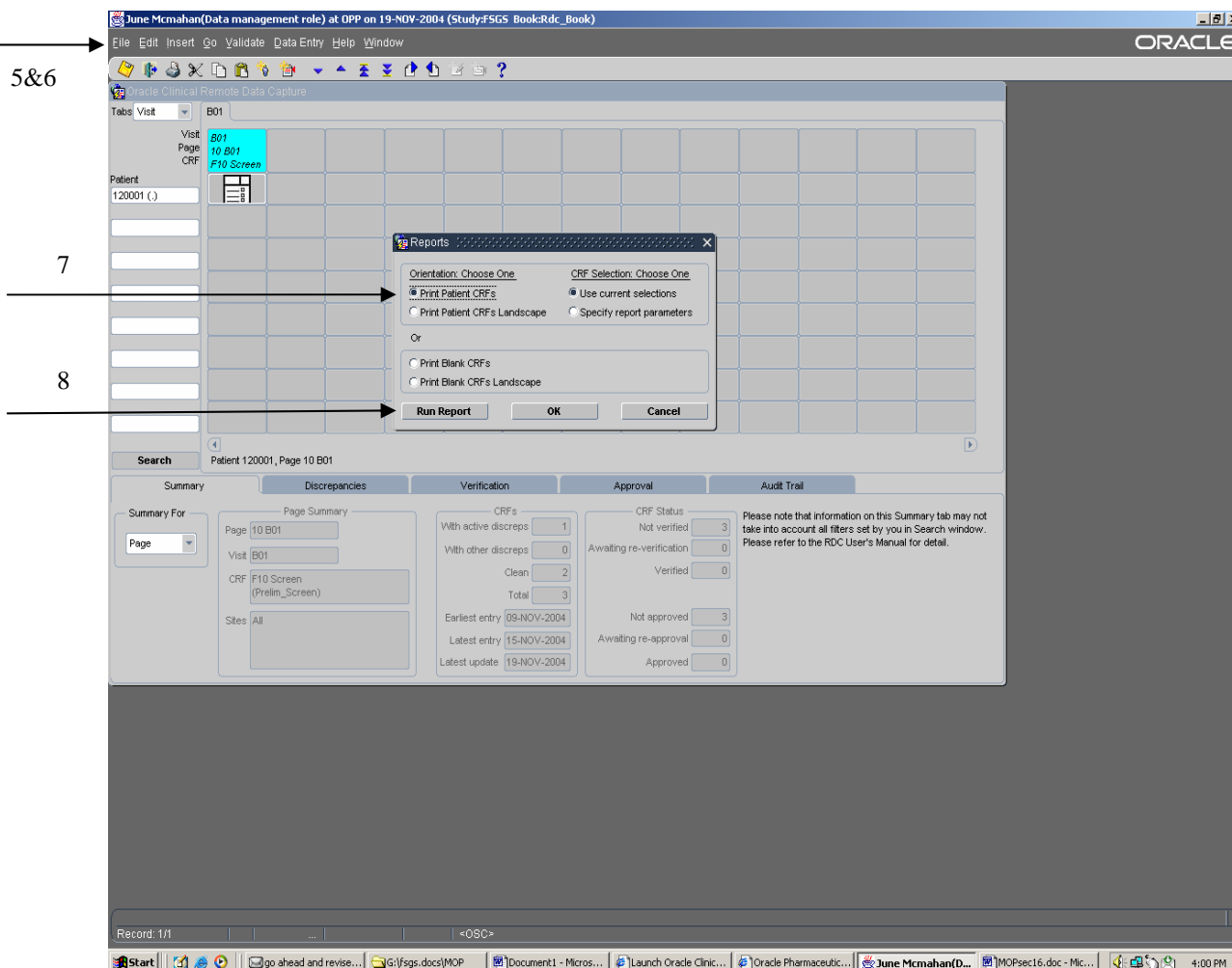
1. While logged into the Production Database, click on the **Search** button (located below the Patient column and above the Summary tab).
2. Click on the **Patients - Specify** button and select (highlight) the desired PID you want to print a CRF for. Click **OK**.
3. Click on the **Visit/Pages – Specify** button and select (highlight) the desired CRF you want to print (Note: if you do not specify a CRF the default is to print all the CRFs within that visit).
4. Click **OK** to accept the Search criteria.



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Notice that only the specified “Visit/Page” (CRF) is now displayed.

5. On Menu bar click on **File**.
6. Select **Reports**.
7. Double check that for “Orientation” - **Print Patient CRFs** is selected.
8. Click on **Run Report** button.



- This will open a Submission of Module window. Click on **Submit Job** button.

Oracle Clinical

Submission of Module: RXCDMLPD (Study: FSGS [T])

Report selected patient data in CRF format

Server/Queue: **JOB_SET_SERVER** Report Server Job
Printer: **RXC_PRINTER**

Description	Current Value	Mand- atory?	LOV ?	Pat- tern?
Mark values changed since what date/time	None	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Specific date/time for marking		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Report Discrepancies?	Y	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Report Response History?	Y	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Exit Submit Job Job Details Job Status Schedule Change Study

Summary Discrepancies Verification Approval Audit Trail

Please select a CRF by clicking on a cell to view discrepancy information

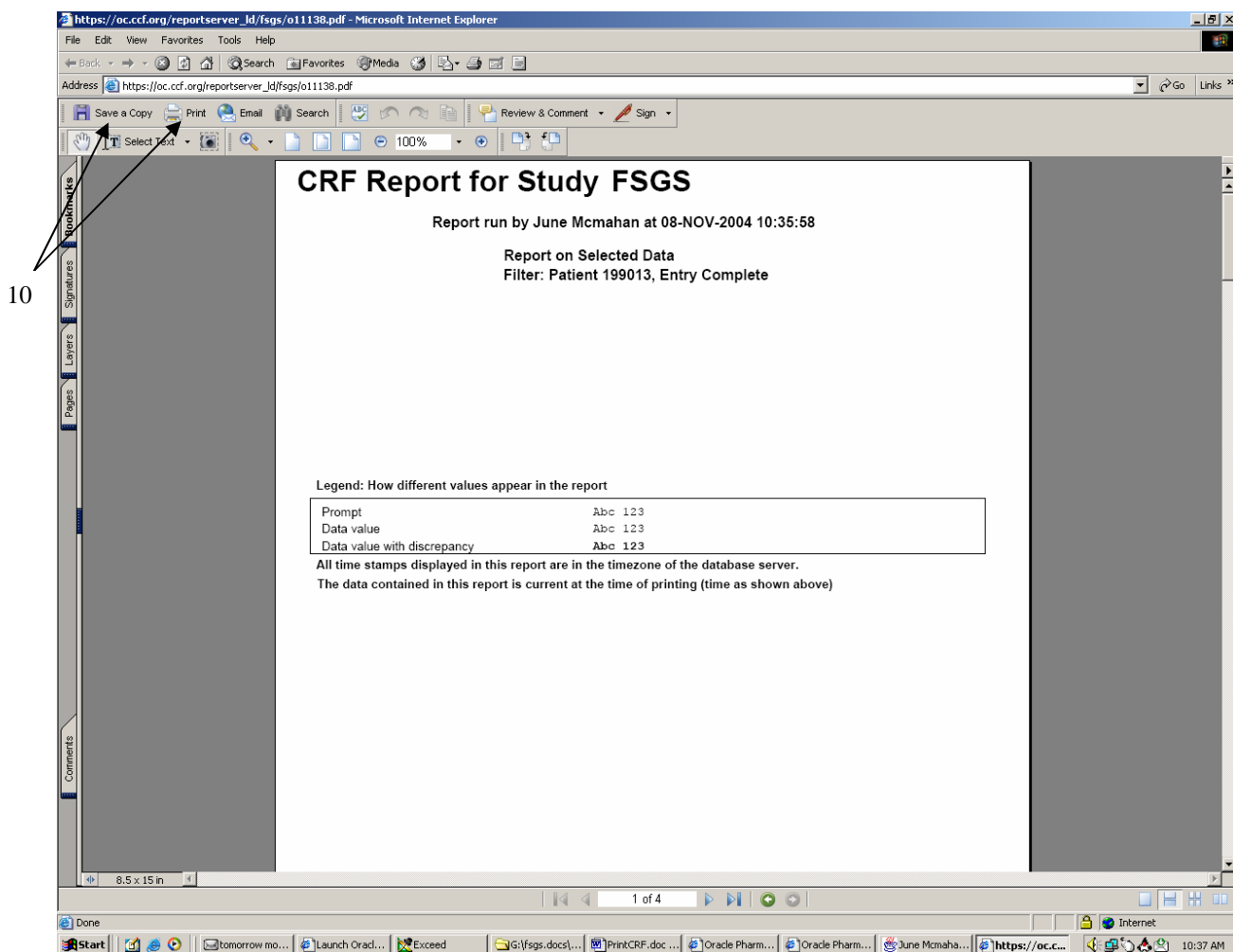
Record: 1/1

Checkboxes show if response is Mandatory, if LOV available, if % search allowed

Oracle Clinical

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10. An Adobe Acrobat application window will open containing your requested document. Either **Print** the pdf document or **save** the document to your hard drive.

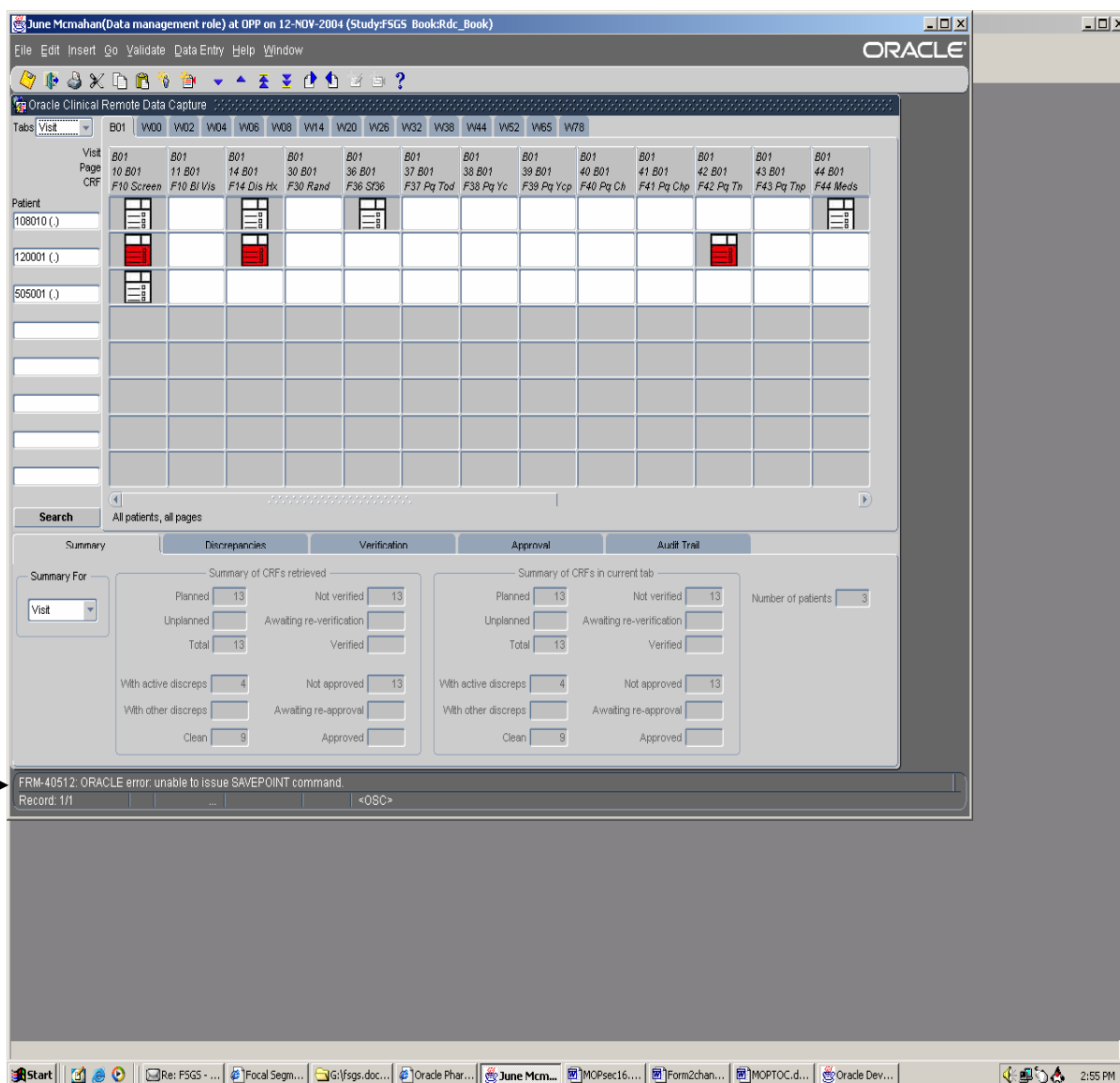


11. Once you have either printed or saved the document, **close** the Adobe Acrobat window. Click **Exit** to close the Submission of Module window.

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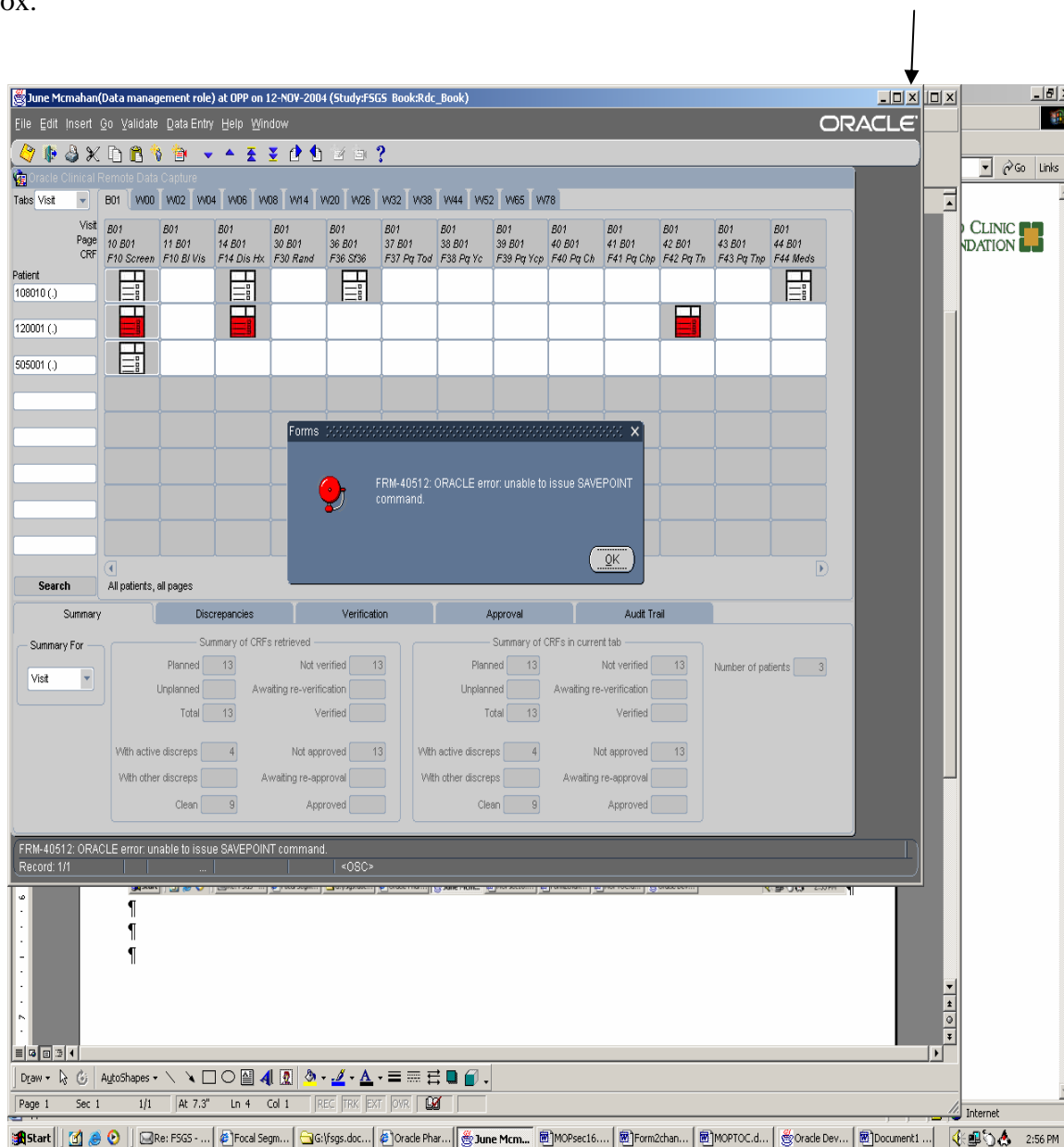
16.3.3. What to do if you get timed-out of the [OC Remote Data Capture Production Database!](#)

1. The Oracle Clinical database has been setting idle for a while. Not realizing you have been “timed-out” you try accessing a form for data entry, or you go under File and click on Exit to get out of the database but instead you get an error message that states “FRM-40512: ORACLE error. Unable to issue SAVEPOINT command” or “FRM-40733: PL/SQL DBMS_ERROR_TEXT failed”.



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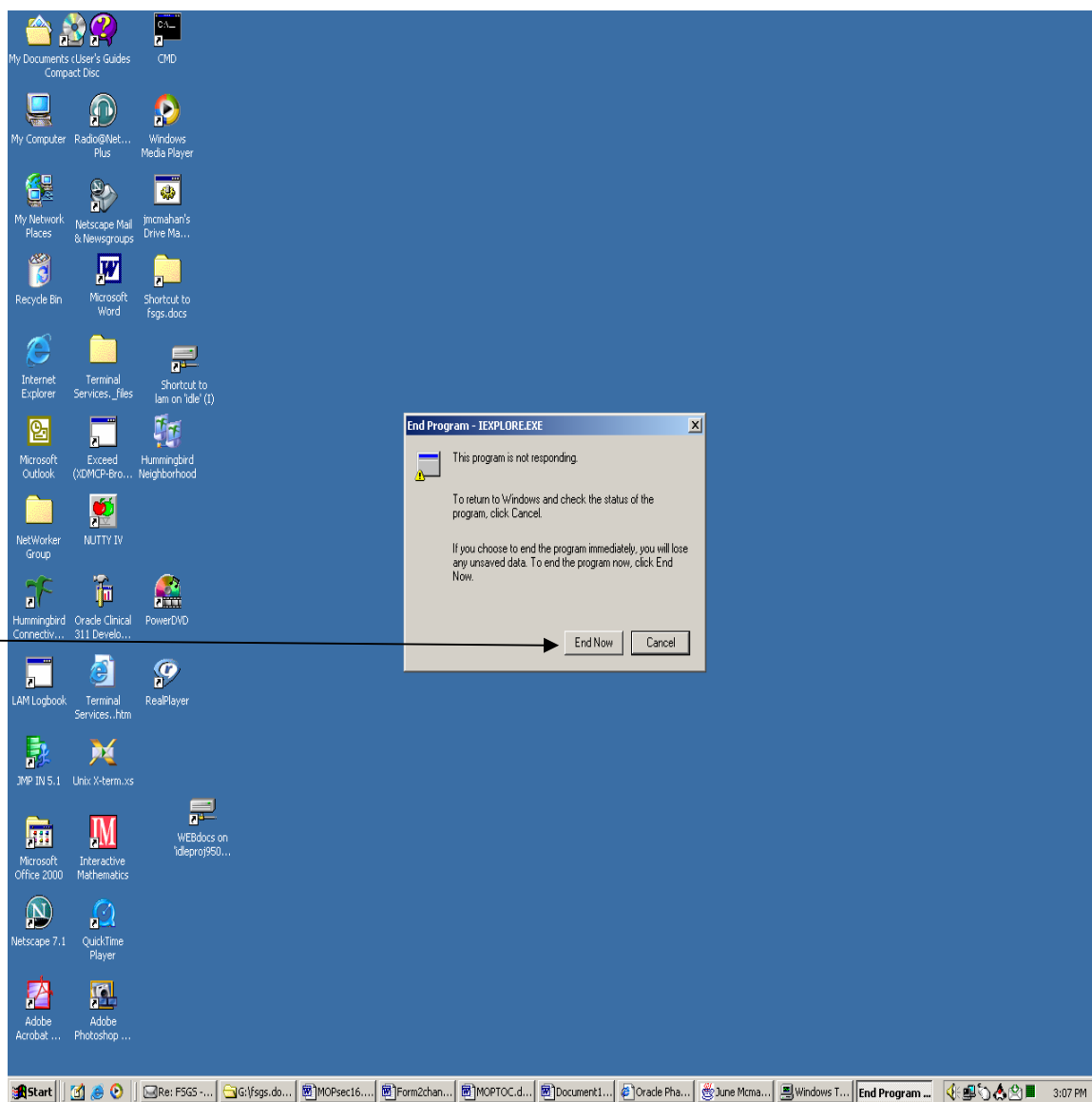
2. You **click** on the **X** button in the top right corner, but you get an Error Message pop-up box.



