FHN MANUAL OF OPERATIONS
Daily and Nocturnal Trials
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1. PROTOCOL CHANGES

1.1 General principles

During the conduct of the Study, protocol changes are not desirable and should not be made unless patient safety is compromised or unless new information arises, strongly suggesting changes that would strengthen the scientific validity of the study. In the event that alterations are necessary, the following procedures will be followed.

1.2 Procedures

Recommendations for protocol changes may originate from the DSMB, the NIDDK, the Data Coordinating Center, or one of the working committees. All proposed changes will be submitted to the Executive Committee for consideration. The Executive Committee will make a recommendation to the Steering Committee as to whether the proposed modification merits consideration and the method of incorporating the proposed change into the protocol. Approval by the Steering Committee must have support from two-thirds of the voting members. The recommendations of the Steering Committee will then be presented to the DSMB, which will advise the NIDDK as to whether the protocol change is advisable. The NIDDK may seek further advice from other experts outside the Study before making the final decision whether to approve the protocol change.

2. Daily Study Overview

2.1 Introduction

The daily dialysis study is randomized in-center study in which patients are dialyzed according to Kt/V goals 6 days/week compared to their receiving 3x week adequate therapy. Actual daily dialysis times can vary from 1.5 to 2.75 hours. In the daily HD group dialysis prescriptions will target an eKt/V_n of 0.9 at each of the 6 weekly dialysis sessions. In the conventional HD group subjects will remain on their usual dialysis prescriptions subject to a minimum prescribed eKt/V of 1.1. Based on simulation studies the projected median weekly standard Kt/V is 3.82 in the daily HD arm and 2.46 in the conventional HD arm. The projected median weekly treatment time is 14.2 hours in the daily-HD arm and 10.5 hours in the conventional HD arm. Because the intervention, by necessity, is unblinded, significant efforts will be made to reduce bias. These include the use of objective outcomes such as left ventricular mass index as measured by MRI , blinding the assessment of primary subjective outcomes, and when possible, standardizing the use of co-interventions in both arms of the study. Subjects will be treated and followed for 12 months.

Up to 250 patients will be studied in two consortia, one headed by Renal Research Institute in New York and the other by the UCSF in California. A Canadian subset of the RRI will be studied in London, Ontario.

After randomization patients will be followed for 1 year. The purposes of the trial include:

i. The feasibility of recruiting patients for a randomized trial with many requirements for special examination and data collection. Examination of adherence of patients to the need for doubling of visits to the dialysis facility and participation in all requirements of the study.
ii. Safety of daily dialysis.
iii. The effect of daily dialysis vs routine 3x week treatments on a composite of change within 12 months in LV mass as measured by MRI, with mortality.
iv. A composite of change in 12 months on the SF-36 physical health composite (PHC) with mortality.
v. Hypertension and anemia are main outcome domains without single first priority outcomes. Changes in LV mass and PHC will be analyzed as main secondary outcomes for evaluation of cardiovascular structure and function and health related quality of life/ physical function domains respectively: Dialytic characteristics of the two treatments including kinetic measures of dialysis urea clearance, treatment times, and volume removal.
vi. Nondialytic component of the treatments including SF-36 Survey, v2, Health Utilities Index-3, Feeling Thermometer, MOS Sleep Scale, Beck Depression Inventory, v1, Trail Making B, Modified Mini Mental Status, and Physical Function.

vii. Cost of daily dialysis will be estimated in comparison to routine therapy and estimates of cost effectiveness and cost benefit compared to this dialysis population. Barriers to daily dialysis will be evaluated.

2.2 Schedule of Procedures

1. Baseline

The purpose of the baseline evaluation is to collect detailed data on eligibility and exclusion criteria and to document the following baseline characteristics and clinical information.

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

The following data must be collected: SF-36 Survey, v2; Health Utilities Index –3; Feeling Thermometer; MOS Sleep Scale; Beck Depression Inventory, v1; Trail Making B; Modified Mini Mental Status; Physical Function

- why that data must be collected

- what forms must be completed/by whom

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Interdialytic urine for urea, creatinine, phosphate; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone; Intravenous iron; Erythropoietin/Darbopoetin; IV vitamin D metabolites; Phosphorus binders; All other medications; Serum/plasma samples for biorepository

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Cardiac cine-MRI; 24-hour Holter monitoring; Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate; Bioimpedance

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions; Number of shortened treatments; Minutes to recovery question; Modality preference question

Also collected during the baseline evaluation is data regarding the patient's demographic information and insurance, as well as treatment, laboratory, and medication records. Questionnaires and a physical function test will also be administered.

2. 2 Weeks

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

No data necessary.

3. Month 1 (same format as baseline, continue through month 12)

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate; Bioimpedance

iv) Mineral Metabolism and Anemia Measures
see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions; Number of shortened treatments; Time spent with health-care professionals; Frequency of reductions to ideal weight prescriptions; Frequency/method of vascular access monitoring; Compliance to medications question

4. Month 2

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin,

calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

5. Month 3

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

6. Month 4

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

The following data must be collected: SF-36 Survey, v2; Health Utilities Index –3; Feeling Thermometer; MOS Sleep Scale; Beck Depression Inventory, v1; Trail Making B; Modified Mini Mental Status; Physical Function

- why that data must be collected

- what forms must be completed/by whom

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Interdialytic urine for urea, creatinine, phosphate; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone; Intravenous iron; Erythropoietin/Darbopoetin; IV vitamin D metabolites; Phosphorus binders; All other medications; Serum/plasma samples for biorepository

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate; Bioimpedance

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions; Number of shortened treatments; Minutes to recovery question; Modality preference question; Time spent with health-care professionals; Frequency of reductions to ideal weight prescriptions; Frequency/method of vascular access monitoring; Compliance to medications question

7. Month 5

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

8. Month 6

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

9. Month 7

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

10. Month 8

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone; Intravenous iron; Erythropoietin/Darbopoetin; IV vitamin D metabolites; Phosphorus binders; All other medications

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions; Number of shortened treatments

11. Month 9

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

12. Month 10

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

13. Month 11

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

No data necessary.