3. Click **OK** and this should kill your session in Oracle Clinical.
4. If you get stuck in a loop of Error Messages, you may want to use your Task Manager to kill the session. **Right click** on your Windows **status bar** (gray in color), located at the bottom of your screen (same "line" as your Start button). **Click** on the **Task Manager** option. **Highlight** (select) the appropriate session to kill (OPP session) and **click** on the **End Task** button.

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5. An End Program pop-up box appears that states the “program is not responding”. Click on the **End Now** button.



6. You will need to open another session of Oracle Clinical to access the FSGS database.

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16.4. Numbering Visit/Sub-Visit Instructions

Once a participant has been randomized, the W00 visit has been held, the Participating Site is to go to Form 2 ➔ Reports ➔ 104:Visit Schedule Report and generate an Appointment Schedule for their participant. Print this Report and keep a copy conveniently located for quick and frequent reference.

All **Protocol Visits** will be sub-visit number 00.

Unplanned Visits will be numbered sequentially starting with 01 and will be based upon which target window the unplanned visit occurred (refer to the participants' Appointment Schedule).

Using the Appointment Schedule:

- ❑ Determine the target window in which the unplanned visit occurred (a visit window indicates the Visit week/month, as well as the “upper & lower” window dates.
- ❑ Sequentially number the first unplanned visit as 01, even if this occurred before to the actual Protocol Visit (which will always be labeled sub-visit 00).
- ❑ All CRFs completed at that unplanned visit (e.g. Form 16 – Follow-up visit form, Form 44 – Medication Form, Form 60/61 - AE/SAE Forms, etc.) should have the same sub-visit number 01.
- ❑ Keep track of participant unplanned visits, the actual face to face contacts, again starting with sub-visit 01 within each new target window.

Example scenario:

The example Appointment Schedule for Participant 999001 states:

Absolute Visit	Earliest Date	Recommended Earliest Date	Target Date	Recommended Latest Date	Absolute Latest Date
W02	30-Nov-2004	30-Nov-2004	07-Dec-2004	14-Dec-2004	14-Dec-2004
W04	15-Dec-2004	15-Dec-2004	21-Dec-2004	28-Dec-2004	28-Dec-2004

My participant is scheduled to come in on his 07-Dec-2004 W02 Protocol Visit, but prior to this visit came in to the office on December 1, 2004. Checking his appointment schedule I determine that it is within the W02 window. Seeing that this is his first “unplanned” visit before the Protocol Visit, the Form 16 (Follow-up Visit Form) question 3 Visit Number is completed/entered as W02-01.

On 07-Dec-2004 the participant comes in for his Protocol Visit in which Forms 16, 44, 46, 80, 83 are completed/entered with Visit Number as W02-00 (because it is the Protocol Visit).

On 13-Dec-2004 the participant *calls* into the office and the Principal Investigator determines that one of the study medications dose should be adjusted, therefore, a Form 44 – Medication Form is completed/entered as W02-02.

On 16-Dec-2004 the participant was hospitalized and therefore, the Participating Site completes a Form 62 - Hospitalization Form as well as a Form 61 – Serious Adverse Event Form.

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According to the Appointment Schedule, this event happened within the W04 window; hence, the Visit Number is W04-01 for forms 61 and 62.

16.5. Unplanned Visit or Page in the Oracle Clinical Production Database

An example of an unplanned visit would be that the Core Lab requested another urine sample be collected in addition to the two initial samples submitted. For whatever reason the participant was seen at the Participating Site and an additional CRF was completed and should be entered into the database.

16.5.1. Inserting an Unplanned Visit

Determine whether you need to insert either:

- 1) “Page” – a specific CRF that would not be displayed in a typical follow-up visit (i.e. Forms for AE, SAE, Hospitalization, Toxicity, Death, etc.)
- 2) “Visit” – a duplicate set of CRFs displayed in the database for an actual protocol visit (i.e. Follow-up Forms including Follow-Up Visit, Medication, Physical Exam, Urine Mailing, Blood and Serum Mailing)

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To insert a “Visit”; while logged into the Oracle Clinical Production database, with a specific PID selected (patient number highlighted), and making sure that you are within the appropriate visit tab, **click** on **Insert** located on the top Menu bar → select by **clicking Visit**.

The screenshot shows the Oracle Clinical Production database interface. The top menu bar includes 'Insert', 'Go', 'Validate', 'Data Entry', 'Help', and 'Window'. The 'Insert' menu is open, showing options like 'Visit', 'Page', 'CRF', and 'Discrepancy'. The 'Visit' tab is selected, displaying a grid of visit tabs (W00 to W79). The patient number 199013 is highlighted in the left sidebar. The bottom section contains a 'Summary' tab with various data entry fields and a 'Discrepancies' section.

Summary

Patient Summary

Patient: 199013

Initials: []

Birthdate: []

Sex: [] Age: []

Site: FSOS199

Discrepancies

Active: 17

Other: 0

Closed: 0

Total: 17

CRFs

With active discreps: 12

With other discreps: 0

Clean: 5

Total: 17

CRF Status

Not verified: 17

Awaiting re-verification: 0

Verified: 0

Not approved: 17

Awaiting re-approval: 0

Approved: 0

Visits

First: B01

Latest: B01

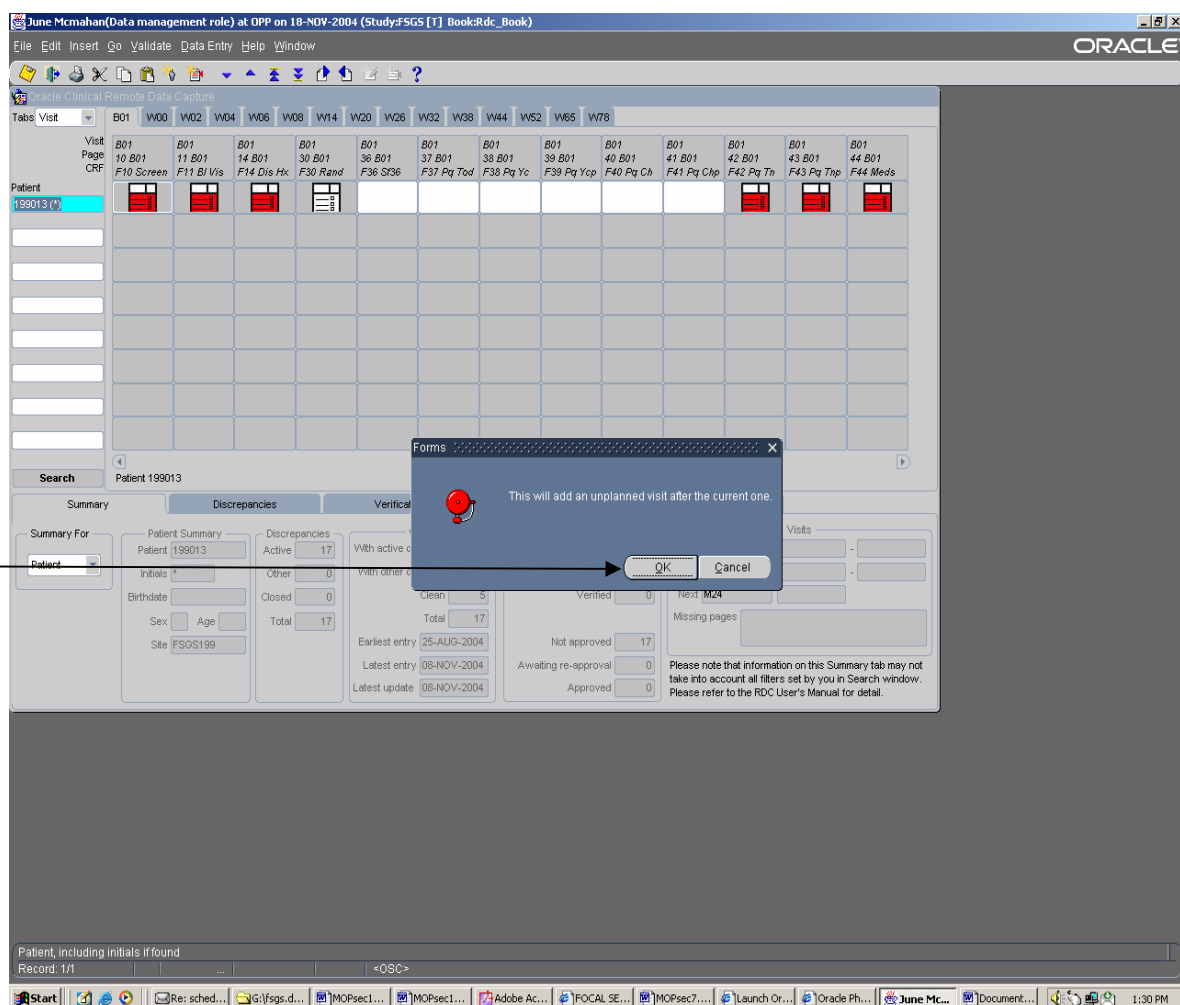
Next: M24

Missing pages: []

Please note that information on this Summary tab may not take into account all filters set by you in Search window. Please refer to the RDC User's Manual for detail.

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A popup window will appear indicating that this will add an unplanned visit after the current one. Click **OK** if you are sure you want to add a sub-visit for this participant. Click Cancel if you do not want to add a sub-visit.



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Notice that -

1. A whole set of CRFs for this participant within the specified visit window is displayed. If a CRF was automatically opened when you clicked OK to create the sub-visit, click on the X in the upper right corner of the CRF (do not click on the X in most upper right corner, this will kill your current session).
2. Using your scroll bar, **scroll** to the desired CRF and click in the **blank cell**.
3. The B01 tab has a sub-visit description **B01.1**.

The screenshot displays the Oracle Clinical Remote Data Capture application. The main window shows a grid of CRFs for Patient 199013. The grid has columns for visits (B01, W00, W02, W04, W06, W08, W14, W20, W26, W32, W38, W44, W52, W58, W78) and rows for CRFs (F10 Screen, F11 BI Vis, F14 Dis Hx, F30 Rand, F36 SI36, F37 Pg Tod, F38 Pg Yc, F39 Pg Ycp, F40 Pg Ch, F41 Pg Chp, F42 Pg Tn, F43 Pg Tnp, F44 Meds). The B01.1 sub-visit is highlighted. The interface includes a search bar, a summary section, and a taskbar at the bottom.

Annotations:

- 1: Points to the 'Visit Page' dropdown menu.
- 2: Points to the 'Search' button.
- 3: Points to the 'B01.1' sub-visit description.

16. DATABASE AND DATA ENTRY

16.5.2. Inserting a Page

Determine whether you need to insert either:

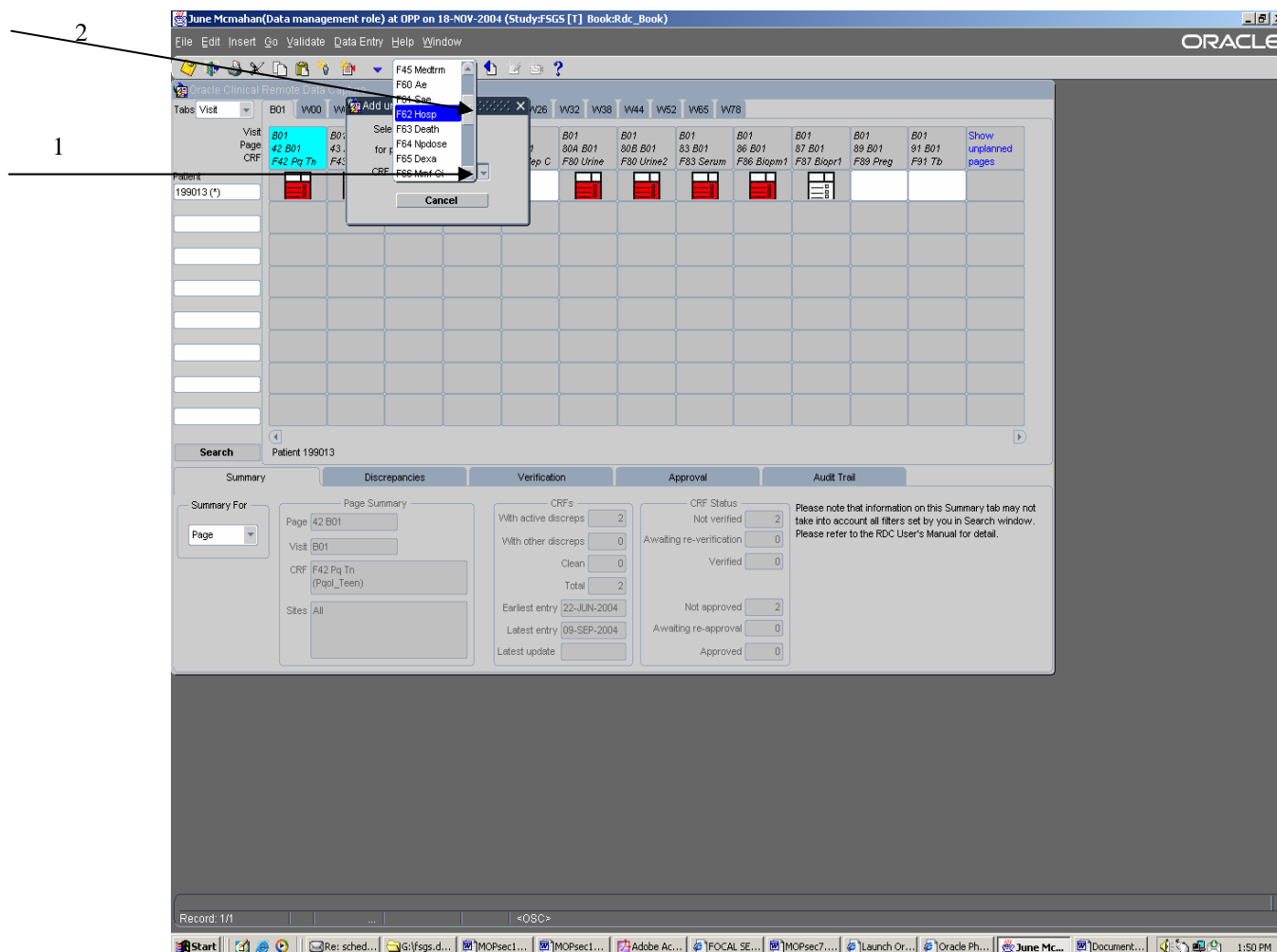
- 1) “Page” – a specific CRF that would not be displayed in a typical baseline visit (i.e. Randomization application Form 30, Exit before randomization Form 31, etc.) or follow-up visit (i.e. Forms for AE, SAE, Hospitalization, Toxicity, Death, etc.)
- 2) “Visit” – a duplicate set of CRFs displayed in the database for an actual protocol visit (i.e. Follow-up Forms including Follow-Up Visit, Medication, Physical Exam, Urine Mailing, Blood and Serum Mailing)

Then, while logged into the Oracle Clinical Production database and with a specific PID selected (patient number highlighted) and making sure that you are within the appropriate visit tab, **click** on **Insert** located on the top Menu bar → select by **clicking Page**.

The screenshot displays the Oracle Clinical Production database interface. The top menu bar includes 'File', 'Edit', 'Insert', 'Go', 'Validate', 'Data Entry', and 'Help'. The 'Insert' menu is open, showing options like 'Page', 'Visit', and 'Discrepancy'. The 'Page' option is selected. Below the menu, a table lists various CRFs (e.g., B01, F42 Pg Tn, F43 Pg Tn, F44 Meds, F46 Exam, F75 Hep C, F80 Urine, F80 Urine2, F83 Serum, F86 Biopm1, F87 Biopr1, F89 Preg, F91 Tb) and a 'Show unplanned pages' button. The 'Patient' field shows '199013 (*)'. The 'Search' field contains 'Patient 199013'. The bottom section shows a 'Summary' tab with a 'Page Summary' section, including fields for 'Page' (42 B01), 'Visit' (B01), 'CRF' (F42 Pg Tn), and 'Sites' (All). The 'Summary' section also includes a 'Discrepancies' table with columns for 'CRFs', 'With active discreps', 'With other discreps', 'Clean', and 'Total'. The 'CRF Status' section shows counts for 'Not verified', 'Awaiting re-verification', 'Verified', 'Not approved', 'Awaiting re-approval', and 'Approved'. The 'Record' field shows '11/23' and the 'OSD' button is visible.

16. DATABASE AND DATA ENTRY

When “Page” is selected a pop-up window appears. Click the 1) **down arrow button**, and using the 2) **Scroll bar** select by **clicking** on the desired **CRF**. This will insert the desired CRF into that participant’s visit window.



Enter the desired CRF into the Oracle Clinical database following the Form Instructions pertaining to that particular CRF.

16. DATABASE AND DATA ENTRY

Note the database labeling of an unplanned visit versus a page. The unplanned visit is labeled with a sequential decimal place indicating the order that the unplanned visit was entered. Whereas the inserted “Page” (CRF) is labeled with the same tab as the protocol visit without any sequential decimal place. This is because an inserted “Page” indicates that a CRF was needed in addition to the required protocol visit CRFs.

Oracle Clinical Remote Data Capture

Visit Page CRF

Patient 199013 (*)

Search Patient 199013

Summary Discrepancies Verification Approval Audit Trail

Summary For CRF

CRF Summary

Patient 199013 Visit B01.1

Page CRF F10 Screen

Date Document #

Status Not Complete

Audit Summary

Created on

By June McMahon

Last modified on

Last transaction on

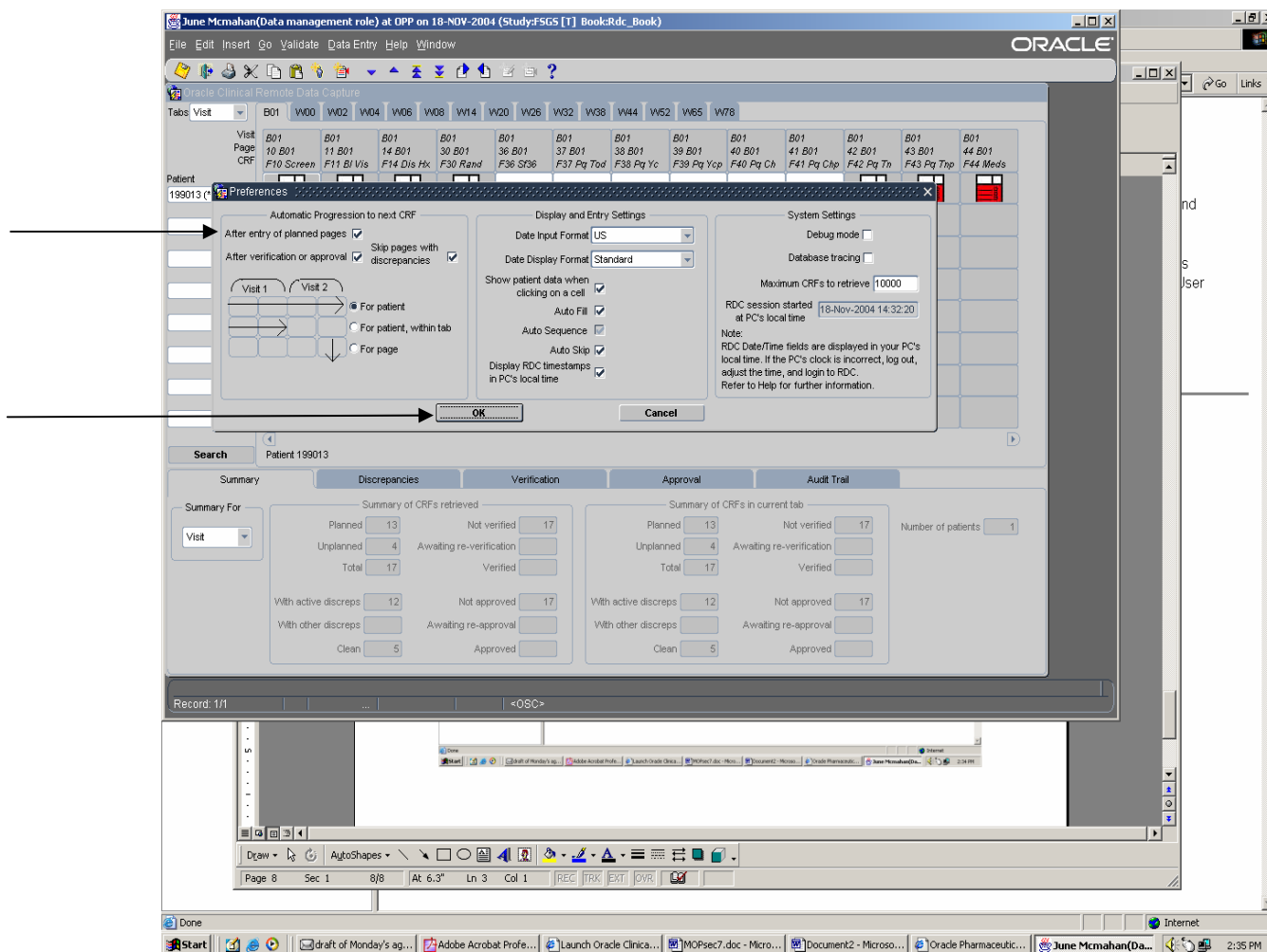
By

Record: 28/50

Start Re: sched... G:\fsgs.d... MOPsec1... MOPsec1... Adobe Ac... FOCAL SE... MOPsec7... Launch Or... Oracle Ph... June Mc... Document... 1:53 PM

16. DATABASE AND DATA ENTRY

“Uncheck” the box labeled “After entry of planned pages”. Click **OK**. Please do not change any other settings in the Preference menu.



16. DATABASE AND DATA ENTRY

“Unchecked”

The screenshot displays the Oracle Clinical Remote Data Capture (RDC) interface. The main window is titled "June McMahan(Data management role) at OPP on 18-NOV-2004 (Study:FSGS [1] Book:Rdc_Book)". The interface includes a menu bar (File, Edit, Insert, Go, Validate, Data Entry, Help, Window) and a toolbar. Below the menu bar, there is a tabbed interface with tabs for "Visit", "Page", and "CRF". The "Visit" tab is active, showing a list of visits (B01, V00, V02, V04, V06, V08, V14, V20, V26, V32, V38, V44, V52, V66, V78) and a corresponding list of CRFs (F10 Screen, F11 Bl' Vis, F14 Dis Hk, F30 Rand, F36 SF36, F37 Pg Tod, F38 Pg Yc, F39 Pg Ycp, F40 Pg Ch, F41 Pg Chp, F42 Pg Th, F43 Pg Trp, F44 Meds). A "Patient" field shows "199013".

The "Preferences" dialog box is open, showing three main sections: "Automatic Progression to next CRF", "Display and Entry Settings", and "System Settings". The "Automatic Progression to next CRF" section has a checkbox "After entry of planned pages" which is unchecked, and a checkbox "Skip pages with discrepancies" which is checked. The "Display and Entry Settings" section includes "Date Input Format" (US), "Date Display Format" (Standard), "Show patient data when clicking on a cell" (checked), "Auto Fill" (checked), "Auto Sequence" (checked), "Auto Skip" (checked), and "Display RDC timestamps in PC's local time" (checked). The "System Settings" section includes "Debug mode" (unchecked), "Database tracing" (unchecked), "Maximum CRFs to retrieve" (10000), and "RDC session started at PC's local time" (18-Nov-2004 14:32:20). A note at the bottom of the dialog states: "Note: RDC Date/Time fields are displayed in your PC's local time. If the PC's clock is incorrect, log out, adjust the time, and login to RDC. Refer to Help for further information."

Below the dialog box, the "Summary" tab is active, showing a "Summary of CRFs retrieved" and a "Summary of CRFs in current tab". The "Summary of CRFs retrieved" section includes a "Summary For" dropdown set to "Visit" and a table with the following data:

Planned	Not verified
13	17
Unplanned	Awaiting re-verification
4	
Total	Verified
17	
With active discreps	Not approved
12	17
With other discreps	Awaiting re-approval
Clean	Approved
5	

The "Summary of CRFs in current tab" section includes a table with the following data:

Planned	Not verified
13	17
Unplanned	Awaiting re-verification
4	
Total	Verified
17	
With active discreps	Not approved
12	17
With other discreps	Awaiting re-approval
Clean	Approved
5	

The "Number of patients" field shows "1". A status bar at the bottom of the window indicates "Record: 1/1" and "Page 9 Sec 1 9/9 At 6.3" Ln 3 Col 1". The taskbar at the bottom shows various open applications, including "draft of Monday's ag...", "Adobe Acrobat Profe...", "Launch Oracle Clinica...", "MOPsec7.doc - Micro...", "Document2 - Microso...", "Oracle Pharmaceutic...", and "June McMahan(Da...". The system clock shows "2:36 PM".

16. DATABASE AND DATA ENTRY

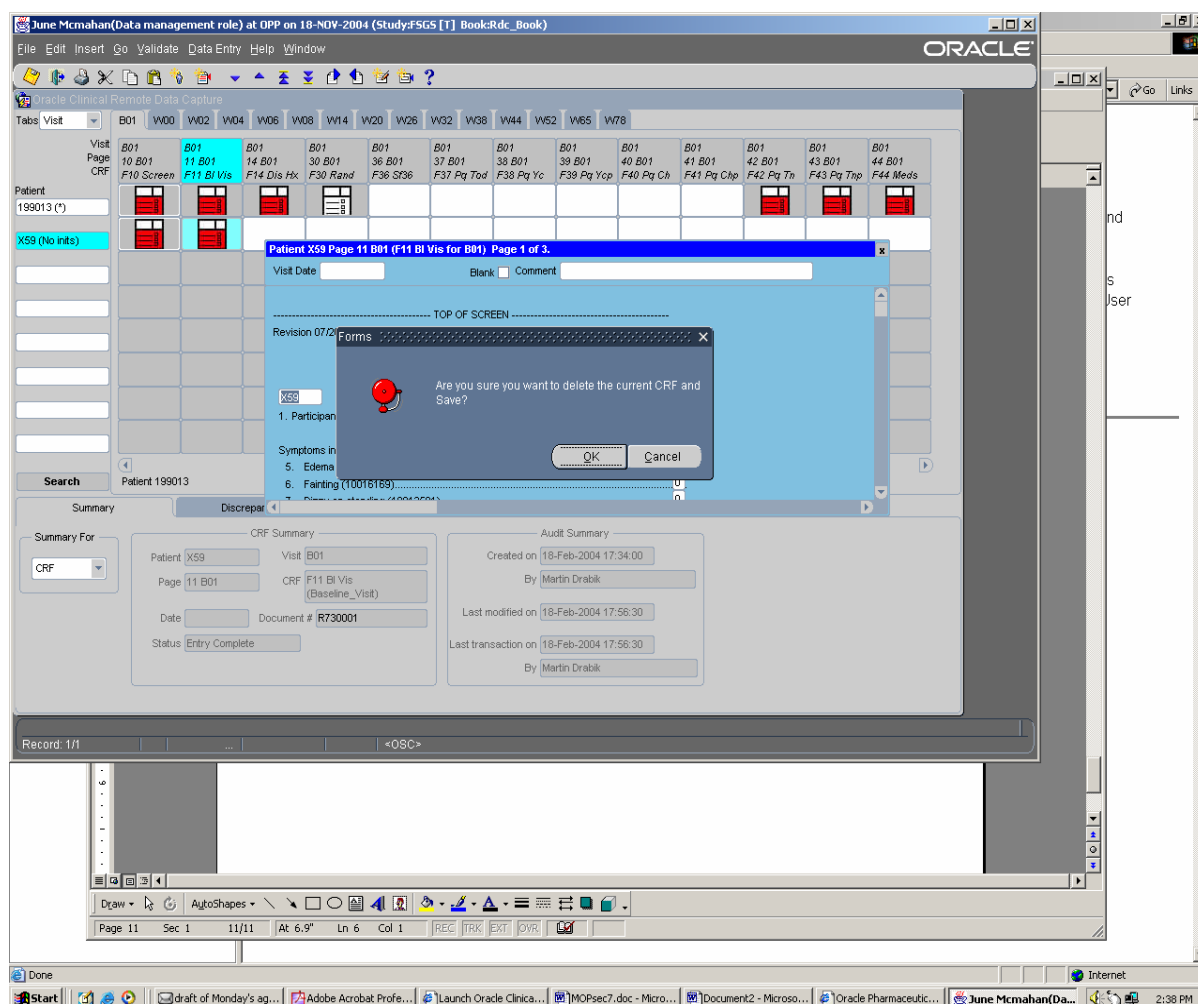
16.7. How to Delete a CRF in Oracle Clinical RDC

It is important to remember that Oracle Clinical (OC) uses the term “Page” in two ways. When using the delete option in OC it defines a “Page” as the *whole* CRF (not just the a specific page within the CRF). When navigating throughout a CRF entered in OC, using the “next page/previous page” buttons on the menu bar, “Page” is referred to as the actual page within the CRF.

The DCC does not encourage any CRFs be deleted out of the database that contain real data pertaining to the FSGS-CT study. However, there may be a need to delete a CRF that was accidentally entered, or for example the wrong QOL questionnaire form was entered. In these types of circumstances it would be appropriate to delete that CRF. To do so, while the CRF that is desired to be deleted is open, click on Edit located on the menu bar, select/click on Delete Page

The screenshot displays the Oracle Clinical RDC interface. The menu bar at the top includes 'File', 'Edit', 'Insert', 'Go', 'Validate', 'Data Entry', 'Help', and 'Window'. The 'Edit' menu is open, showing options like 'Cut', 'Copy', 'Paste', 'Duplicate field', and 'Delete page'. The 'Delete page' option is highlighted. Below the menu bar, there is a grid of tabs labeled V01, V02, V04, V06, V08, V14, V20, V26, V32, V38, V44, V52, V65, and V78. The 'V01' tab is selected, showing a form for 'Patient 199013'. The form includes fields for 'Visit Date', 'Blank', and 'Comment'. Below these fields, there is a section titled 'TOP OF SCREEN' with a revision date of 07/26/2004. The form also includes a 'Baseline Visit Form (Form # 11)' with fields for 'Participant ID Number', 'Alpha code', 'Visit Number', and 'Date of Visit'. The 'Delete page' option is highlighted in the menu bar. At the bottom of the screen, there is a summary window for the CRF, showing details such as 'Patient: X59', 'Visit: B01', 'Page: F11 B01', 'CRF: F11 BI Vis (Baseline_Visit)', 'Date: 15-FEB-2004', 'Document #: R730001', and 'Status: Entry Complete'. The summary window also includes an 'Audit Summary' section with fields for 'Created on', 'By', 'Last modified on', and 'Last transaction on'.

FSGS Manual of Operations



16. DATABASE AND DATA ENTRY

16.8. Using Search in Oracle Clinical RDC

The search button is located below the “Patient” ID column. You will find this a helpful tool to use when needing to narrow parameters relating to your Participating Site’s data. Examples of when to use the Search button would include:

- ❑ Printing CRFs (refer to Section 16.3.2.)
- ❑ To display a specific PID number on your screen
- ❑ To display a specific CRF on your screen
- ❑ To display a CRF that has discrepancies

The screenshot displays the Oracle Clinical Remote Data Capture (RDC) application window. The title bar indicates the user is 'June McMahon (FSGS DCC user)' at 'OPP on 11-JAN-2005 (Study:FSGS [1] Book:Rdc_Book)'. The menu bar includes 'File', 'Edit', 'Insert', 'Go', 'Validate', 'Data Entry', 'Help', and 'Window'. The toolbar contains various icons for file operations and data entry. The main window is titled 'Oracle Clinical Remote Data Capture' and features a 'Tabs' section with a 'Visit' tab selected. Below the tabs, a grid displays patient data for various visits (B01, V00, V02, V04, V06, V08, W14, V20, V26, V32, V38, W44, W52, W65, W78). The 'Patient' column shows '199013 (*)'. Below the grid, a 'Search' button is highlighted with an arrow. The 'Summary' section at the bottom provides a 'Summary For' dropdown set to 'Visit'. It includes two summary tables: 'Summary of CRFs retrieved' and 'Summary of CRFs in current tab'. The first table shows 28 planned, 12 unplanned, and 28 total CRFs, with 9 clean and 19 with other discrepancies. The second table shows 23 planned, 10 unplanned, and 23 total CRFs, with 7 clean and 16 with other discrepancies. The 'Number of patients' is 1. The status bar at the bottom shows 'Record: 1/1' and the system clock '11:32 AM'.

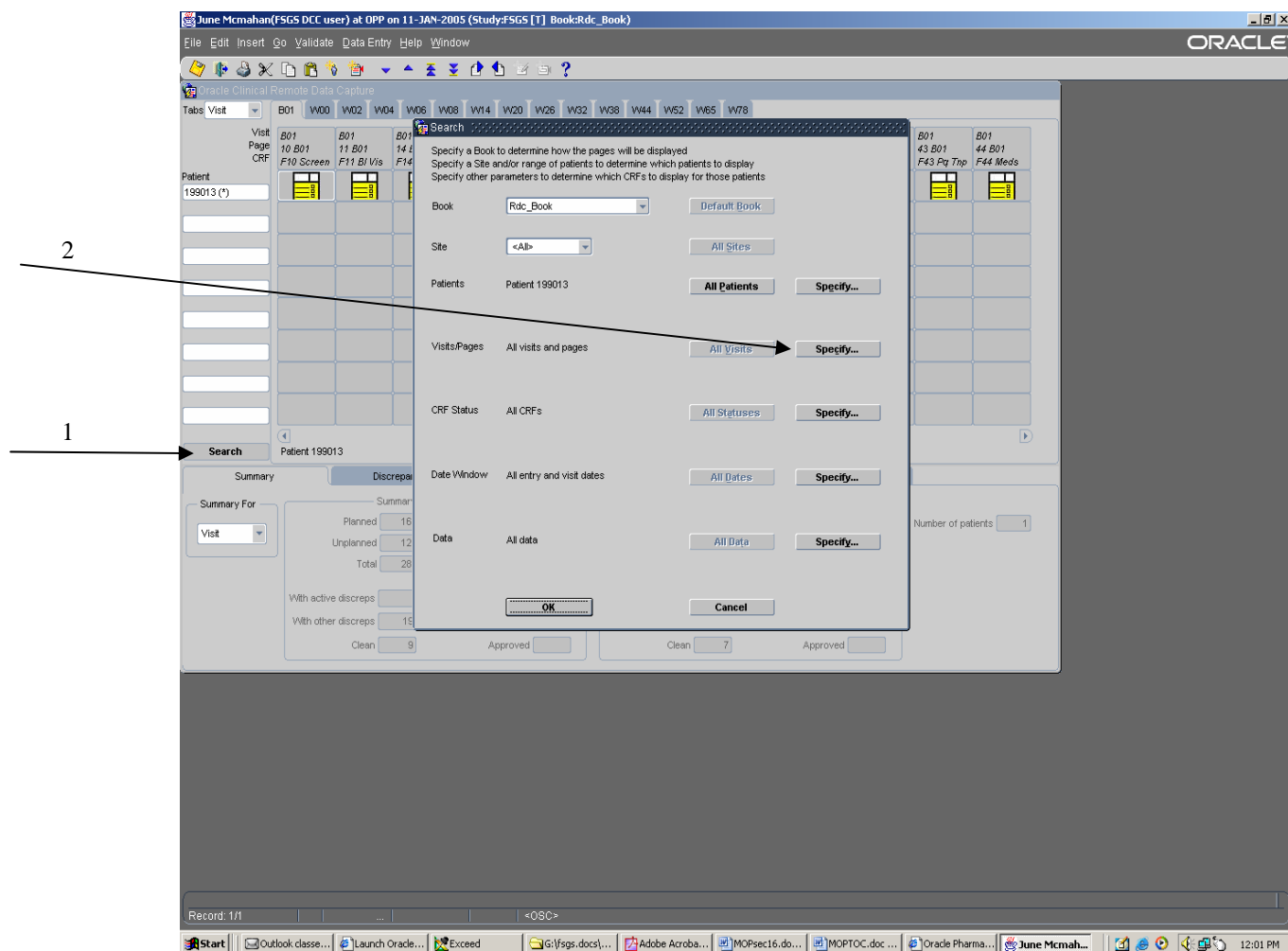
Visit	B01	V00	V02	V04	V06	V08	W14	V20	V26	V32	V38	W44	W52	W65	W78
Patient	10 B01	11 B01	14 B01	30 B01	36 B01	37 B01	38 B01	39 B01	40 B01	41 B01	42 B01	43 B01	44 B01		
CRF	F10 Screen	F11 BI Vis	F14 Dis Hx	F30 Rand	F36 SF36	F37 Pg Tod	F38 Pg Yc	F39 Pg Ycp	F40 Pg Ch	F41 Pg Chp	F42 Pg Tn	F43 Pg Ttp	F44 Meds		

Summary of CRFs retrieved			
Planned	28	Not verified	28
Unplanned	12	Awaiting re-verification	
Total	28	Verified	
With active discreps		Not approved	28
With other discreps	19	Awaiting re-approval	
Clean	9	Approved	

Summary of CRFs in current tab			
Planned	23	Not verified	23
Unplanned	10	Awaiting re-verification	
Total	23	Verified	
With active discreps		Not approved	23
With other discreps	16	Awaiting re-approval	
Clean	7	Approved	

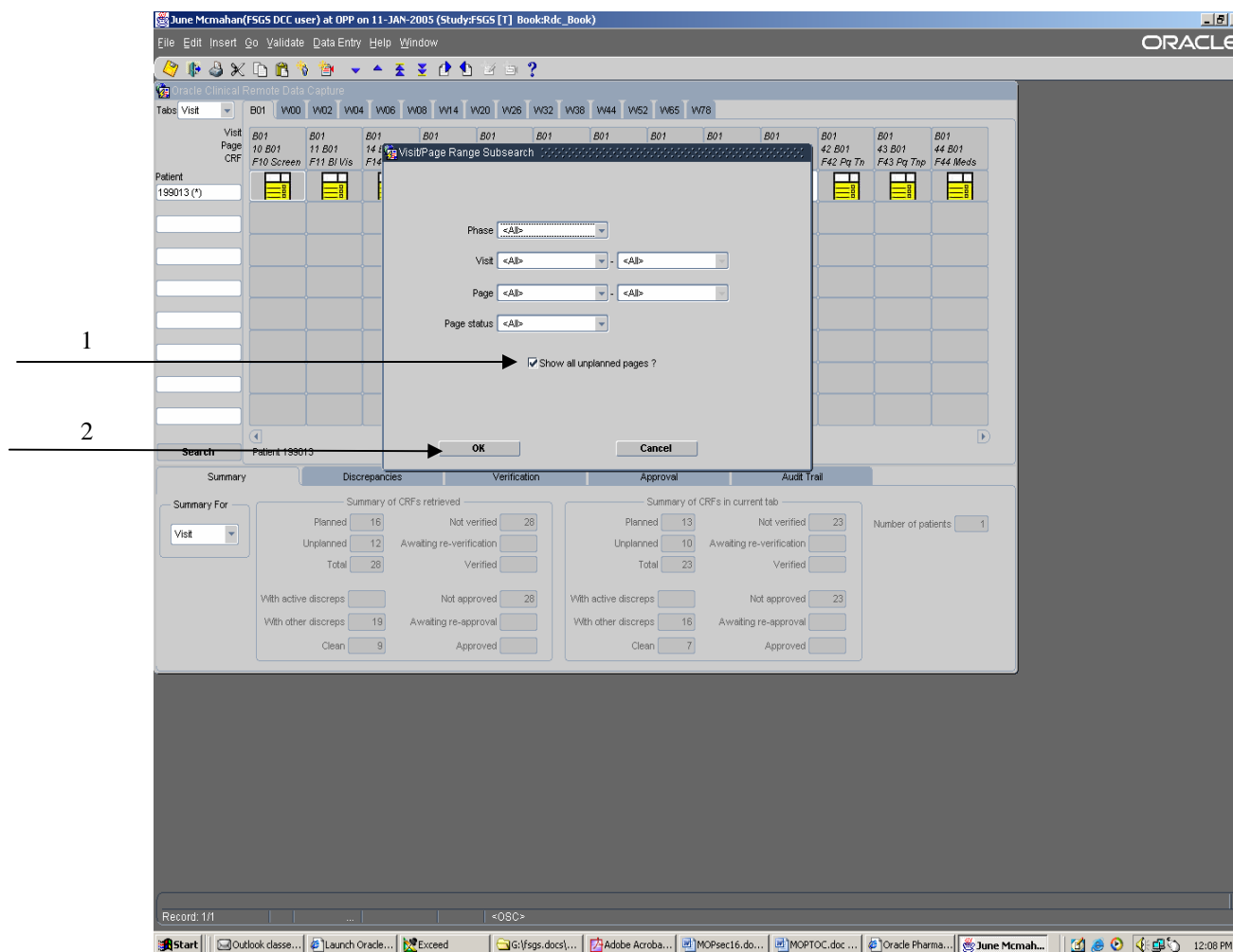
16. DATABASE AND DATA ENTRY

To display CRFs with discrepancies, 1) **click** on the **Search** button; 2) **Click** on the "Specify" button located on the far right of the "Visit/Pages" row.