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions

14. Month 12

i) Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; Characterizing Non-dialytic Aspects of the Intervention

The following data must be collected: SF-36 Survey, v2; Health Utilities Index –3; Feeling Thermometer; MOS Sleep Scale; Beck Depression Inventory, v1; Trail Making B; Modified Mini Mental Status; Physical Function

- why that data must be collected

- what forms must be completed/by whom

ii) Laboratory Measurements and Medications

The following data must be collected: Predialysis serum albumin; Pre and post-dialysis serum phosphate, creatinine, urea; Interdialytic urine for urea, creatinine, phosphate; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; Pre-dialysis parathyroid hormone; Intravenous iron; Erythropoietin/Darbopoetin; IV vitamin D metabolites; Phosphorus binders; All other medications; Serum/plasma samples for biorepository

iii) Cardiovascular, Blood Pressure and Nutritional/Inflammatory Measures

The following data must be collected: Cardiac cine-MRI; 24-hour Holter monitoring; Predialysis and postdialysis systolic and diastolic blood pressures; Predialysis and postdialysis weight; Interdialytic hypotensive episodes; Protein catabolic rate; Bioimpedance

iv) Mineral Metabolism and Anemia Measures
(see Labs and Medications Table)

v) Events (hospitalizations, access compilations, survival, discontinuation of intervention) will be collected throughout follow-up

vi) Treatment Burden and Characterizing the Non-dialytic Aspects of the Intervention

The following data must be collected: Number of missed sessions; Number of shortened treatments; Minutes to recovery question; Modality preference question; Time spent with health-care professionals; Modality preference question; Time spent with health-care professionals; Frequency of reductions to ideal weight prescriptions; Frequency/method of vascular access monitoring; Compliance to medications question

2.2 Schedule of Measurements

Summary of Data Collection Schedule

2A. Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures; and Characterizing Non-dialytic Aspects of the Intervention

Measurement	Central Telephone Interview	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
SF-36 Survey, v2	Yes	✓				✓								✓
Health Utilities Index –3	Yes	✓				✓								✓
Feeling Thermometer	No	✓				✓								✓
MOS Sleep Scale	Yes	✓				✓								✓
Beck Depression Inventory, v1	Yes	✓				✓								✓
Trail Making B	No	✓				✓								✓
Modified Mini Mental Status	No	✓				✓								✓
Physical Function	No	✓				✓								✓

*All physical and cognitive testing to be done pre-dialysis, mid-week within 2 weeks of scheduled time.

2B. Laboratory Measurements and Medications

Measurement	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Predialysis serum albumin	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre and post-dialysis serum phosphate, creatinine, urea	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interdialytic urine for urea, creatinine, phosphate	✓				✓								✓
Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre-dialysis transferrin and ferritin[1]	✓			✓				✓				✓	
Pre-dialysis parathyroid hormone[1]	✓			✓				✓				✓	
Intravenous iron (cumulative monthly dose)	✓				✓				✓				✓
Erythropoietin/Darbopoetin (route, frequency, weekly dose, cumulative monthly dose)	✓				✓				✓				✓
IV vitamin D metabolites (frequency, weekly dose)	✓				✓				✓				✓
Phosphorus binders (daily dose)	✓				✓				✓				✓
All other medications (including antihypertensives)	✓				✓				✓				✓
Serum/plasma samples for biorepository	✓				✓								✓

[1]These local labs to be entered into database <u>at least</u> once every 4 months (center may optionally enter these labs at additional time points)

2C. Cardiovascular, Blood Pressure, and Nutritional/Inflammatory Measures (for labs and medications, see above)

Measurement	Blinded Reading	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Cardiovascular Measures														
Cardiac cine-MRI	Yes	✓												✓
24-hour Holter monitoring (heart-rate variability)	Yes	✓												✓
Predialysis and postdialysis systolic and diastolic blood pressures*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Predialysis and postdialysis weight*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interdialytic hypotensive episodes*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nutritional Measures														
Protein catabolic rate	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bioimpedance	No	✓	✓			✓								✓

*These measures taken at each kinetic modeling session. Additional measurements from dialysis sessions over the prior 1-week interval also recorded once during baseline, and months 1, 4, 8, and 12 of follow-up.

D. Mineral Metabolism and Anemia Measures – see Labs and Medications Table 2B

E. Events (hospitalizations, access complications, survival, discontinuation of intervention) will be collected throughout follow-up

2F. Treatment Burden, and Characterizing the Non-dialytic Aspects of the Intervention

Measurement	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Adherence to Therapy													
Number of missed sessions (over 1 month)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Number of shortened treatments (over last week)	✓	✓			✓				✓				✓
Burden of Treatment													
Minutes to recovery question	✓				✓								✓
Modality preference question	✓				✓								✓
Characterizing the Non-dialytic aspects of the Intervention													
Time spent with health-care professionals		✓			✓								✓
Frequency of reductions to ideal weight prescriptions		✓			✓								✓
Frequency/method of vascular access monitoring		✓			✓								✓
Compliance to medications question		✓			✓								✓

2.3 Template Daily Study Consent Form (RRI)

This template consent form can be downloaded from the FHN web page. It needs to be modified to meet individual IRB requirements.

Subject Information and Consent Form

TITLE: Frequent Hemodialysis Network: Short Daily Hemodialysis Study

A multi-center randomized controlled study to demonstrate the efficacy, safety, and feasibility of "Short-daily hemodialysis" in patients with End Stage Renal Disease.

PROTOCOL NO.:

SPONSOR: National Institute of Health and Center for Medicare and Medicaid Services

Principal Investigator: **Nathan W. Levin, MD** Renal Research Institute

This consent form, a copy of which will be given to you, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. You should feel free to ask any questions you may have accompanying information.

You should only sign this consent form after all your questions have been answered to your satisfaction.

Consent for Participation in Research

1. Rationale of the Study:

Your doctors at this dialysis facility are doing a study to find out whether short-daily hemodialysis treatments (6 times a week, 1hr30min-2hr45mins, depending on body size) improves the health of patients on hemodialysis compared to conventional hemodialysis treatments (3 times a week, 3-4hrs). Your dialysis unit is one of the participating units in a study sponsored by the National Institutes of Health (NIH) and the Centers for Medicare and Medicaid Services (CMS).

The study is under the direction of Nathan W. Levin, MD, Medical and Research Director of Renal Research Institute, working together with your doctor in this dialysis unit.

You have been asked to take part in this study because you are already on hemodialysis three times per week and your doctor thinks that you are a potential candidate for the trial. Many small studies have suggested improvement in patients' health outcomes with short-daily hemodialysis treatments. However, these improvements have not been tested in a randomized clinical trial to show that these clinical benefits are due to increased frequency in hemodialysis. This is the reason for this study.

In order for you to decide to take part in this study, you should understand the possible risks and benefits well enough to make your decision.