16. DATABASE AND DATA ENTRY

A “Visit/Range Subsearch” window will appear. 1) Check on the "Show all unplanned pages?"; 2) Click on OK.



16. DATABASE AND DATA ENTRY

Click on the "Specify" button located in the "CRF Status" row (below the Visit/Pages row). Click on the "Discrepancy Status" dropdown arrow, and select "With actionable or other discrepancies" (or use the other choice depending on the type of Search you want). Click OK on this "Sub search" window, and click OK again on the "Search" window.

The screenshot shows the Oracle Clinical Remote Data Capture application window. The main window has a menu bar (File, Edit, Insert, Go, Validate, Data Entry, Help, Window) and a toolbar. Below the menu bar, there are tabs for "Visit" and "CRF Status". The "Visit" tab is active, showing a grid of visits for patient 199013. The "CRF Status" tab is also visible, showing a grid of CRF statuses. A "CRF Status Subsearch" window is open, displaying a dropdown menu for "Discrepancy Status" with the following options: "Without discrepancies", "With actionable discrepancies", "With other discrepancies", "With actionable or other discrepancies", and "With closed discrepancies". The "With actionable or other discrepancies" option is selected. The "CRF Status" dropdown is set to "<All>". The "Lock status" dropdown is also set to "<All>". The "Search" button is visible at the bottom of the subsearch window. Below the subsearch window, there are summary tables for "Summary of CRFs retrieved" and "Summary of CRFs in current tab". The "Summary of CRFs retrieved" table shows counts for Planned (16), Not verified (28), Unplanned (12), Awaiting re-verification, Total (28), Verified, With active discrepancies, Not approved (28), With other discrepancies (19), Awaiting re-approval, Clean (9), and Approved. The "Summary of CRFs in current tab" table shows counts for Planned (13), Not verified (23), Unplanned (10), Awaiting re-verification, Total (23), Verified, With active discrepancies, Not approved (23), With other discrepancies (16), Awaiting re-approval, Clean (7), and Approved. The "Number of patients" is 1. The bottom of the window shows a taskbar with various applications open, including Outlook, Launch Oracle, Exceed, G:\fsgs.docx, Adobe Acrobat, MOPsec16.do, MOPTOC.doc, Oracle Pharm, and June McMahon.

Tabs will display only visits that contain discrepancies and the unplanned pages will be shown.

If you wanted to see all forms except for unplanned forms, go to the search window by clicking on the **Search** button, and click on the "All Visits" button located in the "Visits/Pages" row. Click on the "All Statuses" button located in the "CRF Status" row, and click on OK. You can keep the unplanned pages checked on all the time if you want (independent of the discrepancy search); that means don't click on "All Visits" (even though that sounds non intuitive). You will have to check that box on each time you log in.

16. DATABASE AND DATA ENTRY

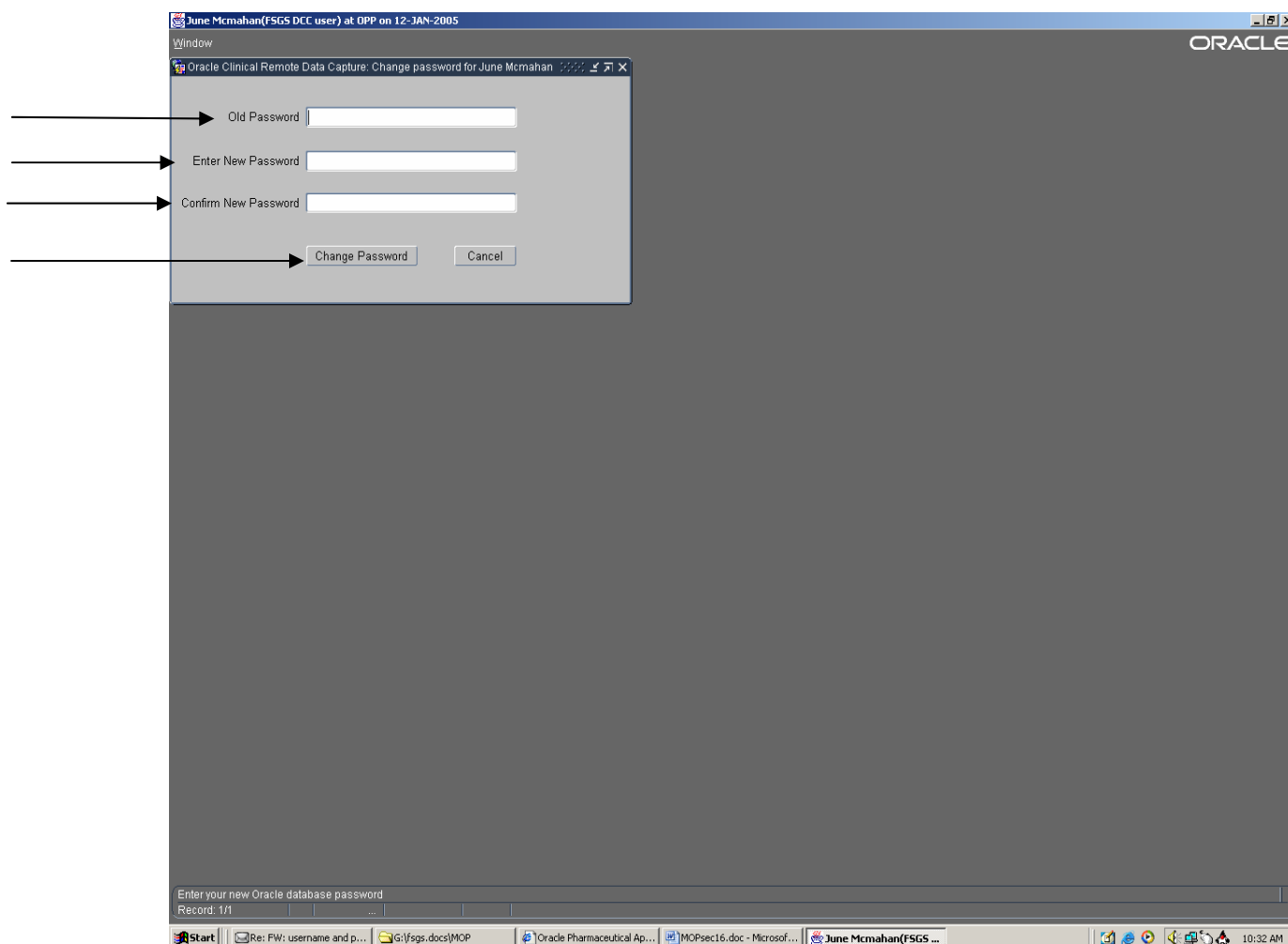
16.9. Changing your Password / Accessing Oracle Clinical

All who obtain an Oracle Clinical account will be notified by e-mail to change their password every 75 days.

To change your password:

- ❑ Use Internet Explorer as your web Browser
- ❑ Go to - <https://clinapps.bio.ri.ccf.org/fsgs/index.html>
- ❑ Click on **Change Password** (Helpful Tools)

A “Logon” pop-up box will appear. **Enter** your username, password, and database. For database enter “opp”. **Click Connect**. An “Change Password” screen will appear. **Enter** your “Old Password”, **enter** your new password, and confirm by **entering** your new password a second time. **Click on Change Password**. A message will be displayed indicating that your password has been changed.



16. DATABASE AND DATA ENTRY

16.10. Possible Reasons Why Oracle Clinical or Reports Will Not Run

JInitiator:

When trying to change your password and the system gives you an error message or will not open the Log-on popup box, it is most likely due to the fact that the 2nd version of JInitiator has not been installed on your computer.

To access the Form 2 database, only the 1st version needed to be installed, but because the "Change Password" is connected with privileges needed for Participating Sites to gain access to the Oracle Clinical Production database the 2nd version must also be installed. Note: Depending on your Institutions policies you may or may not have permissions to install applications on your computer. Contact your IT department, if necessary, for installation.

The two versions of JInitiator that need to be installed (refer to web page <https://clinapps.bio.ri.ccf.org/fsgs/index.html>):

To download JInitiator 1.3.1.9, needed to use Form 2 and reports

[Download JInitiator 1.3.1.9](#)

To download JInitiator 1.1.8.19, needed to use Oracle Clinical RDC

[Download JInitiator 1.1.8.19](#)

Port 9000:

If your Institution has Port 9000 as a firewall your Participating Site will not be able to access the Oracle Clinical Production database until your IT department opens that port for you. The DCC has no control over this and you will need to contact your IT department if Port 9000 is used.

Pop-Up Blocker:

Adobe Acrobat software is used to display generated Reports (from Form 2 database). If your browser is Internet Explorer 6 for Windows XP SP 2, a "Pop-Up Blocker" may be activated and will prohibit you from being able to use Adobe Acrobat. To turn off the "Pop-Up Blocker", with your IE 6 browser open, **click** on **Tools** located on the Menu bar, **selecting Pop-Up Blocker**, and **clicking** on **turn off**. You may need to contact your IT department to resolve this Pop-Up Blocker issue.

www.fsgstrial.org

17.1. Training Procedures for Individual Sites in the FSGS Clinical Trial

Detailed training procedures have been developed for participating sites in order to standardize the conduct of the trial in participants in different parts of Canada, Mexico and the United States. The principal four methods whereby these procedures will be conveyed to the study participants are as follows:

1. A series of training sessions that will be held in five different locations throughout the USA. These will be spread over a 4-month period in order to facilitate maximum participation by sites that obtain local approval for the trial at different times during the first six months of 2004.
2. The material contained within this manual of operations.
3. A website that has been established by the team of investigators at the University of North Carolina will provide updated information that will provide helpful training information.
4. A series of additional materials will be developed over the first year of the trial in order to give the sites specific training in ancillary studies that are approved by the FSGS – CT Steering Committee.

The training sessions for the FSGS Clinical Trial will take place in the following locations in the continental United States:

1. University of North Carolina – Chapel Hill
2. New York City
3. Seattle, Washington
4. Dallas, Texas
5. Cleveland, Ohio

It is possible that one or more of these locations may hold additional training sessions subsequently, but the core PI's, in collaboration with the Steering Committee will determine this.

The major goals of the training sessions for individual sites will be to provide detailed information about the procedures to be performed in the FSGS Study as well as a basic understanding regarding the need for the study.

17.1.1. Training Session Attendees

The number of participants from each site will be from one to three. In many instances we anticipate that the attendees will comprise a physician (usually the site PI) and one or two nurse coordinators, but this will not be a prerequisite. It will be up to individual centers to determine who will be the primary person and who will be the back up person that will attend the training session.

17.1.2. Training Session Format

We anticipate that the training sessions will span a period of two days with the second day being dedicated to coordinator training for local data entry into the Cleveland Clinic database.

17.2. Items to be Discussed During the Training Sessions

Day 1

1. Study Overview

The proceedings will begin with an overview of the development of the concept behind the FSGS Study and a brief history of the events that have taken place up to the time of the training session. This presentation will incorporate some information about previous studies of FSGS that have been conducted and how the results from these studies have been utilized in the development of the current protocol.

2. Study Design and Study Objectives

This presentation will describe the different levels of outcome that we are utilizing in our study design and the methods by which we will determine if participants are deemed treatment failures.

3. Participant Inclusion and Exclusion Criteria

The specific criteria for participant eligibility will be discussed, including our definition of steroid resistance and the use of other medications that are permitted prior to entry into the study. The pathologist responsible for biopsy approval in the core holding the training session will describe the renal biopsy features that are required for entry.

4. Discussion of Participant Visits

This session will provide a detailed description of the specific points of interaction between the study participants and personnel. A table outlining all of the visits and the procedures associated with each of these visits will be provided. We will also describe the study medications and any dosage adjustments that might be made based on laboratory studies and/or interim history. We will also indicate how the sites will be provided with the medication and the restrictions that are being placed in terms of the ways in which they are then dispensed to the participants. Details regarding dosages and handling procedures as well as the labeling methods to be used during the study will be provided.

5. Laboratory Studies and details regarding Specimen Handling and Shipping

This section will feature personnel from the core laboratory (Spectra Laboratories) with examples of the specimen kits that will be provided to each of the centers for the purposes of this study.

6. Consent procedures and IRB

The informed consent forms to be used in the study will be discussed. We will also introduce the specific regulatory aspect of the study, including the FDA involvement and the IND number that will be provided for the study.

7. Adverse events

This session will discuss specific aspects of the identification and management of adverse effects and the reporting mechanisms that each site needs to be aware of. We will discuss dosage modifications that may be necessary when adverse events occur and how the participating site personnel should report the side effects to both the DCC and their core center investigator/coordinator. Specific information will be given regarding the reporting of serious adverse events (SAE) and the documentation that must be obtained when an SAE is encountered.

8. Participant recruitment and retention

The recognition of participants who are eligible for this study and the subsequent recruitment of these participants will be a crucial part of the study. We will discuss methods of participant recruitment and this will involve attempts to identify participants in centers and sites that are not intimately involved in the FSGS study.

9. Data Flow and Data Analysis

This session will provide a more complete overview of how data will be relayed from participating sites to the DCC and will describe the analyses that are anticipated with the participant data.

10. Ancillary Studies

The importance of ancillary studies in advancing our knowledge regarding the pathogenesis of FSGS and the mechanisms involved in its progression to chronic kidney disease will be discussed in this session. Where appropriate, we will briefly describe some of the ancillary studies that have been approved for the study and we will discuss how the ancillary studies will interface with the primary study.

11. Miscellaneous – But Important – Final Items

The final session of the first day of the training session will involve a number of important issues that do not fit conveniently into the other sections. These will include the administrative aspects of the trial in each of the sites, including how the sites will handle the budget and the level of reimbursement that can be expected for each participant enrolled in each study. A description of the administrative structure of the study and phone numbers, etc. for people that they can call when they are “in need” will also be provided. Finally there will be a description of the web-based training modules that will be available for all sites to utilize in order to augment the materials received during the training session.

The second day of the training session will be devoted to a detailed description of how data entry should be conducted in the sites that have opted to enter data directly into the Cleveland Clinic database. This component of the training session will last approximately 5 hours and is not required for centers that plan to provide participant information via case report forms. However, all site participants who attend Day One are invited to attend the second day.

17.3. Computer Training Tutorial

FSGS Trial Computer Training Tutorial

17.3.1. Lesson 1: Accessing the Study Web Page and the Participant Database

Lesson Objectives:

- Navigate to the study web page
- Log into the participant database
- Select study and accept default search options

1. Double click on the Internet Explorer icon on the desktop to start Internet Explorer.
2. In the Address box, type:

<https://clinapps.bio.ri.ccf.org/fsgs/index.html>

and press Return. The FSGS main web page is displayed. Notice that the address begins with https.

3. Click on the “OC Remote Data Capture (TEST)” link. The Oracle Pharmaceutical Applications login page is displayed. Note that once the study starts, the link will no longer read “TEST”; you will be connecting to the real database.
4. Click on the Login button. The login page is displayed.
5. In the Username box, enter your assigned training username and press the Tab key.
6. In the Password box, enter your assigned password and press the Tab key.
7. In the Database box, enter **opp** and click on the Connect button. The Select Study box is displayed.
8. Click on the List button. Study FSGS is automatically selected, and the Search box is displayed.
9. Click on the OK button to accept the default search options. The participant/form spreadsheet is displayed.

17.3.2. Lesson 2: Browsing Previously Entered Data

Lesson Objectives:

- Locate a participant whose data you wish to browse
 - Open the data entry window for a form
 - Move and resize the data entry window
 - Close the data entry window
1. Locate your assigned participant number in the list on the left. If your participant is not displayed, click on the arrow of the dropdown box just below the word “Participants.” Find the range that your participant falls in, then click on the range in the dropdown to display the participants in that range.
 2. Click on the icon immediately to the right of your participant number. The data entry window for Form 10 is displayed.
 3. Note and write down the alpha code assigned to your participant.
 4. Click on the title bar of the data entry window.
 5. Move and/or resize the window so that you are comfortable with its position and size. Click on the Done button. If any error messages are displayed, click on the OK button.
 6. Use the slider on the right side of the window to scroll down to see all of the data on this page.
 7. Click on the next page icon to display the next page of data.
 8. When finished reviewing the Form 10 data, click on the X in the upper right corner of the data entry window to close it.

17.3.3. Lesson 3: Entering New Data

Lesson Objectives:

- Enter data in the data entry window
 - Display and use a list of values
 - Search for MedDRA codes
 - Create a single item discrepancy
1. Click in the blank cell immediately to the right of the Form 10 icon for your participant. The data entry window for Form 11 opens.
 2. Press Enter to skip past the header fields and display the data entry form.

3. Enter your assigned participant ID number and press Enter.
4. Enter the alpha code for your participant that you noted when reviewing Form 10 and press Enter.
5. Enter the Date of Visit as 15FEB2004 and press Enter.
6. Click on the ellipses (...) to the right of the field for Edema. The list of values for Edema is displayed.
7. Click on the row with value of 1 to highlight it.
8. Click on the OK button.
9. Press Enter to accept the response for Edema and move to the next field.
10. Enter a response of 0 for Fainting and press Enter.
11. Enter a response of 0 for Dizzy on standing and press Enter.
12. Enter a response of 1 for Nausea and press Enter.
13. Enter a response of 0 for Vomiting and press Enter.
14. Enter a response of 1 for Diarrhea and press Enter.
15. Enter a response of 0 for Cough and press Enter.
16. Enter a response of HEADACHE for Other Symptoms column and press Enter.
17. Enter %HEADACHE% in the MedDRA Code field, then click on the ellipses just to the right of the field. The list of values of MedDRA codes is displayed.
18. Click on the row 10019211 HEADACHE, then click on the OK button.
19. Press Enter to accept the response for the MedDRA Code and move to the next row.
20. Enter a response of SPRAINED KNEE for Other Symptoms column and press Enter.
21. Enter %KNEE% in the MedDRA Code field, then click on the ellipses just to the right of the field. The list of values of MedDRA codes is displayed.
22. Click in the Find field, select the text in the field, type %SPRAIN%, then press Enter.
23. In the list of values, click on the row 10023478 KNEE SPRAIN, then click on the OK button.

24. Press Enter to accept the response for the MedDRA Code and move to the next row.
25. Press the Page Down key to leave the MedDRA block and move to the next page.
26. Enter a response of 1 for “Current menarche status” and press Enter.
27. Enter a response of 9 for “Does participant agree to practice birth control?” and press Enter. The Univariate Validation Failure popup is displayed.
28. Notice that message indicates that the code entered is not among the valid responses. Press Cancel to avoid creating a discrepancy and return to the data field.
29. Change the response to 8 and press Enter.
30. Enter a response of 2 for “Participant preference for study medication formulation?” and press Enter.
31. Enter a response of 0 for “History of a positive PPD?” and press Enter.
32. Enter a response of 8 for “Was a Chest X-ray done?” and press Enter.
33. Press Enter without typing anything to leave the “Date of Chest X-ray” field blank.
34. Enter a response of 8 for “Results of Chest X-ray” and press Enter.
35. Enter a response of 8 for “TB Medicine” and press Enter.
36. Enter a response of 1 for “Heath insurance” and press Enter.
37. Enter a response of 06 for “Highest level of education” and press Enter.
38. Enter a response of 4 for “Participant’s gross household income?” and press Enter.
39. Enter a response of 02 for “Number of adults in the same household?” and press Enter.
40. Enter a response of 00 for “Number of children in the same household?” and press Enter.
41. Enter a response of 17FEB2004 for “Date this form completed” and press Enter.
42. Enter a response of JOYCEJ for “Person completing this form.”
43. The Univariate popup is displayed. In the comments field, enter “Dr. James Joyce should be in the list of usernames” Press the OK button to create the discrepancy. The popup closes and the data entry window for Form 14 is displayed.
44. Click on the X in the upper right corner of the data entry window.