2. Study Design:

This is a randomized, controlled study, meaning you will be assigned by chance (like a flip of a coin) to either continue with your usual schedule of ***conventional*** hemodialysis (3 days per week for about 3-4 hours) or to have short-***daily*** hemodialysis (6 days per week for 1hr30min – 2hr45min). If you decide to participate and meet our eligibility requirements, you will be enrolled in the study for only12 months.

Total number of subject to be enrolled 250. After randomization 50% of subjects will undergo in center short daily hemodialysis and other 50% will continue conventional hemodialysis. Therefore you have a 50% chance of being in either group.

The main goals of the research are to measure over a period of a year:

1) If there is a change in your Quality of Life and,
2) If there is a change in the size of your heart when measured by Magnetic Resonance Imaging (MRI).

An estimated total of 250 patients from the dialysis units in the United States and Canada will take part in this study. Locally subjects will be enrolled at Beth Israel dialysis unit at

Yorkville Dialysis Center, Upper Manhattan Dialysis Center, Irving Place Dialysis Center , Queens Artificial Dialysis Kidney Center and other dialysis units as necessary.

Subjects will be enrolled during the second half of 2005 and enrollment will continue for 3 to 4 years. You will asked to follow your assigned therapy for only 12 months once you decide to participate.

3. Study Procedure:

Screening evaluation:

The purpose of screening evaluation are to identify potential study subjects for trial enrollment, to provide potential study subjects with information regarding the study, to obtain written informed consent for participation and randomization

If you agree to participate and have signed the Informed Consent Form the researcher will ask you to complete baseline evaluation.

Baseline evaluation:

The purpose of the baseline evaluation are to collect detailed data on eligibility and exclusion criteria and to document following baseline characteristic and clinical information:

-demographic information (which includes age, gender, race, etc.),

-insurance data,

-treatment records, laboratory records, medication record

-questionnaires and physical function test will be administered during baseline period to obtain information on health related Quality of life/physical function, depression, cognitive function.

Baseline period will have two visits. During these visits your blood will be tested for the following

- Serum albumin, pre- and post dialysis serum urea nitrogen, creatinine, PTH, iron parameters, phosphorus, calcium, sodium, potassium, hemoglobin.
- 24 hour urine collection (if you make urine)

record your monthly labs data that will determine whether you fulfill all requirements to continue with the study.

- All these baseline tests will be performed within 2 weeks after you agree to participate. We will also address specific concerns about transportation issues related to the possibility of coming 6 times a week to the dialysis unit. Once the baseline assessment is completed, you will be re-evaluated for eligibility to be randomized so that you can be assigned to either conventional or short daily hemodialysis as described previously. If you do not want to be randomized, or are found ineligible for randomization at any time during the baseline period, you will be withdrawn from the study and a baseline dropout form will record the reason(s)

Treatment period:

During the 12 months that you are in the study, you will be followed closely and undergo a number of tests. All the following tests that are performed at baseline will be repeated at 4 and 12 months. Some of them will be repeated more frequently as noted below. Total amount of blood collected for the purpose of the study will be no more than 36 ml (about 3 tablespoons).

These tests include:

a) The dose of dialysis will be measured from blood samples taken before (pre-dialysis) and after (post-dialysis) on two separate treatments during the baseline period, at 2 weeks point and every month thereafter, just as they being done now.

b) If you still produce urine, a 24-48 hour urine collection (between hemodialysis treatments) will be obtained for evaluation of your kidney function. This test will be done at baseline and repeated at the 4^{th} and 12^{th} month.

c) You will undergo a scan of your heart using the MRI machine at baseline and after 12 months. This scan will be done at a nearby hospital and transportation will be arranged for you at no extra cost. The MRI uses powerful magnets and radio waves without x-ray radiation to produce high quality images of the inside of the human body. This test will tell us about the size and function of your heart. Because the MRI machine acts like a large magnet, it could move metallic objects in the MRI room during your examination, which could in the process possibly harm you. Therefore, precautions are taken to prevent such an event; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you may not be allowed to have an MRI. The MRI machine surrounds you during the test and produces a banging noise. It may bother some people with feelings of claustrophobia. It may be recommended to wear ear plugs during the study. There has been no documented significant side effects from magnetic fields and radio waves from MRI to date. Each specific radiology department will provide you with more information and require a separate consent for the MRI test.

d) You will be asked to answer a series of questionnaires over the telephone about your health and your quality of life at baseline and thereafter, at the 4^{th} and 12^{th} month. If you do not have a telephone, you can complete the questionnaires in the dialysis unit with the help of study personnel. These questionnaires take about 30 minutes to complete.

e) At the start of the study, after 4 months and at 12 months, you will be asked to complete tests of memory, attention and concentration. These tests will take approximately 20 minutes to complete. These tests will be done at your dialysis unit before dialysis on a Wednesday or Thursday, depending on your dialysis schedule.

f) If you are physically able, you will be asked to walk down a corridor and to rise 5 times from a chair. You will be asked to have a test that measures the fluid in your body with an EKG-like device known as BIA (Bioelectrical Impedance Analysis). BIA is a test used to measure your body's fat, water, and muscle content. This test

involves lying on a bed for about two minutes while two electrodes (sticky pads with a wire attached to them) are attached to your foot and hand. A tiny current is passed through your body (less electricity than that of a "AA" battery so that you will not feel it) and a reading is taken which is stored in a computer, along with your height and weight, to calculate your body fat, water, and muscle mass contents. No pain is caused by this procedure. The sticky pads may leave a small residue, which is easily washed off with water. We will measure this at the baseline visit and after the 4^{th} and 12^{th} months. There are no known risks associated with Bioelectrical Impedance Analysis.

g) We will measure your heart rate and rhythm using an EKG-like device known as "Holter monitors" that we will provide. The Holter monitor allows for a continuous 24-hour recording of your heart rate and rhythm while you go about your normal daily routine. The electrodes are taped to your chest with wires attached to the Holter monitor before you leave the dialysis unit after your treatment. A carrying case comes with it so you can wear it comfortably. This device will be worn for 24 hours after which you will return it to us on your next hemodialysis treatment. You will be asked to keep an activity log to record your symptoms, medications, any emotional stress, and activities while wearing the monitors. This test will be done at baseline and after 12 months.

h) We will get lab test results and physical findings from your medical record every month, all information that is already routinely collected and reviewed by your physician.