45. Click on the Edit menu item and choose Preferences.
46. The Preferences window is displayed. Click on the “After entry of planned pages” checkbox so that it changes to unchecked.
47. Click on the OK button. This disables automatic navigation to the next form upon completing entry of a form.

17.3.4. Lesson 4: Entering Concomitant Medications

Lesson Objective:

- Enter non-study medications by searching the Redbook list
1. Click in the cell at the intersection of the column for the Medication CRF (Form 44) and the row for your participant. The data entry window for Form 44 is displayed.
 2. Press Enter to skip past the header fields and display the data entry form.
 3. Enter your assigned participant ID number and press Enter.
 4. Enter the alpha code for your participant that you noted when reviewing Form 10 and press Enter.
 5. Enter a response of 19FEB2004 for “Date of Visit” and press Enter.
 6. Enter a response of TYLENOL FOR COLDS for “Non-Study Medications” and press Enter.
 7. Enter %TYLENOL% in the Medication Code field, and press Enter. The list of values for medication names (Redbook) is displayed.
 8. Click on the row TYLENOL COLD, and then click on the OK button.
 9. Enter a response of 2 for the Start/Continue/Stop field and press Enter. The cursor moves to the next row.
 10. Enter a response of OMIPRIZUL for “Non-Study Medications” column and press Enter.
 11. Enter %OM%PR%Z%L% in the Medication Code field, and press Enter. The list of values for medication names (Redbook) is displayed.
 12. Click on the row OMEPRAZOLE then click on the OK button.
 13. Enter a response of 2 for the Start/Continue/Stop field.

14. Press the Page Down key to leave the non-study medications block and move to the “Date this form completed” field.
15. Enter a response of 19FEB2004 for “Date this form completed” and press Enter.
16. Enter your assigned user ID as the response for “Username of person completing this form” and press Enter. The top of the data entry form is redisplayed.
17. Click on the X in the upper right corner of the data entry window.

17.3.5. Lesson 5: Entering an Unscheduled Visit Form

Lesson Objectives:

- Create an unplanned visit
 - Enter a form for the unplanned visit
 - Hide unplanned visit forms
1. Click on menu Insert and select item Visit. A confirmation popup window is displayed.
 2. Click on the OK button on the popup window. The unplanned visit is created, and the data entry window for an unplanned Form 10 is displayed.
 3. If necessary, click on the title bar of the data entry window, move and/or resize the window so all of the spreadsheet is displayed, and then click on the Done button.
 4. Use the horizontal slider for the spreadsheet to scroll to the right until a column for CRF Conmed at visit B1.1 is displayed.
 5. Click in the cell at the intersection of this column and the row for your participant. The data entry window for Form 44 is displayed.
 6. Press Enter to skip past the header fields and display the data entry form.
 7. Enter your assigned participant ID number and press Enter.
 8. Enter the alpha code for your participant that you noted when reviewing Form 10 and press Enter.
 9. Enter a response of 20FEB2004 for “Date of Visit” and press Enter.
 10. Press the Page Down key to leave the non-study medications block and move to the “Date this form completed” field.
 11. Enter a response of 20FEB2004 for “Date this form completed” and press Enter.

12. Enter your assigned user ID as the response for “Username of person completing this form” and press Enter. The top of the data entry form is redisplayed.
13. Click on the X in the upper right corner of the data entry window.
14. Use the horizontal slider for the spreadsheet to scroll until the rightmost column, titled “Hide unplanned pages,” is displayed.
15. Click on the column header for that column. The unplanned visit forms are no longer displayed.

17.3.6. Lesson 6: Reviewing, Responding To, and Routing Discrepancies

Lesson Objectives:

- Review a summary of all discrepancies for a participant form
 - Reply to a discrepancy by changing data
 - Route a discrepancy for review by the core site
1. Click in the Form 11 cell for your participant. The Form 11 that you entered is redisplayed.
 2. If the data entry window is obscuring the tabs area at the bottom of the screen, move and/or resize the data entry window so that you can see all of the Summary tab.
 3. Click on the Discrepancies tab located just to the right of the Summary tab. The Discrepancies tab is displayed with the List subtab selected.
 4. Locate the discrepancy that has been created indicating that the participant is male (from Form 10), but that menarche status has not been entered as Not Applicable. Note the number to the left of that row. Click on the Active subtab with the number corresponding to the number of that discrepancy. The discrepancy details are displayed.
 5. Click in the Value column for the “Current menarche status” row.
 6. Click on the arrow to the right of the Action box and click on “Go to data field.” The data entry form changes to display the “Current menarche status?” field.
 7. Change the value to 8 and press Enter. The Audit Information popup window is displayed.
 8. Click on the ellipses (...) next to the Change Reason field.
 9. Click on “FSGS PARTICIPATING SITE CORRECTION” to highlight it, then click the OK button.

10. Click in the Comments box, then enter “Forgot that participant is male” Click on the Save button.
11. In the discrepancy tab, locate the discrepancy indicating that the date of entry of the Form 11 is before the date of entry of the Form 10. Note the number to the left of that row. Click on the Active subtab with the number corresponding to the number of that discrepancy. The discrepancy details are displayed.
12. Click on the arrow to the right of the Action box and click on “Go to data field.”
13. The data entry form for Form 10 is displayed, with the cursor in the “Date form completed” field. Change the value to 10-FEB-2004 and press Enter. The Audit Information popup window is displayed.
14. Leave the Change Reason code as DATA ENTRY ERR. Click the Save button.
15. Locate the single item discrepancy that you created during entry of the Form 11, noting that JOYCEJ is not among the username list of values. Note the number to the left of that row. Click on the Active subtab with the number corresponding to the number of that discrepancy. The discrepancy details are displayed.
16. Click on the arrow to the right of the Action box and click on “Send to core site.” The Internal Comments for Discrepancy window appears containing the text you entered when the discrepancy was created.
17. Click on OK button in the popup window. The status of the discrepancy is updated to Closed, but the CRF icon is highlighted in yellow to indicate that a discrepancy is under review by another study unit.
18. Click on the X in the upper right corner of the data entry screen.

17.3.7. Lesson 7: Randomizing a Participant

Lesson Objectives:

- Randomize a participant
 - Exit the participant database
1. Click in the cell at the intersection of the column for the Randomization CRF (Form 30) and the row for your participant. The data entry window for Form 30 is displayed.
 2. Press Enter to skip past the header fields and display the data entry form.
 3. Enter your assigned participant ID number and press Enter.

4. Enter the alpha code for your participant that you noted when reviewing Form 10 and press Enter.
5. Note that the cursor moves down to the field for Question 101, “Do you confirm that you have received an express mail package with this participant’s negative HIV test results?” Enter a response of 1 and press Enter.
6. Enter a response of 1 for “Do you confirm that based on the best of your knowledge the participant is eligible?” and press Enter.
7. Enter a response of 1 for “Do you want to randomize the participant now?” and press Enter.
8. Navigate back to the bottom of the data entry screen to view the randomization assignment for the participant.
9. Click on the File menu and select Exit.

17.3.8. Lesson 8: Running Study Reports

Lesson Objectives:

- Log into the site and report database
 - Select a report to run and specify report parameters
 - Exit the site and report database
1. In an Internet Explorer window, return to the FSGS main web page:
<https://clinapps.bio.ri.ccf.org/fsgs/index.html> The FSGS main web page is displayed. Notice that the address begins with https.
 2. Click on the “Form 2 and Reports (Production)” link. The login page is displayed.
 3. Click on the Login button. The login page is displayed.
 4. In the Username box, enter your assigned training username and press the Tab key.
 5. In the Password box, enter your assigned password, and then click on the Connect button. The site and reports database main screen is displayed.
 6. Click on menu REPORTS then click on item Enrollment Report. The parameter screen for the Enrollment Report is displayed.
 7. In the Participant ID parameter box, enter your assigned participant ID.
 8. Click on the Get Report button. Acrobat Reader starts and displays the report output in a new browser window.

9. Click on the X in the upper right corner of the report output window.
10. Click on the Exit button on the Enrollment Report parameter screen.
11. Click on menu EXIT, then click on item EXIT.

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

18.1. Retention and Recruitment Committee

A Retention and Recruitment Committee has been developed with the goal of continually evaluating participant recruitment and retention strategies.

Extramural Recruitment Efforts:

- Providing clinicians with Multilanguage flyers that are easy-to-read and IRB approved
- Providing clinicians with brochures that are available on the internet and for office distribution
- Sample letters to clinicians and primary nephrologists introducing them to this trial
- Providing educational opportunities to clinicians and renal nurses introducing them to this trial
- Providing information to pathologists regarding this trial and how they may contact physicians with a potential study subject
- Announcements in newsletters, websites available to participants
- Presentations at participant meetings

Intramural Recruitment Efforts:

- Providing IRB approved, Multilanguage flyers and brochures to the offices of PIs and associates for distribution
- Providing laminated charts with inclusion/exclusion criteria for PIs, colleagues, study coordinators and nurses
- Reviewing medical records in order to identify potential subjects
- Encouraging primary nephrologist to inform potential subjects about the study
- Encouraging PI to maintain open communication with associates in order to capture potential new subjects

Steering Committee Efforts:

- Collecting data on failed screens
- Continual evaluation of barriers to recruitment

The Principal Investigator's *Toolbox*:

- #1 Flyer for potential subjects
- #2 Brochure for nephrologists to display in office
- #3 Letter to referring nephrologists
- #4 Letter to area pathologists
- #5 Laminated chart with Inclusion/Exclusion Criteria
- #6 Primer on Subject Recruitment (see below)
- #7 Primer on Consent Process (see below)
- #8 Primer on Subject Retention (see below)
- #9 Subject Handbook

TOOL #6

Primer on Subject Recruitment

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

- Avoid approaching potential subjects until trust and rapport has been built.
- Appropriate introductions to a potential subject must be done if PI is not the primary physician. This is necessary to build trust in the PI and to reassure the subject that primary physician supports enrollment and study plan.
- Assure subject and family that continuity of care is not contingent upon participation.
- Explain fully partial compensation for travel, parking, meals, etc while attending study visits.
- Explain opportunity to receive some primary care under the auspices of the study, with potential of medical costs.
- Explain opportunity to received closer medical attention and exposure to newer medications.
- Highlight opportunity to contribute to the advancement of medical knowledge.

TOOL #7

Primer on Consent Process

- Consent and assent should be available in primary language of the subject.
- Ideally the PI and study coordinator should be present.
- Allow enough time to speak with the subjects.
- Have both parents present if a minor is the subject.
- Go over all items in the consent and assent forms with as much explanation as possible.
- Allow time for questions in each section.
- Provide a copy of forms to take home for discussion and thought.
- Provide a realistic assessment of time, procedures, length of trial, benefits and risks involved with participating in the study.
- Emphasize that voluntary withdrawal from the trial at any time will not affect relationship with physician.
- Provide copies of signed forms to subject.

TOOL #8

Primer on Subject Retention

- Schedule subject visits at a convenient time for subjects.
- Consider home visits if appropriate.
- Consider use of convenient lab for venipuncture between visits.
- Maintain close communication with subjects and families
- Confirm f/u appointments
- Reminder to bring unused medications, participant handbook and two first morning urine samples.
- Inform subject of any abnormal laboratory values.
- Return phone calls promptly.
- Have a phone number available for after-hours emergencies.
- Instruct subject to inform team of any adverse events.
- Maintain open communication with referring physicians and primary care physicians.

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

18.2. Center Recruitment and Retention Strategies

In an effort to assist participating sites with enrollment/recruitment, we have developed a payment structure that allows for payment associated with expedited study start up costs and long term follow-up costs associated with enrolled subjects. There will be continual review of potential adult as well as pediatric clinicians to join the study.

Extramural Center Recruitment Efforts include:

- Announcements in journals, newsletters, websites
- Presentations at medical meetings

Steering Committee Center Recruitment Efforts Include:

- Reimbursement analysis with modification as needed and supported
- Training support

Clinical Cores Center Recruitment Efforts include:

- Training support
- On-site support as needed
- Help with IRB submission

18.3. Recruitment Tool - Training Synopsis slides – May 6, 2004 (some slides modified to reflect June 2005 Protocol revisions)

FSGS Clinical Trial

NIH/NIDDK FSGS Workshop

- Accounts for ~ 15% of pediatric ESRD North
- Few randomized therapeutic
- Poor outcome with 50% renal survival in 10 years
- High recurrence rate following

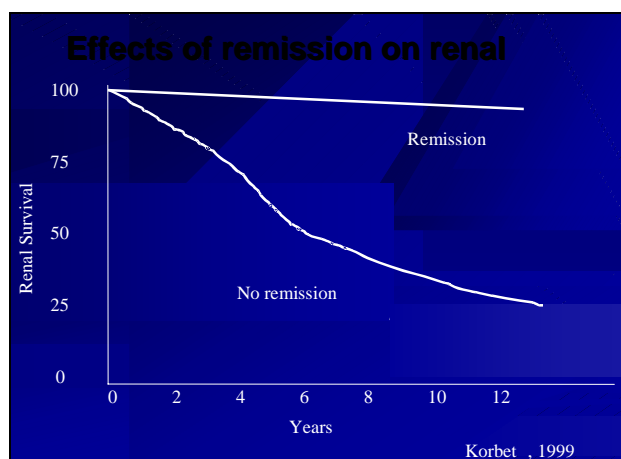
18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

RFA Defined Starting Rules

- Trial of idiopathic FSGS
- Steroid resistance
- No placebo arm
- Inclusion of children and young adults
- Collaboration of selected sites to create single protocol

STEERING COMMITTEE

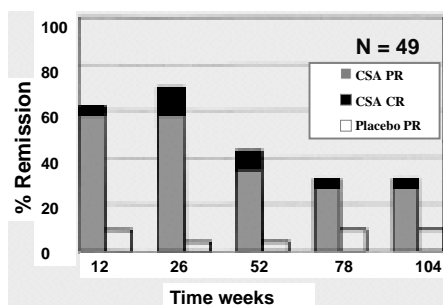
- Review existing literature
- Survey of Participating Sites
- Protocol Development
 - 500 children and young adults
 - Multi center, prospective, randomized trial with two active arms
 - Arm A: Standard of
 - Arm B: More



Previous Therapies

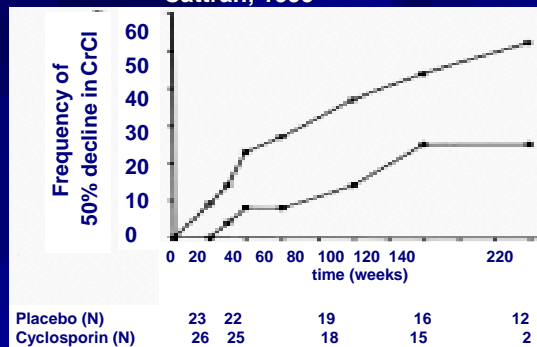
- Anti – inflammatory agents
 - Corticosteroids
 - Oral (ISKDC)
 - Pulse (Tune Mendoza)
- Immunosuppressive
 - Cyclophosphamide
 - Cyclosporine
 - Anecdotal reports of MMF, Sirolimus, Tacrolimus
- Anti proteinuric/reno-protective agents

CSA vs. Prednisone



Kidney Function with CSA

Catran, 1999



18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

Previous Therapies

- MMF (Briggs 98; Monatne 99; Choi 02)
 - No randomized controlled trials
 - Observation of nephrotic syndromes with modest protein reduction
 - Concern regarding strength of effect
- Rapamycin
 - No data
- Tacrolimus
 - Anecdotal data only
- Pirfenidone (Kopp)
 - Antifibrotic with no effect on proteinuria

Pulse Corticosteroids

- Kopp, 2002
 - Dexamethasone pulses
 - Adults
- Tune Mendoza, 1995
 - IV solumedrol w/or w/o alkylating
 - No control group
 - 25/32 needed alkylating agents with pulse
 - 21/32 complete
 - Toxicity & generalizability to adult

Participating Site Surveys

- 45% response (91 of 200)
 - 67 pediatric, 23 internal medicine
- 502 incident patients per year
- 879 prevalent patients satisfying criteria

Participating Site Surveys

- 58% unwilling to consider > 6 mos qod prednisone
- 38% unwilling to consider Tune/Mendoza
- 34% unwilling to consider MMF + pulse CTX
- 20% unwilling to consider MMF, Tacro, SCA+MMF, MMF+Pulse MP or sirolimus

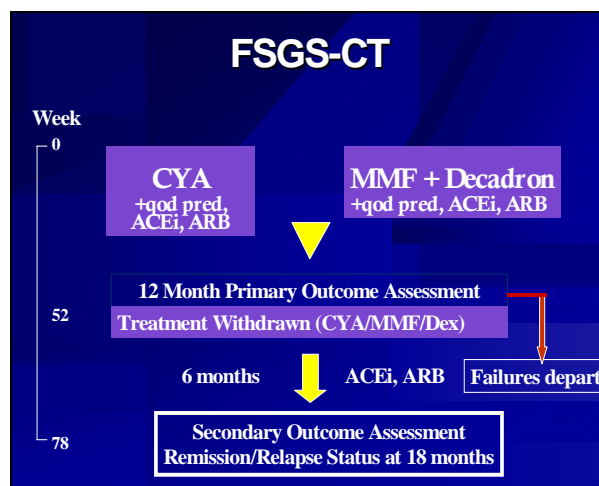
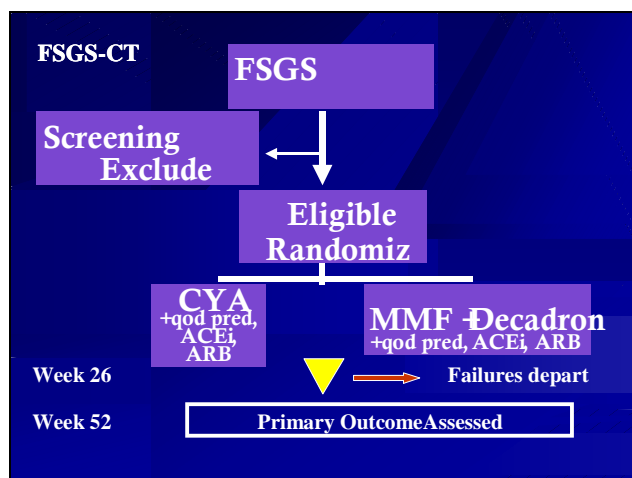
ARM A

- Cyclosporine (12 months)
 - 5-6 mg/kg/day BID
- Lisinopril or Losartan (18 months)
 - Dose based on weight and tolerance
- Prednisone (tablets) or prednisolone (liquid)
 - 0.3 mg/kg/dose, max 15 mg QOD x 6 mos

ARM B

- MMF- 12 months
 - 25-36 mg/kg/day, max 2 g/day
- Dexamethasone 12 months
 - 0.9 mg/kg/dose x 2 days QW x 8, QOW x 9, QM x 6
- Lisinopril or Losartan for 18
 - Dose based on weight and tolerance
- Prednisone (tablets) or prednisolone (liquid)
 - 0.3 mg/kg/dose, max 15 mg QOD x 6 mos

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES



Study Timeline

Sept 2002	Funding begins
May 13, 2003	Protocol submitted to DSMB
May 27, 2003	DSMB approval
Aug 2003	Core lab and pharmacy selected
Nov, 2004	Patient enrollment begins
Mar 1, 2007	Patient enrollment ends
Oct 1, 2008	Final collection of follow-up data
Jan 1, 2009	Completion of primary analysis

Slide modified to reflect June 2005 Protocol rev.