4. Potential Risks of Short-daily Hemodialysis

The risks for every particular hemodialysis treatment are about the same for both treatment groups. However, due to more treatments in the Short-Daily group you are slightly more exposed to these l risks:

a) Vascular Access Complications: Your access will be used twice as much every week. This may increase the chances of your access getting infected, abnormally narrowed and/or getting clotted.

b) Iron Losses: More dialysis exposure might lead to more iron loss. Iron stores are monitored regularly and supplements will be given as needed.

c) Loss of Nutrients: There might be increased loss of water-soluble vitamins and other nutrients. This might be compensated by increased appetite that has been noted in previous small studies. Regardless, all patients will be prescribed daily multi vitamins.

d) Patient/Caregiver Fatigue: The increased frequency of hemodialysis treatments may put an added burden on you and if applicable your caregiver. This may affect your lifestyle, attitude and/or relationships. Previous small studies have shown that some patients might get fatigued however it has also shown that some patients get energized with the therapy.

5. Potential Benefits of Short Daily Hemodialysis:

Based on the results from previous research, if you are placed in the group that will receive short, daily hemodialysis, you might experience a more stable blood pressure, heart size may decrease or stay stable , you may experience improvement in appetite and an increase in food and fluid intake, and my experience increased energy.

If you are placed in the conventional dialysis group, your health may improve, worsen or stay the same. Your participation in the study may help people on hemodialysis in the future but no direct benefit to you can be granted.

6. Pregnancy:

All women of childbearing potential (who are able to have children) must use an effective birth control method of their choice before start of study and throughout the study. They must also have a negative pregnancy (serum beta HCG) test within 4 weeks of randomization. Women with amenorrhea (cessation of monthly periods) for at least 12 months are not considered of childbearing potential.

If you are unsure whether the method of birth control you use is acceptable while participating in this study, you should ask your study doctor before you begin the study.

Since you are participating in a study that involves drugs or treatment with potential risks to a developing fetus, it is recommended for your protection that you or your partner not become pregnant for the duration of the study. Therefore, practicing effective contraception is important. Recommended methods of birth control are: the consistent use of an approved oral contraceptive (birth control pill), an intrauterine device (IUD), hormone implant (Norplant), contraceptive injection (Depo-Provera), double barrier methods (diaphragm with spermicidal gel or condoms with contraceptive foam), and sexual abstinence (no sexual intercourse) or sterilization. Oral contraceptives, hormone implants and injections are only considered effective if used properly and started at least one month before you begin the study, continuing throughout the study and for one month after the study. If you are unsure whether the method of birth control you use is acceptable to use while participating in this study, you should ask you study doctor before you begin the study. If you or your partner becomes pregnant or thinks either of you may be pregnant at any time during the trial (or in the 2 "month" following it), it is important that you tell your study doctor immediately. The trial drug may be stopped and a referral will be made to an obstetrician/gynecologist for follow-up. If you have any questions about birth control, your study coordinator or study doctor will be able to answer these and give you advice.

7. Research-Related Injury:

We do not anticipate injury that is directly related to the study. However, if you are injured as a result of your study participation, you should seek medical help and inform your study doctor immediately.

If you are physically injured by the study procedures and you have followed the directions of the study personnel, only immediate essential medical treatment will be provided free of charge. The sponsor, Renal Research Institute will cover the reasonable medical expenses necessary to treat the injury. No other funds have been set aside to cover the costs of continuing medical care.

By signing this consent form, however, you do not give up your right to pursue a claim through the legal system.

8. Cost and Payment:

You or your insurance provider will not be charged for any extra hemodialysis treatments or any study-related tests-things, which are directly related to research. You and/or your insurance will be charged for routine care related to hemodialysis treatment.

In return for your time and effort, you will receive $25 each time you complete the Cardiac MRI scan. This will occur at baseline and 12 month visit. You will not receive payment for general study participation or for the completion of other study tests.

9. Alternatives:

You may choose not to participate in this study. If you do not participate in the study, you will continue on your **conventional** (usual) hemodialysis, depending on the advice of your doctors. Refusal to participate will not jeopardize your medical care in any way.

10. Voluntary Participation/Termination:

Your decision to take part in this research study is completely voluntary. You may refuse to take part. Even if you choose to take part in this study, you can change your mind at anytime and withdraw from the study at anytime. Your decision will not affect your medical care or eligibility for future care at Beth Israel Medical Center or Renal Research Institute, nor will you lose any benefits you might otherwise receive.

For your own safety, if you decide not to continue in this study for any reason, you should notify your study doctor and Dr. Nathan Levin at 212 360-4954 to let them know. For your own safety, you should have all Discontinuation Visit procedures (blood tests and survey forms) performed.

Your study doctor may withdraw you from this study without your consent, if he or she feels that it is in your best interest to do so. This may happen if you experience a bad side effect or you do not follow instructions. The study sponsor may also cancel the study. A full explanation for stopping your participation and possible alternatives will be discussed with you.

11. Confidentiality

Information collected from you and about you will be treated as confidential (private) as possible. The National Institute of Diabetes and Digestive and Kidney Diseases, other Regulatory Agencies, and the Institutional Review Board (IRB) may also examine your medical records. The IRB is a group that oversees research in human subjects.

You will be given a unique study identification number. This number will be used to record your study information. You will never be tracked through the study by name, medical record number or other personal information. A list of participant names, participant identification numbers, and personal information (such as home address, telephone number, and emergency contact information) will be maintained in a locked area at the clinical site only. Your personal information will not be used for any published information about this study.

All study data (except personal information such as home address, telephone number, and emergency contact information) will be sent to the Data Coordinating Center. Only authorized research staff will have permission to see this data. The study information from all research centers, after removing all identifying information, will be stored in secure electronic files at the RTI-Database Repository at Research Triangle Park, NC 27709.

By signing this document, you agree (consent) to have the above-mentioned groups look at your records. Although complete confidentiality cannot be guaranteed, these groups know they must keep this information as private as possible. If you agree to participate in this study, we will ask for your separate written permission on a form called ("Research Authorization") to use and disclose your personal information only for certain purposes related to the study.
We will ask you to tell us your social security number. This number will be recorded but it will not be open to anyone outside of the research study. It will be stored in a scrambled fashion so that the numbers cannot be easily figured out. When used to track your health status, it will be unscrambled to connect to other sources of medical information, such as Medicare. Only authorized study personnel will be permitted to view your social security number and then it will be scrambled again after the necessary medical information is obtained. Please respond to the following statement and **CIRCLE** either "***YES***" or "***NO***" and write your initials and today's date:

			Initials	**Date**
I will provide my Social Security Number.	***YES***	***NO***	_____	_____

You will be asked to give the study coordinator the names of people to contact if you cannot be reached. If you miss a study visit, the study staff may contact you at home by phone to schedule another visit and to see if you still want to be in the research study. If the study staff is unable to contact you at home, the other people you named will be contacted.

12. Questions/Contacts

If you have any questions about this study at any time, or if at any time you feel you have experienced a research-related injury or a reaction to the study medication, contact your study doctor, Dr. Nathan Levin at 212 360-4954 or your study coordinator Olga Sergeyeva at 646-672-4071. You can also contact your the patient representative, Laura Weil at 212-420-3818 if any questions about your rights as a research subject.

13. Statement of Consent

I have been fully informed of the study described in the attached document and of its risks and benefits, and I hereby consent to the procedure set forth in that document. I have received a copy of this signed consent form.

Subject Signature: _____

Date: _____

Print Name: _____

Signature of Person Obtaining Consent: _____

Date: _____

Print Name: _____

Investigator Approval Signature: _____

Date: _____

Print Name: _____

2.4 Template Daily Study Consent Form (UCSF)

This template consent form can be downloaded from the FHN web page. It needs to be modified to meet individual IRB requirements.

UNIVERSITY OF CALIFORNIA SAN FRANCISCO

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Frequent Hemodialysis Network

Sponsors: National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases

Centers for Medicare and Medicaid Services

Researchers: Glenn M. Chertow, MD, MPH, Principal Investigator

Thomas A. Depner, MD, Co-Principal Investigator

George O. Ting, MD, Co-Principal Investigator

Juan Carlos Ayus, MD, Co-Investigator

William G. Goodman, MD, Co-Investigator

George A. Kaysen, MD, PhD, Co-Investigator

Manjula Kurella, MD, MPH, Co-Investigator

Charles E. McCulloch, PhD, Co-Investigator

Ravindra L. Mehta, MD, Co-Investigator

John Moran, MD, Co-Investigator

Allen R. Nissenson, MD, Co-Investigator

Patricia L. Painter, PhD, Co-Investigator

Rudolph A. Rodriguez, MD, Co-Investigator

Isidro B. Salusky, MD, Co-Investigator

A. Purpose and Background

Dr. Chertow and his colleagues are conducting a study to determine whether more frequent hemodialysis therapy improves the health condition of patients with kidney failure who need dialysis.

You have been asked to participate in this study because you have kidney failure and your doctors have decided that you need hemodialysis. The kidneys act as filters to help the body remove waste products and to prevent build-up of extra fluid. When the kidneys are not working, waste products and extra fluid can build up and be harmful to the body. Kidney failure is a serious problem. Every year, about one in five persons dies despite receiving hemodialysis. For persons who live, many need to be hospitalized for infections, heart problems and other complications of kidney failure.

Hemodialysis helps to remove waste products and extra fluid. Hemodialysis has been used to prevent complications of kidney failure for more than 50 years. Usually, hemodialysis is

used 3 times per week for about 3-4 hours per day. Some persons who have tried hemodialysis more frequently (for example, 6 times per week) have felt better. Doctors and nurses do not know whether the frequency of dialysis (number of days per week) actually helps persons with kidney failure feel better or have fewer complications of kidney failure.

None of the hemodialysis treatments being provided in this study are experimental. Rather, we are trying to understand the best ways to give hemodialysis to persons with kidney failure. We are testing two schedules of hemodialysis (3 times per week for 3-4 hours versus 6 times per week for a shorter time, approximately 2-2.5 hours). The study will last for 12 months. Approximately 300 persons at 50 dialysis units in the United States and Canada will participate in this study. The National Institutes of Health and the Centers for Medicare and Medicaid Services are sponsoring this study.

Procedures

The doctors taking care of you will decide whether you qualify for the study based on a number of factors.

If you agree to be in this study, and sign this form, the following things will happen.

For one week, you will travel to the hemodialysis center on your non-dialysis days. During this week, you and the research staff will make sure that transportation to and from the dialysis unit can be arranged.

A member of the research team will collect information from your medical record. You will have a physical examination. You will have two blood tests (approximately 15 mL or 1 tablespoon) to evaluate how well dialysis removes waste products from your blood. If you make urine, you will be asked to collect your urine for 24 hours and bring it to the dialysis center.

You will be asked to have a scan of your heart called a Cardiac MRI. The Cardiac MRI will be done at a nearby University hospital. For the Cardiac MRI test, you will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud noise. You may feel warm during this procedure.

If you are eligible to participate, you will be assigned by chance (like the flip of a coin) to continue with your usual schedule of hemodialysis (3 times per week for approximately 3-4 hours) versus more frequent hemodialysis (6 times per week for a shorter time, approximately 2-2.5 hours). The study will last for 12 months.

At the start of the study, after 4 months, and at the end of the study, you will be asked to complete a series of questionnaires about you and your health. These questionnaires can be done by telephone at a time convenient to you. If you do not have a telephone, you can complete the questionnaires in the dialysis unit with the help of study personnel. These questionnaires will take about 30 minutes to complete. You should try to answer all of the questions, but you may skip individual questions if you find them upsetting in any way.

At the start of the study, after 4 months, and at the end of the study, you will be asked to complete several tests of physical performance. If you are physically able, you will be asked to walk down a corridor, to climb 6 stairs and to rise 5 times from a chair. These tests will take approximately 20 minutes to complete. These tests will be done at the dialysis center before dialysis on a Wednesday or Thursday, depending on your dialysis schedule.

At the start of the study, after 1 month, after 4 months, and at the end of the study, you will be asked to have a test that measures the fluid in your body, an EKG-like device known as BIA (bioelectrical impedance analysis). BIA is a test used in health clubs to measure body composition and causes no pain. You will have EKG leads placed on your wrist and ankle and will be asked to lie still for less than one minute. These tests will be done at the dialysis center before dialysis on a Wednesday or Thursday, depending on your dialysis schedule. If you have an implantable defibrillator, you should not do BIA.

At the start of the study, after 4 months, and at the end of the study, you will be asked to complete tests of memory, attention, and concentration. These tests will take approximately 20 minutes to complete. These tests will be done at the dialysis center before dialysis on a Wednesday or Thursday, depending on your dialysis schedule.

At the start of the study and at the end of the study, you will be asked to wear an EKG-like device known as a Holter monitor to measure your heartbeat. The Holter monitor is a small box connected to EKG leads that are placed on your chest. A carrying case comes with the Holter monitor so that you can wear it comfortably for a day. You will be asked to keep a one day diary to record any symptoms, physical activity, and any emotional stress you may have during that day.