Basis of Primary

- Large decline in proteinuria demonstrate clear
- PR included since too few
- CR more favorable
- No -responders designated Month 6 so alternative therapy without affecting primary

Definition of Remission

- **Partial Remission:** 50% decline in first morning Up/c from mean of 2 baseline measurements to a level 0.2 – 2.0
- **Complete Remission:** Decline in Up/c to a level? 0.2

FSGS STUDY OUTCOMES

- Primary outcome
 - Attainment of partial or complete remission
- Main Secondary Outcome
 - Relapse after immunosuppressives withdrawal
- Secondary Outcomes
 - Treatment failures
 - Change in estimated GFR
 - Side effects
 - Quality of Life

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

Study Power

- Assumes 5% Type 1 error primary outcome is ascertained in 95% of the 500 randomized patients
- Depending on remission rate in CSA group, study has 80% power to detect absolute increase of 10.5% - 11.5% in remission rate (levels 1, 2, or 3) for MMF + Dex vs. CSA

Maximizing Study Power

- Achieve enrollment
- Avoid randomizing patients demonstrating high probability of protocol non-compliance
- Implement intervention protocols
- Avoid non-essential dose reductions, termination of study drugs, or use of prohibited drugs
- Retain patients for full follow-up period
- Complete and accurate data

Minimizing Bias

- Obtain all scheduled Up/c measurements
- Continue patient visits and study measurements even if patient stops study drug or deviates from protocol

INCLUSION CRITERIA

1. Age 2 -40 years at onset of s/sx of FSGS
2. Age 40 years at time of randomization
3. Estimated GFR 40 ml/min/1.73m² prior to randomization
4. First morning Up/c ratio >1.0 prior to randomization
5. Biopsy confirmed as primary FSGS (including all subtypes) by CCC pathologist

Slide modified to reflect June 2005 Protocol rev.

INCLUSION CRITERIA

Steroid resistance: The participant must have demonstrated steroid resistance (defined as a failure to achieve a sustained Up/c \geq 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.

Slide modified to reflect June 2005 Protocol rev.

EXCLUSION

1. Secondary FSGS
2. Prior therapy with, CSA, tacrolimus, MMF, sirolimus or azathioprine
3. Cytosan, chlorambucil, levamisole, methotrexate or nitrogen mustard within 30 days
4. Lactation, pregnancy or refusal of birth control in women of child-bearing potential
5. Participation in another therapeutic trial within 30 days of randomization

Slide modified to reflect June 2005 Protocol rev.

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

EXCLUSION CRITERIA

7. Active/serious infection (including but not limited to Hepatitis B or C, HIV)
8. Malignancy
9. Uncontrolled HTN (> 140/90 or 95th%)
10. ≥ 4 antihypertensives to treat HTN
11. Diabetes mellitus Type I or II
12. Clinical evidence of cirrhosis or liver disease
13. ANC < 2000 or HCT < 28%
14. Significant GI disease

EXCLUSION CRITERIA

15. Organ transplantation
16. Obesity based on estimated dry weight at FSGS onset defined as either
 - a. BMI > 97th %ile for age <20 years
 - b. BMI > 35 for age >21
17. Allergy to study medications
18. Inability to consent/assent

Study Population

- 500 children and young adults with steroid resistant idiopathic FSGS
- ≤200 subjects in each of three age groups:
 - 2 –12 years
 - 13 – 24 years
 - 25 – 40 years

Slide modified to reflect June 2005 Protocol rev.

Logistics

- **18 Month trial**
 - 15 visits with specimens obtained
 - Baseline followup labs
 - Then Q 6mos until close
- **Central laboratory: All tests provided**
- **Central pharmacy: All drugs provided**
- **On-line or paper reports**

Biopsy Confirmation

- **5 Core Biopsy Reading Centers associated with 5 Core Coordinating Centers**
- **PS to send to Core Pathologist:**
 - At least one H&E slide
 - At least one special stain slide
 - Electron microscopy prints
 - Immunofluorescence report

Schedule of Visits & Procedures

Study Week	<0	0	2	4	6	8	14	20	26	32	38	44	52	65	78*	Var
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	99
Study Drugs**	Arm A	CSA (BID for the 12-month duration therapy)														
	Arm B	MMF (BID 12 months) Discontinuation (weeks 1-8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 34, 38, 42, 46, 50)														
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel***	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UpC	XX	X	X	X	X	X	X	X	XX	X	X	XX	X	XX	X	X
Urine Pregnancy Test	X	X					X		X		X		X			
QOL Questionnaire	X								X				X		X	
**** ANA and ESR Viral Studies	X															

* Subject will be followed every 6 months until the end of the trial. Visits will include physical exam, labs and med use.
 **Both treatment arms will receive prednisone QOD for the first 6 months of treatment and Lisinopril for the duration of the treatment.
 ***Includes Fasting Lipids at Visits 1, 4, 9, 13 and 15.
 ****HIV-1 antibody, Hep B Surface Antigen, Hep C Virus Antibody

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

Visit Schedule

- Baseline-Week 8 visits every 2 weeks
- Week 14-44 visits every 6 weeks
- Week 52 visit 8 weeks after Week 44
- Week 65-78 visits 13 weeks apart
- Week 78+ subjects followed q. 6 mos. until end of trial

Relapses

- For subjects with PR or CR during therapy relapse defined as
 - a) CR (Up/c <0.2) followed by Up/c >2.0
 - b) PR (Up/c $0.22-2.0$ and $<50\%$ of baseline value) followed by Up/c >2.0 which is 2x greater than nadir Up/c

Treatment of Relapses

- Optional whether to treat
- Relapse therapy allowed up to 2x during first 12 months of treatment
- Additional relapses remain untreated
- Prednisone 2 mg/kg/day to max of 60 mg qd for 2 weeks, then qod for 1 week
- Recheck Up/c after 3 weeks
- Prescribed locally

NIH Repositories

Purpose

Collect and store biological samples for future investigation of mechanisms related to FSGS which are beyond scope of the therapeutic clinical trial

NIH Repositories

Three NIH Repositories

- NIH— data
- Fisher – biological specimens
- Rutgers - DNA

NIH Repositories

- Participation by PS and individual subjects is voluntary
- Separate consent required for banking
- Subject may consent to any one of the repository collections
- Subject may withdraw consent anytime

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

NIH Repositories

Biological Specimens

- Collect Weeks 0, 26, 52, 78
- Serum: 4-16 mL (per age)
- Plasma: 4.5-18 mL (per age)
- Urine: 10-120 mL (per amount voided)

DNA

- Collect at Week 0 or any visit during treatment
- Whole blood: 7-17 mL (per age)

Ancillary Studies

- Ancillary studies will propose collection or analysis of data not encompassed by therapeutic clinical trial
- Proposals must be submitted to ASC and Steering Committee for review

Ancillary Studies

- All ancillary studies will be reviewed for
 - Scientific merit
 - Relevance to FSGS
 - Sound design and methodology
 - Feasibility
 - Non-interference with therapeutic trial
 - External funding source

Ancillary Studies

- Upon approval of ancillary study, Core will forward to PS for consideration
- Participation by each PS is optional
- Ancillary study budget will cover all associated expenses
- Separate informed consent may or may not be required

REIMBURSEMENT

- Based on survey of PS
- \$1600 per center start-up
 - IRB application and contract
 - Pharmacy start-up
 - Lab start-up
 - Administrative fees
 - Payment upon receipt of IRB approval & signed subcontract
- Travel reimbursement to training sessions

REIMBURSEMENT

- \$4200-4950 per subject randomized
 - \$1500/2250 upon randomization*
 - \$500 upon receipt of Wk 26 CRFs
 - \$500 upon receipt of Wk 52 CRFs
 - \$1500 upon receipt of Wk 78 CRFs
 - \$200 at close of study
 - \$250 subject transfer fee
- *Larger payment for earlier enrollment due to extended longterm followup

REIMBURSEMENT

- **Per subject reimbursement based on**
 - Biopsy slide prep and mailing
 - Clinic visits with H&P
 - Lab draws and specimen handling
 - Pharmacy dispensing, relapse therapy
 - CRF completion
 - Subject parking, meals, etc
 - Study coordination
 - Indirects for non-patient care costs

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

18.4. Pathologist Monthly Contacts

To identify prospective enrollees into the study, the FSGS Steering Committee has requested assistance from the pathology community. This group of professionals is collectively responsible for evaluating a large portion of the kidney biopsies performed in the United States and Canada and it is felt they have a unique position to help with this study.

Starting in November of 2005, each Core Coordinating Center will contact the pathologists who perform biopsies for its affiliated Participating Sites to obtain contact information of the referring nephrologists of biopsies diagnosed as FSGS from patients between 2 and 40 years of age. The pathologist assignments for each core are stored by the DCC, and include all pathologists listed in the Form 2 (Oracle database), irrespective whether the Participating Site is “ready to enroll”. If an interested pathologist has not been linked to a specific Participating Site, the DCC will assign that pathologist to a Core Coordinating Center and will be added to the assigned Core’s Form 2 information. If a pathologist is working with multiple Participating Sites, that pathologist will be assigned by the DCC to one of the Cores associated with those sites.

The initial contacts between a Core Coordinating Center and its assigned pathologists should be made by either by the Core Coordinating Center’s Principal Investigator or a designated physician co-investigator. Subsequently, arrangements may be made for the Core’s study coordinator to communicate on a monthly basis with either the pathologist or with administrative personnel associated with the pathologist to obtain the biopsy information.

On the initial contact with a pathologist, that pathologist will be requested to provide contact information for the referring nephrologist responsible for all patients between 2 and 40 years of age with FSGS biopsies during the past 6 months, or as far back as the pathologist is able to investigate if a 6-month review is not feasible. Subsequently, on a monthly basis a Core Coordinator will contact the pathologist’s office to obtain contact information for referring nephrologists responsible for patients between 2 and 40 years of age with new FSGS biopsies in the last month.

The Cores should obtain the following information from the pathologists:

1. Name of pathologist reading the biopsy
2. Date of biopsy
3. Age of patient at biopsy
4. Name of referring nephrologist
5. Location and Institution of referring nephrologist
6. Phone number of referring nephrologist
7. E-mail of referring nephrologist
8. Fax number of referring nephrologist.

During the initial contact between the Core and the pathologist the Core should discuss with the pathologist whether an IRB waiver would be required by the pathologist’s institution to allow the pathologist to provide the requested contact information. It is expected that waivers will often not be required because patient-identifying information is not being requested. If a waiver is

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

required, the template in Section 18.3B may be modified as necessary to meet the requirements of the pathologist's institution.

It is not necessary for the pathologist to provide the patient name. However, in some cases, Cores may find that biopsy numbers may be useful in identifying specific biopsies during their discussions with the referring nephrologists. Therefore, if the Core and the pathologist feel that provision of the biopsy number would be useful and acceptable, they may obtain agreement from the IRB for the pathologist's institution to allow the biopsy number could be provided. At no time would study personnel directly contact potential patients.

A Pathologist contact form (Form 4) should be used by the Core Coordinator's to tabulate summary information regarding their contacts with the pathologists. Instructions of use of this form are provided on Section 18.3.C below.

After obtaining the referring nephrologists' contact information, the Core Coordinating Center should contact the nephrologist to determine whether the patient may be suitable for the trial. The Core should keep a log of all the biopsies identified by the pathologists, in order to tabulate the number of FSGS biopsies identified, the fraction of the patients which are eventually enrolled in the trial, and reasons for ineligibility for those patients who do not satisfy the study's entry criteria. This information will be tabulated on Form 3.

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

18.4.1. Template for IRB Waiver

The following template may be modified as needed in those cases where a pathologist feels that an IRB waiver is required.

Summary Proposal for an IRB Request for a Limited Waiver of HIPAA Authorization for Nephropathology Laboratories to Identify Potentially Eligible Patients for the FSGS Trial

For identification of subjects who may be eligible for the NIH-sponsored Focal Segmental Glomerulosclerosis Trial, participation of nephropathology laboratories is critical. To date, recruitment for the trial has depended on identification of patients by treating physicians at sites participating in the trial. However, there are limitations to this approach. This method of patient identification does not provide information on the total number diagnosed and/or potentially eligible for the trial and, therefore, does not maximize recruitment and allow for all patients to have the opportunity to participate in the trial. Many patients, especially older teens and adult patients, are seen in private practices, and, therefore, may not be seen at a site that is participating in the trial. For example, patients aged 2 to 14 (n=35) who were diagnosed by renal biopsy through the University of North Carolina (UNC) Nephropathology Laboratory (9/2000 - 8/2005, n=353), were all seen in academic centers participating in the trial. In contrast, 50% of patients aged 15 to 19 (n=41) and 93% of patients aged 20 to 40 (n=277) were seen in private nephrology practices. These numbers highlight a need to inform a broad base of physicians about the trial so that patients have equal opportunity to participate. Few treatment trials have been conducted in this disease, none of this scale. The broad inclusion of patients to form a nationally representative sample is important to the mission of the NIH sponsored trial as well as to applying the study results beyond the study. With over 100 sites conducting the trial around the country, patients seen in non-participating locations can be accommodated at a participating site that is located near them. Alternatively, private practices may work with a study core to become a participating site or partner with a core or participating site to share study visits. Patients are evaluated for response to treatment 6 months after randomization.

In order to define a denominator of patients diagnosed with the disease and to maximize recruitment, a HIPAA waiver is requested for release of information on all patients aged 2 to 40 diagnosed by renal biopsy with idiopathic FSGS to one of the 5 study cores (**Information from this nephropathology laboratory will be released to XXXX** FSGS Core Coordinating Center). Information that will be provided to the core from the nephropathology laboratory will include:

- 1) Age at biopsy
- 2) Physician who conducted the biopsy and/or who follows the patient
- 3) Location/address, name of practice or institution and contact information for this physician, including telephone number, FAX number and email address
- 4) Date of biopsy

This information will be provided to the FSGS Core Clinical Coordinating Center on a monthly basis throughout the recruitment phase of the trial, although the first contact will provide information of those diagnosed over the previous 12 months. The **Core Coordinating Centers will then be responsible for contacting the physicians**. For practices or institutions that are not already participating in the trial, information on the closest participating study site(s) will be provided as well as information on the requirements for becoming an approved site. The

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

primary nephrologist may contact the nephropathologist to clarify the identification of the patient, as needed. The patient's own physician may then contact the patient with details about the study. The patient's physician will also provide information to the core as to why the patient is not eligible (GFR too low, already on a study treatment drug, age corrected and not within the study range, not interested, etc.). This information is particularly important in assessing the impact of different entry and exclusion criteria on recruitment for the study and other reasons for non-participation.

A limited waiver of HIPAA authorization to identify potential subjects for recruitment into this treatment trial is requested. The limited waiver provides access to protected health information to confirm potential eligibility and facilitate initial contact with the patient's physician. Eligible patients have a specific kidney disease that can only be diagnosed by a kidney biopsy. Without obtaining limited protected health information from the renal biopsy records, it would be impossible to identify all patients with the disease of interest. The only alternative is to ask individual physicians to identify the patients and contact the trial investigators and coordinators. This is not a practical solution as many of the physicians are not set up with databases for uniform and systematic identification of all patients with specific diagnosis. This is especially true for private practice physicians who see the majority of adult patients.

There is only minimal risk for patients with this project. The specific potential risk is loss of privacy. By not using names, dates of birth or other identifiers, except the renal biopsy specimen number, this risk is as limited as practical while still allowing the physician to contact the nephropathologist to identify the patient. Once the recruitment phase of the FSGS trial is over, the study cores will destroy the renal biopsy number. All other information will be kept by the core for continued assessment of recruitment potential for future trials and other studies of patients with FSGS.

In summary, communication between the nephropathology laboratories and the 5 cores for the FSGS trial will allow for a population-based approach to the identification of patients for the FSGS trial. This method of patient identification and recruitment will also increase the likelihood that patients are given the opportunity to learn about and participate in the trial. Identification of patients using limited identifiers is critical, and using the proposed method there is minimal risk of loss of privacy. Use of the renal biopsy specimen number and date will allow the correct identification of patients and will eliminate the possibility of duplicate patients. Furthermore, by working with all nephropathology laboratories across the country, recruitment will be maximized and a population-based estimate of overall trial participation, sample representation (trial versus all patients diagnosed) will be possible.

18. SUBJECT RECRUITMENT AND RETENTION STRATEGIES

18.4.2. Instructions for Use of the Pathologist Contact Form (Form 4)

All pathologist's that have been entered into Form 2 and that have been indicated to the DCC as either an "individual" or "group" (how you'll be contacting them) have been assigned a number. FYI: The structure of the 4-digit assigned number is 1st digit = 6 (individual) or 7 = (group), 2nd digit = Core #, and 3rd/4th digits are sequential numbers.

Please note that on Form 4, question 4 two codes have been added: 5=pending contact and 6=no longer available (explained below).

Form 4 Data Entry Instructions:

Go to: <https://clinapps.bio.ri.ccf.org/fsgs/index.html>

Click on: Form 2 and Reports (Production)

Select: FORMS Pathologist contact info – Core only

Do not "query" your Core Number (as you would in Form 2). The cursor will be in Core No. field, type (enter) your Core No; Calendar Month (3 digit alpha); Calendar Year (yyyy). Hit <Enter>. Your Core Pathologist Code Detail list will populate. The only fields you'll be able to enter are Q4, 5, 6, and 7. Make sure to SAVE once you have entered the responses before Exiting the Form.

The default code of "5=pending contact" is populated in Q4 for all your entries. If you do not have a Form 4 (hard copy) completed/available for a particular individual/group then leave Q4 as "5" for that row. If an individual/group for some reason does not want to be contacted any longer or is no longer at that Institution, etc. then select "6=no longer available". If Q4 is code 5 or 6 then Q5-7 should be left blank.

All "5=pending contact" fields must be updated to a response of 0=no, 1=yes, or 6=no longer available before the Form 4 for that specific month is considered complete.

To print a copy of the entries you made, click on "Get Report" and a snap shot of your entries will open in Adobe Acrobat.

19. FINANCIAL OVERVIEW

19.1. Reimbursement Schedule

Subcontractor will be reimbursed on the following payment schedule. All figures are inclusive of applicable Subcontractor indirect/facilities and administrative costs.

Start Up Costs

One time, nonrefundable reimbursement payable upon..... \$1,600
Participating Site's submission of IRB approval and signed subcontract.

Subject Reimbursement

Subjects completing entire study- as detailed below

Enrolled prior to June 30, 2005	\$5,450
Enrolled prior to December 30, 2005	\$5,200
Enrolled prior to June 30, 2006	\$4,950
Enrolled on or after July 1, 2006	\$4,700

Detailed Breakdown - Payable upon:

- Screening *-\$500
- Randomization **
 - Prior to 06/30/05..... \$2,250
 - Prior to 12/30/05..... \$2,000
 - Prior to 06/30/06..... \$1,750
 - On or after 07/01/06 \$1,500
- Receipt of complete*** Week 26 CRFs \$500
- Receipt of complete*** Week 52 CRFs \$500
- Receipt of complete*** Week 78 CRFs \$1,500
- Receipt of complete*** CRFs due at close of study \$200

Screening Fee Note

Participating sites that process potential subjects who sign consent/assent and complete Visit B1 (including all laboratory specimens and biopsy samples/reports and case report forms) will be reimbursed \$500 for effort expended in screening. Screening failures due to central biopsy interpretation, low urine protein/creatinine ratio, low GFR, pregnancy or infection detected by baseline laboratory results will be reimbursed for the screening visit.

Transfer Fee \$250

If a subject transfers to another Participating Site and continues on the study, upon receipt of the transfer form to the FSGS Study Desk, the recruiting site will receive the transfer fee. Subject reimbursement for the work performed by the two Participating Sites will be prorated.

Travel

Investigators and coordinators will be reimbursed for travel expenses to attend required training sessions. Travel expenses shall be reimbursed following completion of the "FSGS Travel Reimbursement Request" form (Exhibit E).

*Receipt of complete Screening visit specimens, biopsy material, biopsy reports and CRFs must be received before payment is made

**Complete Baseline CRFs must also be received

***All queries must be resolved before payment is made

20. APPENDICES

- 20.1. Percentiles of Blood Pressure for Boys
- 20.2. Percentiles of Blood Pressure for Girls
- 20.3. BMI for Boys
- 20.4. BMI for Girls
- 20.5. NCI Drug Log
- 20.6. GFR Formulas for Adults and Children
- 20.7. Certificate of Confidentiality Application Instructions
- 20.8. Examples of Language Describing Certificate of Confidentiality Protection of Privacy
- 20.9. WHO Diabetics

20.1. Percentiles of Blood Pressure for Boys

TABLE 2. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Boys Aged 1 to 17 Years by Percentiles of Height

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

* Blood pressure percentile was determined by a single measurement.

† Height percentile was determined by standard growth curves.