During each month of the study, study personnel will review your dialysis treatments, routine laboratory tests, medications, and other side effects or problems you may have.

If you make urine, after 4 months, and at the end of the study, you will be asked to complete a 24 hour urine collection and bring it to the dialysis center.

In order to monitor your hemodialysis treatments for the purpose of this study, some additional blood tests will be needed. These blood tests will be drawn through the dialysis lines, and you will not need to have extra needle sticks. The total amount of blood collected

for the purpose of the study will be no more than 200 mL (approximately 14 tablespoons), of which approximately 150 mL (10 tablespoons) will be stored with your permission.

At the end of the study, you will be asked to have another Cardiac MRI. If you do not complete the 12 months of the study, but you complete at least 4 months of the study, you will be asked to have the Cardiac MRI within 2 weeks after you stop the study.

Participation in this study will not change any of your medical care other than your hemodialysis treatments. The doctors taking care of you will decide whether you need to change the schedule of hemodialysis for health reasons, or whether you need to change any other medicines or other treatments.

You will be asked to complete a Release of Information form. This form will be used to permit us to contact any place where you received care for information about your time there. If you wish, you may refuse to sign the Release of Information form.

If we cannot contact you by telephone or mail, we will determine whether you are alive based on information reported to national data registries.

You may withdraw from the study at any time without affecting your medical care. If at any time your doctor feels that you should no longer participate in this study, he or she may ask to have you withdrawn from the study.

You will be asked to provide your social security and medical insurance numbers so that the researchers can collect information about hospitalization and other health services provided to you. Please indicate whether you are willing to allow the researchers to have your social security and medical insurance numbers by initialing one of the lines at the end of the form.

Future research: In the future, the researchers will want to connect information about you with your hospital and other health records. Your information will be stored at the United States Renal Data System's Coordinating Center. The United States Renal Data System is managed by the National Institutes of Health, the Study sponsor. Your information will be available only to researchers specifically approved to do these studies. Some of your blood samples may also be used in the future for research purposes. The blood samples will be stored at a repository managed by the National Institutes of Health. These samples may be used to learn more about kidney failure and may result in new products, tests or discoveries. In some instances, these may have potential commercial value. You will not receive any payment or financial benefit from any products, tests or discoveries. You will not be told the results of any future research. You may also be asked in the future if you are willing to be in additional research studies. Participation in this extra research is voluntary. Your samples will be kept for up to 50 years. You may contact Dr. Chertow and the other researchers during the study at (415) 476-2173 and ask that your samples be

withdrawn from research use, and any identifiable samples will be destroyed. If you have any questions about the National Institutes of Health sample repository, you may call the NIDDK Repository Project Officer at (301) 496-3583. Please indicate whether you are willing to allow storage of your blood for future research by initialing one of the lines at the end of the form.

C. Risks and Discomforts

You will be assigned to a treatment program by chance. The treatment you receive may prove to be less effective or to have more side effects than the other study treatment or other available treatments.

All medical care and procedures are associated with some degree of risk including risks that are currently unforeseeable. All possible precautions will be taken to minimize any risks related to the study. None of the treatments being used in the study are experimental. The study treatments may or may not improve your overall health and quality of life, but we will not know this until after the study is finished.

Hemodialysis may also be associated with complications. Hemodialysis can lead to low blood pressure, bleeding, tachycardia (rapid heart rate) and other abnormal heart rhythms, electrolyte (chemical) imbalances, clotting or infection of the vascular access, and rarely, death. Risks associated with hemodialysis will be present whether or not you choose to participate in this study. It is unknown whether more frequent hemodialysis will increase or decrease the risk of these complications.

Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could in the process possibly harm you. Precautions have been taken to prevent such an event; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI. Your participation may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked not to swallow for a while, which can be uncomfortable.

There are no known risks to the BIA and Holter monitor. The EKG leads used for the BIA and Holter monitor may leave a sticky residue which can be easily washed off with water.

During the telephone interview, you may be asked some questions of a personal nature. You are free to decline to answer any question at any time.

You may experience some inconvenience associated with participation in the study. If you are treated with more frequent hemodialysis, you will spend more days in the dialysis unit and more hours on hemodialysis, even though the number of hours per day will be lower.

More frequent dialysis may increase the risk of problems with your vascular access, including the risk of infection and clotting. There may be other risks of frequent dialysis that are unknown. Dr. Chertow and the other researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Participation in research will involve a loss of privacy, but information about you will be kept as confidentially as possible. Representatives from the National Institutes of Health, Centers for Medicare and Medicaid Services and other authorized study personnel may review information about you to check on the study. If you sign this consent form, you are allowing the study sponsors to review your medical records. Your name will not be used in any published reports about this study.

If you are injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California depending on a number of factors. The University of California does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at (415) 476-1814.

D. Benefits

The potential benefit to you is that the treatment you receive may prove to be more effective than the other study treatment or than other available treatments, although this cannot be guaranteed. It is also possible that you may not receive any direct benefit from participating in this study. However, your involvement in this study will help the researchers in treating persons with kidney disease in the future.

E. Alternatives

You may choose not to participate in this study. If you do not participate in the study, you will continue on conventional (usual) hemodialysis, depending on the advice of your doctors. Refusal to participate will not jeopardize your medical care in any way.

F. Costs

You will not be charged for any extra hemodialysis treatments or any study-related tests.

G. Payment

In return for your time and effort, you will receive $25 each time you complete the Cardiac MRI scan. You will have to provide your social security number and address in order to be paid. A check will be mailed to you approximately six weeks after each Cardiac MRI is done.

H. Questions

Dr. Chertow or the person who signed below has explained the study to you and your questions were answered. If you have any other questions about the study, you may call Dr. Chertow at (415) 476-2173 or pager (415) 719-9719.

I. Consent

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without jeopardy to your medical care.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

If you wish to participate, you should sign below.

_____	_____
Date	Subject's Signature
_____	_____
Date	Signature, Person Obtaining Consent
_____	_____
Date	Interpreter's Signature

If you are less than 18 years old, and you wish to participate, you should sign below.

_____	_____
Date	Adolescent's Signature

_____ _____

Date Parent's Signature

J. Additional Permission

Please circle either "Yes" or "No" to the questions below:

I give the researchers permission to store my blood for future research

Yes No Initial _____ Date _____

I give the researchers permission to collect my social security number and medical insurance number

Yes No Initial _____ Date _____

Appendix 1

PROTOCOL SIGNATURE PAGE

Protocol Title:	Frequent Hemodialysis Network – Daily Trial
Sponsor:	National Institute of Diabetes and Digestive Diseases Paul Eggers, Ph.D., Project Officer
Date of Original Protocol:	September 14, 2005

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____
Principal Investigator Name (Printed)	Principal Investigator's Institution
_____	_____
Principal Investigator's Signature	Date

Please retain a copy of this page for your study files and return the original signed and dated form to:

Gerald Beck, Ph.D.
Department of Quantitative Health Sciences, Wb4
Cleveland Clinic Foundation
9500 Euclid Avenue Wb4
Cleveland, OH 44195

Appendix 2

This section describes the procedures that are to be performed during the screening, randomization, baseline, and follow-up periods. These assessments are critical to the goals of this study and, therefore, must be carefully standardized across all the participating sites.

1. Study Visit 1: Baseline Visit (B-01)

Detailed description of what is expected from the Baseline Visit (B-01) – Evaluation Visit to Determine Eligibility

OBTAIN CONSENT

a) Explain the study protocol in detail to the participant and caregiver (if applicable). Go over the inclusion and exclusion criteria to verify that the participant meets all criteria.
b) If no known disqualifying criteria are found, invite the participant and caregiver (if applicable) to ask any questions they may have about the study. Once all their questions have been answered, have the participant sign and date the consent form. Make sure to provide them with a copy of the signed and dated informed consent. Also, if applicable we must explain the Bill of Rights. If the consent form is signed, explain in detail the ancillary studies and the storage of repository blood for future research. A separate consent may be signed for HIPPA, storage of blood, and ancillary studies.
c) If applicable, at time of consent, ask the subject to sign a medical release of information at this time.

IF PARTICIPANT CONSENTS:

Each subject will be assigned a six digit ID. It will be made up of the consortium number (2 digits), clinical center number (2 digits), and clinic number (2 digits). Once an ID number has been assigned to a specific participant, this participant CANNOT be assigned a different number throughout the study. This number CANNOT be reused for another participant in the study. Once the screening form (Form 110) has been entered into the database, a 2 digit alpha 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. Refer to the MOP, section 5, page 2 for more detail.

Daily Trial Eligibility Confirmation Form 110

This form is to be completed during the screening period. Screening begins once the subject has signed the FHN consent form and may continue for up to 2 weeks.

Use this form to guide you in your chart review process (pre-screening) before approaching the subject. It is especially important to review question 20 through question 34 before

approaching the potential subject to ensure that the patient is a good candidate for the FHN study. Once the subject has signed the FHN consent form, make sure that the participant's primary care nephrologist is aware of it. This can be done with a letter, e-mail, or a call. Questions 13, 16, 17, 20, 21, 25, 26, 32, & 34 should be answered by the subject's physician. Questions 6-10, 12, 15, 17-19, 21 28, 29, 30-31 (if female), 32, 33, 35-40 need to be answered by the subject. The remaining questions should be answered by the study coordinator with assistance from the dialysis clinical staff only as needed. The following questions 6-9 & 12a can be found on the subject's clinic admission form. Form 110 should be completely filled out and retained as a source document at your center.

The baseline period is 12 weeks long starting from the date of the visit identified in Q4 on Form 110.

Complete for all consenting patients
Refer to MOP chapter 5, page 2 for more detail on questions 1-3

1. Enter the subject ID # - See MOP Chapter 5 on how the subject ID is assigned.
2. The alpha code is generated after saving the entire form. Write down this alpha code as you will need to write the subject ID # and alpha code on every form you enter.

3a. Enter Visit Type as "**S**" (Screening). (Valid only for Form 110)
3b. Choose the visit number from the pull down bar menu.

4. Enter the date that this eligibility form was completed. The date might differ from the date you enter the form data into the database. However, this will never be a date prior to the date when the informed consent was signed.
5. Make sure that this date correlates with the date signed on the subject's consent form.

Demographic Data (Q6-Q8):

6. Date of birth. If the subject provides you with a different birth date than is provided in the chart, it should be entered as the subject stated and noted on the source document.
7. Gender: Male or Female. If subject is male, enter "1". If subject is a female, enter "2". If the subject associates with a gender opposite to the one assigned at birth (transgender), but has all original sex organs, record gender assigned at birth. If the subject has had surgery to change gender assigned at birth, or a sex change, record gender as the present sex post surgery.
8. Race/Ethnicity: If the subject communicates a race/ethnicity different than the one listed in the medical chart, use the race/ethnicity which the subject states. If the study coordinator thinks that a person is a different race than the subject states, the subject's stated race must still be the one recorded for the FHN trial. Make note of this discrepancy in the source document.

If the patient say he/she is only Latino, Hispanic, then ask whether he considered himself black, white or multiracial (depending on what the patient looks like – if the patient is obviously not black, then she could ask about white or multiracial). If the patient refuses to say, then code 8a=9, but then put 8b=1. The idea is not to assign a race or ethnicity that the patient doesn't identify with, but it doesn't always hurt to ask.

Communication Data (Q9-Q10): Most of this information will be listed on patient admission forms but can also be found in a social work assessment. If it is unclear if the

subject can read English or Spanish, hand her/him an upside down piece of paper. Ask him/her what he/she thinks about what it says.

Height and Weight (Q11):

11a. This information can be found on HD treatment (flow) sheets. Enter the lowest weight achieved post dialysis during the previous two weeks.

11b. Measure the subject's height after the participant has signed the study consent. If this is not possible, the most recent height should be found on the subject's flow sheet. Unfortunately, many dialysis clinics do not measure the height of the patients after they are admitted to the HD clinic. In this case, record the height presented on the patient's admission form.

Kidney Failure and Dialysis Treatment (Q12-Q19):

12a. This is the day when the subject first received HD, PD, or transplant. This is not the subject's first day receiving treatment at that particular clinic. If a subject had a kidney transplant and received HD or PD prior to this procedure, record the date of the first HD/PD treatment prior to this transplant. If the subject has been transplanted and the transplant failed OR has changed modality of treatment, the subject must receive HD for 3 months prior to entering the FHN study.

12b. Do not assume that the subject has been on treatment for 2 weeks just because it is 2 weeks since his first HD treatment. It is possible that he/she has missed some treatments. Double check with the flow sheets that the subject has had 6 hemodialysis treatments.

13. Review the subject's chart and confirm with the subject's nephrologist whether or not the subject requires any additional UF.

14. There is an access section in the subject's HD clinic chart where you can double check that the patient has a non-tunneled catheter (temporary catheter i.e. Quinton catheter). If this information is not available, look on the flow sheet. If the information is not there, follow up with clinic charge nurse or patient's nephrologist and make a note in your source document.