20.2. Percentiles of Blood Pressure for Girls

TABLE 3. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Girls Aged 1 to 17 Years by Percentiles of Height

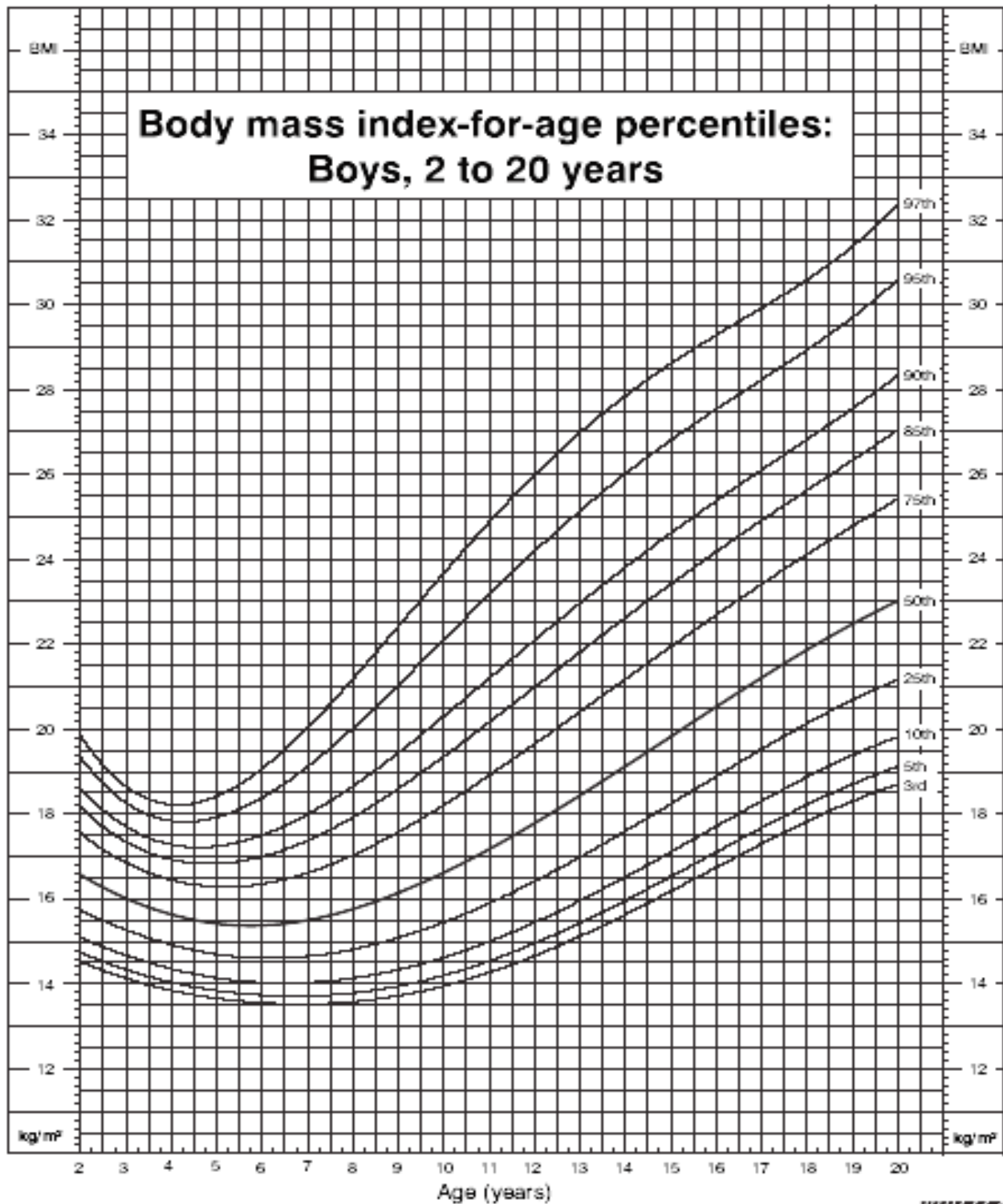
Age, y	Blood Pressure Percentile*	Systolic Blood Pressure by Percentile of Height, mm Hg†							Diastolic Blood Pressure by Percentile of Height, mm Hg†						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	90th	97	98	99	100	102	103	104	53	53	53	54	55	56	56
	95th	101	102	103	104	105	107	107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

* Blood pressure percentile was determined by a single reading.

† Height percentile was determined by standard growth curves.

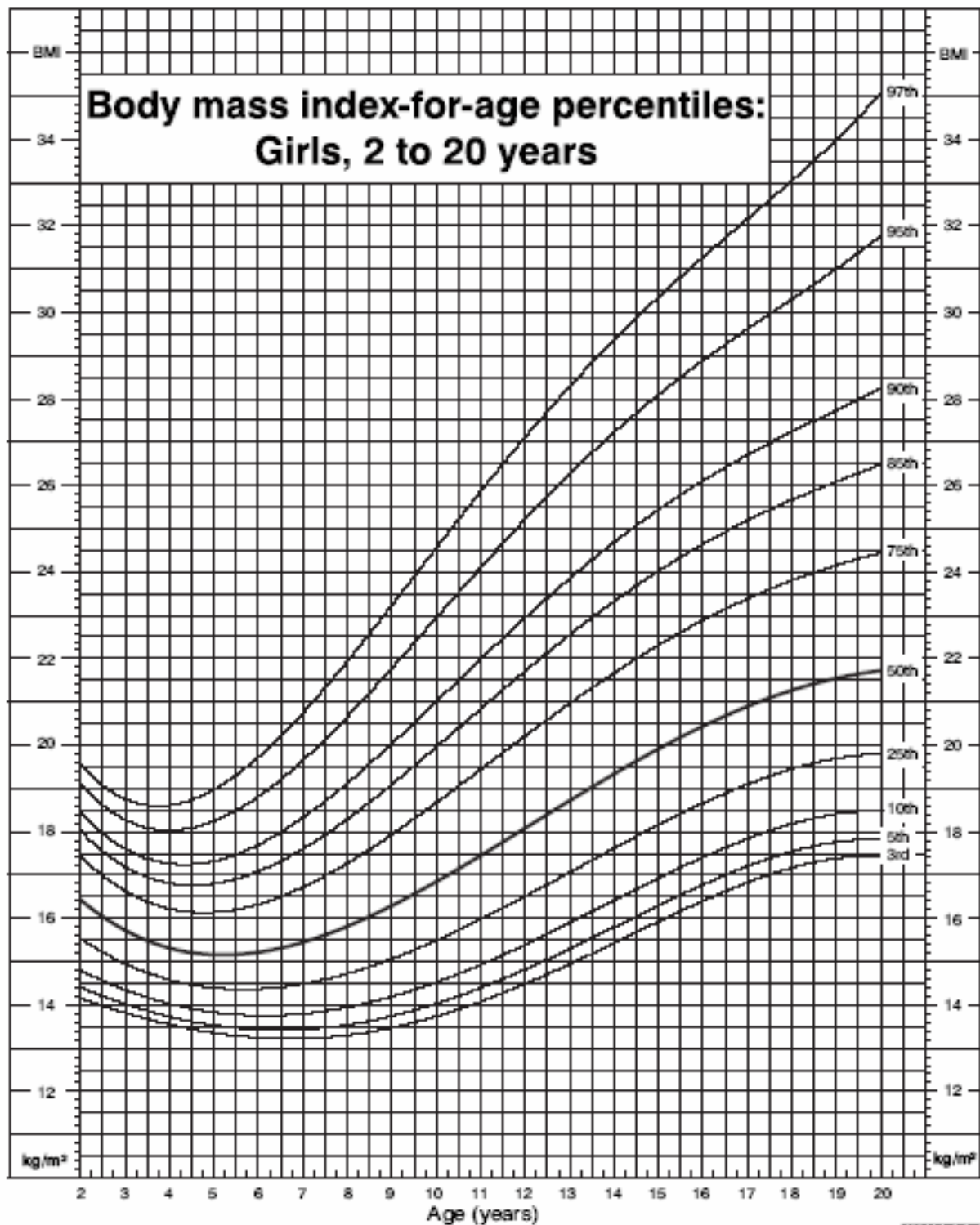
20.3. BMI for Boys

CDC Growth Charts: United States



20.4. BMI for Girls

CDC Growth Charts: United States



SAFER • HEALTHIER • PEOPLE™

20.5. NCI Drug Log

Form approved: OMB No. 0925-0240 Expires: 4/30/2004

Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

National Institutes of Health National Cancer Institute

Investigational Agent Accountability Record

PAGE NO. CONTROL
RECORD 10 SATELLITE
RECORD 10

Name of Institution:	NCI Protocol No.:
Agent Name:	Dose Form and Strength:
Protocol Title:	Dispensing Area:
Investigator Name:	NCI Investigator No.:

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received Balance	Balance Forward	Manufacturer and Lot No.	Recorder's Initials
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
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20.								
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22.								
23.								
24.								

NIH-2564

20.6. GFR Formulas for Adults and Children

GFR for adults

Cockroft-Gault Formula

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

For men: $CrCL = \{ [(140 - \text{age}) \times W] / (72 \times SCR) \} \times 1.73 / BSA$

For women: $CrCL = \{ 0.85 \times [(140 - \text{age}) \times W] / (72 \times SCR) \} \times 1.73 / BSA$

Where $CrCL = GFR$ in ml/min/1.73m²

W = body weight in kg – based on F46, Q5b

SCR = serum creatinine in mg/dL – based on R85

Age based on F10, Q3 and date of R85

The formula for BSA is:

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

Where BSA = body surface area in m²

W = weight in kg – based on F46, Q5b

H = height in cm – based on F46, Q5a

The reference is:

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

GFR for kids

Schwartz formula

$Schwartz = (k \times \text{height in cm}) / \text{serum creatinine in mg/dL}$

Where k = 0.55 for children (2 – < 13) and adolescent girls (age 13 – 18)

k = 0.70 for adolescent boys (age 13-18)

Height is based on F46, Q5a

Serum Creatinine is based on R85

Age based on F10, Q3 and date of R85

The references are:

Schwartz GJ, Brion LP, Spitzer A: The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents.

Pediatric Clinics of North America. 34(3): 571-590, 1987.

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

20.7. Certificate of Confidentiality Application Instructions

Dear Applicant:

To apply for a Certificate of Confidentiality from the Food and Drug Administration (FDA) under the Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)) to protect against involuntary disclosure of the identities of research subjects, please direct a letter to the following address:

Julie A. Unger
Food and Drug Administration
Division of Scientific Investigations (HFD-45)
7520 Standish Place, Room 102
Rockville, Maryland 20855

Containing the following information using the numbering scheme shown.

1. Investigational New Drug (IND) number
2. Drug name
3. Name and address of sponsor
4. Name of entity (e.g., university, center, manufacturer, etc.) who should be named as the holder of the certificate
5. Concise description of the study aims and research methodology; include number, source and description of the human subjects
6. Reasons for requiring confidentiality
7. Means used to protect subjects' identities (e.g., coded by number, kept in locked files).
8. Assurances of the following:
 - (a) that for all projects conducted under a FDA investigational exemption (Investigational New Drug Application), all personnel involved with the conduct of the research will comply with the human subject protection requirements of 21 CFR Parts 50, 56 and 312, and that personnel involved in the conduct of the research supported by grants from the Department of Health and Human Services (DHHS) will comply with all the requirements of 45 CFR Part 46 "Protection of Human Subjects;"
 - (b) that the Certificate of Confidentiality will not be represented as an endorsement of the project by the FDA or the DHHS or used to coerce individuals to participate in the research project;

- (c) that the recipient of the Certificate of Confidentiality will use the vested authority to protect the identity of research subjects;
- (d) that all subjects be informed that a certificate has been issued and that subjects will be provided with a description of the protection covered by the certificate;
- (e) that subjects who enter the project after termination of the certificate will be informed of the termination.

The individual primarily responsible for the conduct of the research must sign the letter requesting the Certificate of Confidentiality.

The Certificate of Confidentiality does not govern a disclosure for which the subject gives permission or a researcher's voluntary disclosure of the identifying characteristics of research subjects, but only protects subjects from compelled disclosure of identifying characteristics. For example, a researcher is not prevented from making voluntary disclosure of personally identifiable information related to child abuse or a subject's threatened violence to self or others. However, if a researcher expects to make such voluntary disclosures, the consent form should clearly indicate this [21 CFR 50.25(a)(5)]. The Certificate of Confidentiality also does not govern disclosure of study information without personal identifiers.

Your request will be processed as rapidly as possible. However, if all of the items of information requested above are not provided in the letter, issuance of your certificate may be delayed. Please do not hesitate to contact me, if you have any questions.

Sincerely yours,

Julie A. Unger
Consumer Safety Technician
Division of Scientific Investigations

20.8. Examples of Language Describing Certificate of Confidentiality Protection of Privacy

1. A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we learn something, that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help.
2. Our research study has an order from the U.S. Government. This order is called a Federal Certificate of Confidentiality. It will help protect your privacy even if the study records are subpoenaed. There are some limits to the researcher's ability to maintain your confidentiality. If you tell me anything that suggests you are very likely to harm yourself, that you are planning to hurt another person, or that someone is likely to harm you, then I will have to tell the appropriate agency.
3. A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, such as the court system, about your participation in the study, without your consent in writing.

There is one exception to the promise of confidentiality. If we see or are told that a child is being abused or neglected or that there is a risk of harm to yourself or others, we will disclose this information to the proper authorities.

4. The U.S. Department of Health and Human Services (DHHS) has issued a Confidentiality Certificate to this research project. Under the Certificate, _____ is authorized to and will protect your identity as a research subject in this project, even if someone tries to find out who you are through any kind of court or other legal proceeding. If we learn that keeping, specific information private would immediately put you in danger, or put in danger someone else we know about, we may discuss it with you, if possible, or seek, help from others to protect you or another person.
5. To further protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services.
With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should understand that a Confidentiality Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research. Also, it does not prevent the investigators from voluntarily releasing information if you give your permission in writing for them to do so.

Finally, you should understand that even with a Confidentiality Certificate, the investigators continue to have ethical and legal obligations to report suspected or actual child abuse and/or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others.

6. It is particularly important for you to know that we have gotten a Certificate of Confidentiality from the Federal Government for this study, to make sure we can best protect your privacy. This certificate means that researchers cannot be forced to tell people who are not connected with the study about your participation, without you giving your permission in writing. This includes courts and the police.

There are some limits to the researchers' ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put in danger someone else we know about, then we will have to tell the appropriate agencies to protect you or another person.

7. The researchers have obtained a Certificate of Confidentiality from the Federal Government which will help them protect your privacy by refusing to disclose personally-identifying information about you, to people who are not connected with the study without your written consent. This protection, however, does not prohibit the investigator from voluntarily reporting information. For example, if they have strong reason to believe you are abusing a child or elderly person, or you have made credible threats of violence to others, they may report it to appropriate authorities.
8. This research is covered by a Certificate of Confidentiality issued by the Department of Health and Human Services (DHHS). This Certificate will protect the investigators from being forced to release any research data in which you are identified, even under court order or subpoena, without your written consent. This protection, however, does not prohibit the investigator from voluntarily reporting information about suspected or known sexual or physical abuse of a child or a subject's threatened violence to self or others. If any member of the program staff has or is given such information, [Note to Investigator: Please describe your intentions to report such information learned through the course of this research.]
9. It is particularly important for you to know we have gotten, a Certificate of Confidentiality from the Federal Government for this study to make sure we can best protect your privacy. This certificate means that the researchers can not be forced to tell people who are not connected with the study about your participation without you giving your permission in writing. This includes courts and the police.

If we learn keeping information private would immediately put you in danger, or put in danger someone else we know about, we may talk with you about what to do, if possible. Or we would release information in order to seek some other help to protect you or another person.

10. The researchers have obtained a Certificate of Confidentiality from the Federal Government which will help them protect your privacy, unless you consent in writing to the release of research information. However, if they learn that you or someone else is in serious danger of harm [such as in cases of child abuse] they may make disclosures to protect you and/or the other persons.

association with very small pancreatic adenocarcinomas, leading some investigators to speculate that these tumors produce some diabetogenic factor or factors.⁴⁸ Five percent to 15% of patients with cystic fibrosis develop diabetes.⁴⁹ Up to half of these patients require insulin either chronically or at times of added stress such as glucocorticoid therapy. Hemochromatosis can cause diabetes.⁵⁰ Since glucose tolerance may improve with phlebotomy, this condition represents an important, potentially reversible cause of diabetes. Fibrocalculus pancreatopathy is seen mainly in the Tropics and is associated with abdominal pain and calcification of the pancreas on abdominal imaging.⁵¹

Endocrinopathies

Cortisol, growth hormone, glucagon, and the catecholamines (epinephrine and norepinephrine) can antagonize insulin action. Tumors that produce these hormones in excess lead to Cushing's syndrome, acromegaly, glucagonoma, and pheochromocytoma, respectively. While all of these conditions are associated with a degree of glucose intolerance, overt diabetes only develops in a subset of patients. The importance of recognizing these secondary forms of diabetes lies in the fact that resection of the underlying tumor can cure the diabetes. The hyperglycemia that is seen in the setting of aldosterone-producing adenomas and somatostatinomas results from alteration of insulin secretion.

Drug- or Chemical-Induced Diabetes

Certain compounds are toxic to β cells.^{52, 53} These include the rat poison vavoc and the anti-*Pneumocystis* drug pentamidine. The hyperglycemia resulting from these agents is usually not reversible. Thiazide diuretics can inhibit insulin secretion by causing hypokalemia. Glucocorticoids and nicotinic acid cause hyperglycemia by impairing insulin action. Both protease inhibitors used in the treatment of human immunodeficiency virus infection and clozapine, a drug used to treat resistant schizophrenia, can cause hyperglycemia via an as yet undetermined mechanism.

Infections

Certain viral infections, including rubella⁵⁴ and coxsackie B virus,⁵⁵ have been associated with diabetes. Some studies suggest that a viral infection can trigger autoimmune destruction of β cells in genetically predisposed individuals, leading to autoimmune type 1 diabetes.

Uncommon Forms of Immune-Mediated Diabetes

The stiff-man syndrome is a rare neurologic syndrome characterized by spasticity of the axial muscles. It is associated with very high titers of anti-GAD antibodies and up to one-third of patients develop diabetes.⁵⁶ Autoantibodies directed against the insulin receptor represent another rare cause of diabetes.⁵⁷ These antibodies have the potential to change from being receptor antagonists (causing insulin resistance) to being receptor agonists (leading to potentially life-threatening hypoglycemia).

Other Genetic Syndromes Sometimes Associated with Diabetes

Many of the genetic syndromes listed under H in Table 53-1 are known to be associated with diabetes. The precise mechanism of the diabetes has not been established for these conditions.

Gestational Diabetes

Gestational diabetes is defined as diabetes with onset or first recognition during pregnancy. The prevalence of gestational diabetes increases in parallel with the prevalence of type 2 diabetes in a population. Approximately 4% of pregnancies in the United States are

complicated by gestational diabetes.⁵⁸ Risk factors include age (commoner among older women), ethnicity (higher rates are seen among women from ethnic groups with a high incidence of type 2 diabetes), prepregnancy body mass index (risk increases with degree of obesity), parity (risk increases with number of previous pregnancies), and family history of diabetes. A previous pregnancy complicated by gestational diabetes or a history of delivery of a macrosomic infant also represent a strong risk factor for future gestational diabetes. The diagnosis of gestational diabetes is important since, if left untreated, adverse fetal or maternal outcomes can occur. The main adverse fetal outcome is macrosomia and neonatal hypoglycemia.⁵⁹ Maternal complication include a higher rate of dystocia and cesarean section as well as a greater risk of future type 2 diabetes⁶⁰ (among women who revert to normal glucose tolerance after completion of the pregnancy).

There are no uniformly agreed upon criteria for the diagnosis of gestational diabetes.⁶¹ The criteria most widely used in North America were developed based on the ability of plasma glucose levels measured during pregnancy to predict future development of type 2 diabetes and not adverse outcomes of that pregnancy. In addition, the 100-g glucose load used in North America is different from the 75-g load used in other parts of the world. Finally, no consensus exists as to who should be screened.⁶² In some countries (e.g., the United States) universal screening is routinely undertaken, whereas in other countries (e.g., in Europe) only women believed to be at high risk are screened.

DIAGNOSIS

Diagnostic Criteria

In addition to recommending changes in the classification system for diabetes, the Expert Committee of the ADA also recommended changes in the diagnostic criteria for the disease in their 1997 report.¹⁰ These criteria were subsequently endorsed by WHO¹¹ and are outlined in Table 53-2. The major differences between the new and the old criteria were a reduction in the fasting plasma glucose cut point used to diagnose the disease and an emphasis on use of fasting plasma glucose as opposed to the oral glucose tolerance test to screen for and diagnose the disease. The fasting plasma glucose level required for a diagnosis of diabetes was reduced from 140 mg/dL to 126 mg/dL. The upper limit of normal for fasting plasma glucose was set at 110 mg/dL. The diagnostic threshold for the 2-hour postglucose challenge plasma glucose level remains at 200 mg/dL. Two other important features of the diagnostic criteria that were retained include the ability to use casual plasma glucose levels in patients with hyperglycemic symptoms and the requirement that a firm diagnosis be based on testing carried out on more than one occasion. The ADA report based its criteria on use of the fasting plasma glucose level, while the WHO report included equivalent cut points for whole-blood venous and capillary glucose (see Table 53-2).

Rationale for the New Diagnostic Criteria

There were three main reasons for the changes recommended in the revised diagnostic criteria. The first reason relates to the lack of equivalence between a fasting plasma glucose value of 140 mg/dL and a 2-hour postglucose challenge value of 200 mg/dL.⁶³⁻⁶⁵ Only approximately 25% of patients with a 2-hour value above 200 mg/dL will have a fasting value above 140 mg/dL. The point at which the two tests approach equivalence (based on receiver operating characteristic curve analysis) is closer to a fasting value of 126 mg/dL. The second reason for changing the criteria comes from epidemiologic studies that have assessed the level of glycemia at which the microvascular complications of diabetes begin to appear.^{63, 66} As seen in Figure 53-1 the fasting plasma glucose value at which retinopathy first occurs is closer to 126 mg/dL than 140 mg/dL. This observation was first reported in a population of Pima Indian subjects who have a very high prevalence of diabetes and a bimodal distribution of glucose. It was subsequently confirmed in a population from Egypt and most recently

Best choice

TABLE 53-2. Diagnostic Criteria for Diabetes Mellitus and Other Categories of Hyperglycemia

	Glucose Concentration (mg/dL [mmol/L])		
	Whole Blood		Venous Plasma
	Venous	Capillary	
Diabetes mellitus			
Fasting	≥110 (≥6.1)	≥110 (≥6.1)	≥126 (≥7.0)
or			
2-hr postglucose load	≥180 (≥10.0)	≥200 (≥11.1)	≥200 (≥11.1)
or			
both			
impaired glucose tolerance			
Fasting concentration (if measured)	<110 (<6.1)	<110 (<6.1)	<126 (<7.0)
and			
2-hr postglucose load	≥120 (≥6.7) and <180 (<10.0)	≥140 (≥7.8) and <200 (<11.1)	≥140 (≥7.8) and <200 (<11.1)
Impaired fasting glucose			
Fasting	≥100 (≥5.6) and <110 (<6.1)	≥100 (≥5.6) and <110 (<6.1)	≥110 (≥6.1) and <126 (<7.0)
2-hr (if measured)	<120 (<6.7)	<140 (<7.8)	<140 (<7.8)

Modified from Alberti KGMM, Zimmet PZ: Definition, diagnosis, and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 15:539-553, 1998. Copyright John Wiley & Sons Limited.

in data from the Third National Health and Nutrition Examination Survey in the United States.¹⁰ Because of differences in the design of the studies the retinopathy prevalence data are not comparable across the three populations shown in Figure 53-1. Nevertheless, the cut point at which retinopathy begins to appear is similar in all three studies. The third reason for recommending a change in the diagnostic criteria for diabetes is a pragmatic one and relates to the fact that, outside of pregnancy, the oral glucose tolerance test is seldom used in routine clinical practice. The expert committees of the ADA and WHO acknowledged this fact by emphasizing that the fasting plasma glucose measurement should be considered the preferred method for screening. The ADA also recommended use of the fasting plasma glucose level in epidemiologic studies.

Implications of the New Criteria

A diagnosis of diabetes can have implications for patients not just in terms of their future medical well-being but also in terms of their psychosocial and even economic well-being. Examples of this would include higher life insurance premiums as well as exclusion of patients treated with insulin from certain occupations (e.g., commercial airline pilot). Screening programs should ideally be able to identify individuals who are most likely to benefit from therapy while at the same time minimizing any unnecessary labeling of individuals who do not have the disease. Any change in the diagnostic criteria for diabetes must

take these complex medical, psychosocial, and economic issues into consideration. To date, most of the literature on the impact of the new diagnostic criteria has focused on the medical implications of the change.⁶⁰

New Categories of Hyperglycemia

One impact of the new criteria has been the creation of two new categories of hyperglycemia, namely, normal fasting glucose and impaired fasting glucose. The term *normal fasting glucose* is used to describe individuals with plasma glucose levels less than 110 mg/dL. The choice of 110 mg/dL as the normal cutpoint would appear to be arbitrary. Many laboratories around the country report the upper limit of normal for plasma glucose as 100 mg/dL. Furthermore, plasma glucose represents a continuous variable and there appears to be a continuum of risk for certain events, including future development of diabetes,⁶¹ as well as atherosclerotic coronary or cerebrovascular events.⁶² Therefore, while a threshold exists for the risk of microvascular complications (see Fig. 53-1) this may not be the case for the risk of macrovascular complications. Indeed some investigators have proposed the term *dysglycemia* to describe the fact that the higher an individual's plasma glucose level (even if within the "normal" range), the greater their risk of subsequent adverse vascular events.⁶³

Impaired fasting glucose represents an intermediate state between normal fasting glucose and overt diabetes. It is the term used to describe individuals with a fasting plasma glucose value between 110

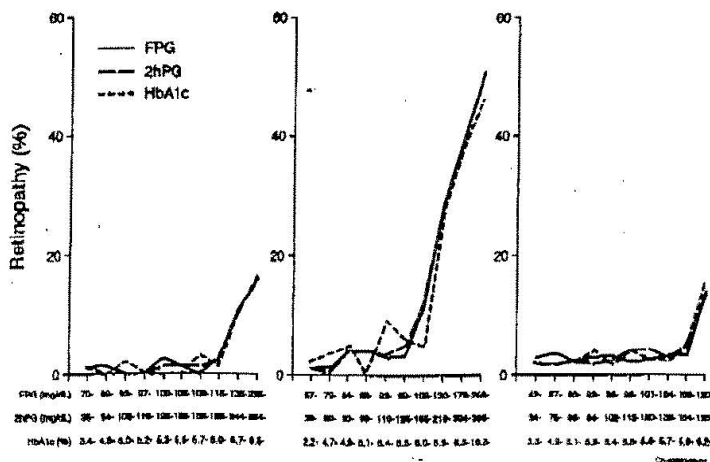


FIGURE 53-1. Prevalence of retinopathy by deciles of the distribution of fasting plasma glucose (FPG), 2-hour postglucose challenge plasma glucose (2hPG), and hemoglobin A1c (HbA1c) level in a population of Pima Indians (left panel), Egyptians (center panel), and a representative sample of the U.S. population aged 40 to 74 years (right panel). (From Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997.)

and 125 mg/dL (see Table 53-2). Individuals with impaired fasting glucose are at increased risk of developing diabetes in the future. This state of abnormal glucose homeostasis is analogous but not identical to impaired glucose tolerance. The latter can only be diagnosed by means of an oral glucose tolerance test. A recent report from Mauritius suggests that impaired glucose tolerance may be a better predictor of future diabetes than impaired fasting glucose.⁷⁰ Both states represent components of the so-called plurimetabolic syndrome, or syndrome X.²⁸ This represents a clustering of metabolic abnormalities, including hypertension, dyslipidemia, central obesity, and abnormalities of the fibrinolytic system. Data from the Framingham Offspring Study indicate that these metabolic risk factors worsen across the spectrum of glucose tolerance categories.⁷¹ Together, they greatly increase an individual's risk of atherosclerotic events. It has been suggested that insulin resistance is the factor that provides a link between these metabolic abnormalities. Evidence to support interventions aimed at treating individuals with impaired glucose tolerance or impaired fasting glucose is beginning to accumulate.⁷² The main endpoint that has been assessed to date is the development of overt diabetes. Studies assessing the impact of treatment on the rate of atherosclerotic events are anxiously awaited.⁷³

Changing the Prevalence and Incidence of Diabetes

Since publication of the initial report recommending new diagnostic criteria for diabetes, many investigators have assessed the impact of the change on the prevalence of the disease in their individual populations.⁷⁴⁻⁷⁷ The majority of these studies were based on existing data sets in which data on fasting and postchallenge glucose levels were available. The largest of these comparative reports looked at the prevalence of diabetes using the new vs. the old criteria among 16 cohorts comprising 26,190 individuals in eight European countries.⁷⁴ As illustrated in Figure 53-2, the new criteria frequently led to a change in the prevalence of the disease, although this was not always in the same direction. The overall change was an increase in prevalence from 7.2% to 7.7%. The risk of disagreement decreased with increasing body mass index and also with increasing age. In contrast, a study which included 4515 elderly people from four centers in North America reported major discrepancies in the prevalence of diabetes using the ADA as opposed to the WHO criteria.⁷⁶ The overall prevalence of newly identified diabetes in this study decreased from 14.8% using the WHO criteria to 7.7% using the ADA criteria. An important report from the National Institutes of Health and the National Center for Health Statistics looked at the impact of the new vs. the old criteria on diabetes diagnostic categories in a probability sample of the U.S. population aged 40 to 74 years.⁷⁷ The prevalence of undiagnosed

diabetes decreased from 6.4% to 4.4% with use of the new ADA criteria.

More recently, a comparison was made between the new ADA criteria and concomitant glycated hemoglobin levels from two large data sets.⁷⁸ The authors reported normal glycated hemoglobin levels in up to 60% of individuals who met the definition of diabetes by fasting plasma glucose criteria. They argue that diabetes should not be diagnosed until evidence of excessive glycosylation is present. Several problems arise with this approach, not least of which is the lack of standardization of assays for glycated hemoglobin. The true test of the appropriateness of the new diagnostic criteria based on fasting plasma glucose levels must await definitive prospective studies looking at the ability of the recommended cut points to predict future diabetic complications.

REFERENCES

1. Gerich J: The genetic basis of type 2 diabetes mellitus: Impaired insulin secretion versus impaired insulin sensitivity. *Endocr Rev* 19:491-503, 1998.
2. Ferrannini E: Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: Problems and prospects. *Endocr Rev* 19:477-490, 1998.
3. King G, Browalee M: The cellular and molecular mechanism of diabetic complications. *Endocrinol Metab Clin North Am* 25:255-270, 1996.
4. Stern M: Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents. *Ann Intern Med* 124:110-116, 1996.
5. McGarry J: What if Minkowski had been agnostic? An alternative angle on diabetes. *Science* 258:766-770, 1992.
6. Chouhan C: It's my life after all. *IDF Bull* 42:32-34, 1997.
7. MacGregor A: Classification criteria for rheumatoid arthritis. *Baillieres Clin Rheumatol* 9:287-304, 1995.
8. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039-1057, 1979.
9. Diabetes Mellitus: Report of a WHO study group. Geneva, World Health Organization, 1985.
10. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997.
11. Alberti KGM, Zimmet PZ: Definition, diagnosis, and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 15:539-553, 1998.
12. LaPorte R, Matsushima M, Chang Y: Prevalence and incidence of insulin-dependent diabetes. In National Diabetes Data Group (ed): *Diabetes in America*. Bethesda, MD, National Institutes of Health, 1995, pp 37-46.
13. Karvonen M, Tuomilehto J, Libman I, LaPorte R: A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization DIAMOND Project Group. *Diabetologia* 36:883-892, 1994.
14. Buzzetti R, Quattrocchi C, Nistico L: Dissecting the genetics of type 1 diabetes: Relevance for familial clustering and differences in incidence. *Diabetes Metab Rev* 14:111-128, 1998.
15. Dahlquist G: The aetiology of type 1 diabetes: An epidemiological perspective. *Acta Paediatr* 425:5-10, 1998.
16. Scott F, Norris J, Hubert K: Milk and type 1 diabetes: Examining the evidence and broadening the focus. *Diabetes Care* 19:379-383, 1996.
17. Zimmet P, Tuomi T, Mackay R, et al: Latest autoimmune diabetes mellitus in adults (LADA): The role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 11:299-303, 1994.
18. Verge C, Gianani R, Kawasaki E, et al: Predicting type 1 diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bde/IA-2 autoantibodies. *Diabetes* 45:926-933, 1996.
19. Molbak A, Christau B, Marner B, et al: Incidence of insulin-dependent diabetes mellitus in age groups over 30 years in Denmark. *Diabet Med* 11:650-655, 1994.
20. Humphrey A, McCarty D, Mackay I, et al: Autoantibodies to glutamic acid decarboxylase and phenotypic features associated with early insulin treatment in individuals with adult-onset diabetes mellitus. *Diabet Med* 15:113-119, 1998.
21. Willis J, Scott R, Brown L, et al: Islet cell antibodies and antibodies against glutamic acid decarboxylase in newly diagnosed adult-onset diabetes mellitus. *Diabetes Res Clin Pract* 33:89-97, 1996.
22. McLarty D, Athaide I, Bottazzo G, et al: Islet cell antibodies are not specifically associated with insulin-dependent diabetes in rural Tanzanian Africans. *Diabetes Res Clin Pract* 9:219-224, 1990.
23. Libman I, LaPorte R, Becker D, et al: Was there an epidemic of diabetes in nonwhite adolescents in Allegheny County, Pennsylvania. *Diabetes Care* 21:1278-1281, 1998.
24. Kenny S, Aubert R, Geiss L: Prevalence and incidence of non-insulin-dependent diabetes. In National Diabetes Data Group (ed): *Diabetes in America*. Bethesda, MD, National Institutes of Health, 1995, pp 47-67.
25. Rudenski A, Hadden D, Adkinson A, et al: Natural history of pancreatic islet β -cell function in type 2 diabetes mellitus studied over six years by homeostasis model assessment. *Diabet Med* 5:36-41, 1988.
26. Leahy J: Natural history of beta-cell dysfunction in NIDDM. *Diabetes Care* 13:992-1010, 1990.
27. Cowie C, Harris M: Physical and metabolic characteristics of persons with diabetes. In National Diabetes Data Group (ed): *Diabetes in America*. Bethesda, MD, National Institutes of Health, 1995, pp 117-164.

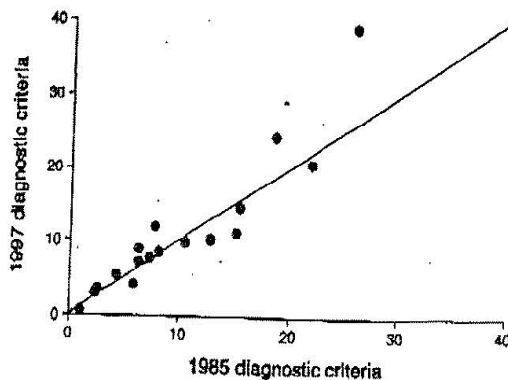


FIGURE 53-2. Prevalence of diabetes in 16 European populations using the 1985 diagnostic criteria of the World Health Organization and the new criteria proposed by the American Diabetes Association in 1997. (From Decode Study Group on Behalf of the European Diabetes Epidemiology Study Group: Will new diagnostic criteria for diabetes mellitus change phenotyped patients with diabetes? Reanalysis of European epidemiological data. *BMJ* 317:1271-1275, 1998.)

Table 29-1. Epidemiologic Determinants and Risk Factors of Type 2 Diabetes

Genetic factors
Genetic markers, family history, "thrifty gene(s)"
Demographic characteristics
Sex, age, ethnicity
Behavioral and lifestyle-related risk factors
Obesity (including distribution of obesity and duration)
Physical inactivity
Diet
Stress
Westernization, urbanization, modernization
Metabolic determinants and intermediate risk categories of type 2 diabetes
Impaired glucose tolerance
Insulin resistance
Pregnancy-related determinants (parity, gestational diabetes, diabetes in offspring of women with diabetes during pregnancy, intrauterine malnutrition or overnutrition)

From Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; 414:782-787.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The diagnosis of diabetes rests on the measurement of plasma glucose levels. The diagnostic criteria for diabetes were changed in 1997¹⁰ with the most significant changes being the level of fasting plasma glucose (FPG) that is recognized as diagnostic for diabetes, which was decreased from 140 to 126 mg/dL, and the introduction of a category of impaired fasting glucose (IFG). Current criteria for the diagnosis of diabetes, impaired fasting glucose and impaired glucose tolerance (IGT), are shown in Table 29-2.

Because plasma glucose concentrations range as a continuum, the criteria are based on estimates of the threshold for the complications of diabetes. The primary end point used to evaluate the relationship between glucose levels and complications is retinopathy. The prevalence of retinopathy in comparison with FPG and 2-hour plasma glucose has been evaluated

Table 29-2. Criteria for the Diagnosis of Diabetes

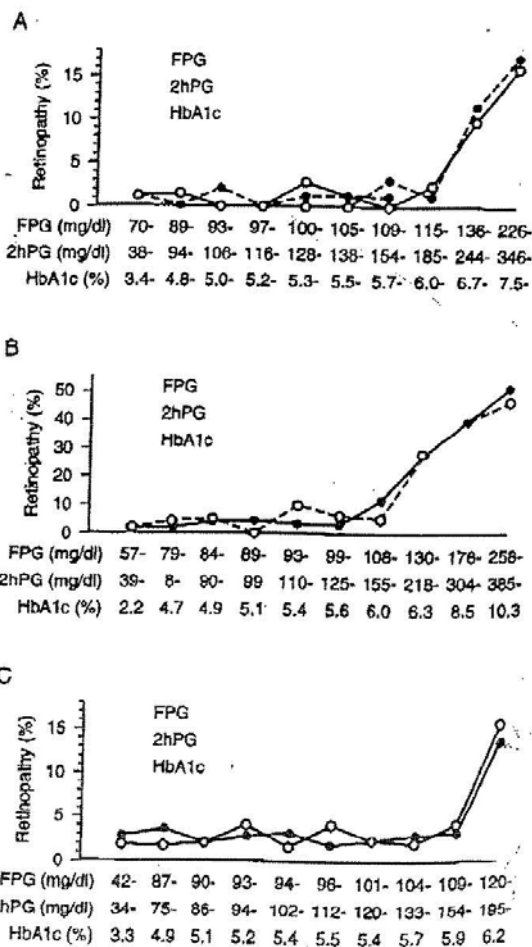
Normoglycemia	Impaired Fasting Glucose or Impaired Glucose Tolerance	Diabetes*
FPG <110 mg/dL	FPG ≥110 and <126 mg/dL (IFG)	FPG ≥126 mg/dL
2-hr PG <140 mg/dL	2-hr PG ≥140 and <200 mg/dL (IGT)	2-hr PG ≥200 mg/dL
		Symptoms of diabetes and casual plasma glucose concentration ≥200 mg/dL

*A diagnosis of diabetes must be confirmed, on a subsequent day, by measurement of FPG, 2-hour PG, or random plasma glucose (if symptoms are present). The FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no caloric intake for at least 8 hours.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

in two relatively large studies.^{11, 12} Both diagnostic criteria were able to predict the presence of retinopathy and, by inference, glucose levels that are diagnostic of diabetes (Fig. 29-1). There is also an association between FPG and 2-hour plasma glucose and risk of macrovascular and cardiovascular disease.¹³⁻¹⁵ For instance, the Paris Prospective Study showed that the incidence of fatal coronary heart disease was related to both FPG and 2-hour plasma glucose that were determined at a baseline examination.¹⁶ Rates of disease were markedly increased at FPG greater than 125 mg/dL (6.9 mmol/L) or 2-hour plasma glucose greater than 140 mg/dL (7.8 mmol/L).

Reproducibility of the plasma glucose concentration is an important issue in the interpretation of the results of diagnostic tests for diabetes. There is significant variation in the results of repeated tests in adults after a 2- to 6-week interval. The intrasubject coefficient of variation in one study was 6.4% for the FPG and 16.7% for the 2-hour plasma glucose value. Thus, it is essential that abnormal results be confirmed by a repeated test. Although the oral glucose tolerance test (OGTT) is an invaluable tool in research, it is not recommended for routine use in the diagnosis of diabetes. It is

**Figure 29-1.** American Diabetes Association consensus.