15. Ask the subject to answer this question.

16. Ask the subject's nephrologist, not necessarily the study PI, to answer this question.

17. Review participant's medical history. MRI is not possible if the subject has any metal in his/her body. This includes, but is not limited to, inner ear (cochlear) implants, brain aneurysm clips, mechanical heart valves, cardiac pacemakers and implanted defibrillators.

Double check that the subject is

a) informed that he or she needs to come in for an MRI twice during the study (at baseline and 12 months)

b) is not afraid of feeling claustrophobic lying on his or her back for ~ 30 minutes during the MRI

c) not more than 300 lbs. (136kg).

18-19. Talk to the patient about how he/she commutes to HD unit. Ask him/her how long it generally takes to get to the clinic and what expenses are involved (parking etc). Make a note of a participant's responses in your source documents.

26. Double check with the subject's nephrologist whether or not the potential subject is within the 1% of the population with ESRD that might have kidney recovery.

Exclusion Criteria (Q20-Q34): Review the participant's medical chart, talk to the subject and his/her nephrologist to determine whether the subject meets exclusion criteria. Any response of "yes" is a reason for exclusion.

Within the next year (Q35-Q40): Review these questions with the participant.

41. Enter "1" if you think this subject meets 100% of the eligibility criteria and does not meet any of the exclusion criteria. Enter "0" if you know that the subject does not meet the eligibility criteria or has at least one of the exclusion criterions.

42. Enter subject's emergency contact information. Study PI's or study investigator's along with study coordinator's and subject's nephrologists' contacts should be provided here.

200. Enter the date when this form was completed.
201. Enter the name of the person who completed this form.
202. If the person entering this form into database (DB) is different than the person completing this form, enter the name of the person entering the form in DB. If it is not a different person, enter the same name as entered in 201.

203. Enter the date when this form was entered into the study database.

Daily Study Documentation of Six Consecutive Days Form 111

Once the subject signs the informed consent, the subject must demonstrate the he or she can make it to the dialysis unit on 6 consecutive days. Record each consecutive date that the subject makes it into the unit. This form must be filled out before the subject can be randomized. It is recommended that the study coordinator utilize this time to do the staff QOL tests. Three out of the six days can be verified on the flow sheet showing that the subject received treatment. If you to decide to do all cognitive and physical tests on the same day, they should be done in the order below.

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) MiniMental
3) Trailmaking B
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

If you decide to do this over a period of 3 or 4 days, it is only essential that the feeling thermometer test is done first. The Holter test may also be done during this period.

Daily Trial Pre-Randomization Dropout Form 112

Fill out this form if a subject has proven to be ineligible for FHN after signing the informed consent, including that he or she has not come into the clinic 6 days per week. Do not fill out this form if a subject has been randomized. Double check with your local IRB whether or not you will need to submit pre-randomization drop-outs as "AEs or SAEs". This is particularly important when a primary

reason for drop out occurs such as death, unexpected events, and hospitalization (including transplant). Run the Subject Eligibility Form on the web site provided by the DCC before randomizing any subject. This should ensure that the subject is eligible for randomization. Note; the subject Holter test is NOT required for randomization but the BIA IS required for randomization. A subject only needs **one** reason to qualify for pre-randomization drop out.

Patient Contact Form 107

Make sure that a patient signs the HIPPA consent before release of this patient contact information. This form should be filled out directly following subject consent. The subject's demographic data, contact preferences, and trial status are recorded on this form. This information is provided to the Quality of Life (QOL) Interviewing Center in order for them to contact the subject. Send to web address https://surveyweb2.ucsur.pitt.edu/DialysisQOL/patient.php or mail to the QOL group by traceable courier.

Patient Future Linkage Form 108

The subject needs to consent to share their personal demographic information with USRDS before this form is filled out. The subject should be given the option to complete this form. The subject may refuse to share his or her Social Security number with the USRDS and still remain part of this study. If the subject consents to share his or her information, fill this form out as soon as the subject has signed the informed consent**.** Ship completed form by traceable courier to the USRDS.

Residual Renal Function Form 206

This form should be filled out for every subject enrolled into the Daily FHN trial at baseline, 4, and 12 months. If the subject states that he or she does not produce urine, he or she must attempt an 18 hour urine collection during baseline. If the subject returns the collection container with less than 80ml/18 hour, the subject does not need to take home an 18 hour urine collection during follow-up. For those subjects who can produce more than 80ml/18 hour, be sure to give them urine containers during the designated time points during the follow-up period.

Instructions will be included.
For a 24 hour Urine collection you will need to have 3000cc container (generally brown or orange in color).

For Baseline Patients: M-W-F or T-T-S
Subjects receiving dialysis on Monday will be given instruction to start a 24 hour Urine collection the following day, Tuesday, at 6am and to finish it 18 hours later on Wednesday. This container should be placed in the refrigerator (in the bag) and stored there throughout the urine collection and until the subject returns to the dialysis unit to perform dialysis on the next day. For T-Th-S group, the instructions are the same as described above with the collection start time occurring on a Wednesday.

After randomization:
Daily group:
If a subject is randomized to the daily group and will receive dialysis 6 times per week, follow the instructions below.

On Monday, the subject will be instructed to start his/her 18 hour urine collection on Tuesday at 6 AM. On Tuesday when he/she returns for treatment, he/she will need to bring the collection container with him/her to the dialysis unit and store it in the dialysis refrigerator during treatment (in case subject wants to go to the bathroom before, during or after dialysis.)
He/she will return home after dialysis and continue to collect urine until the next day, Wednesday, at 6 AM. The subject will bring the container back to the Unit on Wednesday after the urine collection is finished before his/her next dialysis session

If the subject is unable to bring the container with him/her to the dialysis unit on Tuesday, the first day of collection, instruction should be given to resume collecting urine as soon as he/she returns home after the dialysis session that day. The subject should continue collection of the urine until the following day, Wednesday, prior to his/her next dialysis session (minimum time of urine collection for daily group will be 18 hours).

Control group: For subjects randomized to the control group, the 18 hour urine collection post randomization will be identical to the baseline procedure described above.

Note: If the urine collection is less than 100 ml, the sample does not need to be measured by the local lab.

Participant In-Center Log Sheet Form 208

This form is filled out at baseline, 4, and 12 months. Review this form in detail with your study subjects. Have the subject paraphrase back to you his or her understanding on how this form should be filled out. In baseline, only 3 rows of the table will be filled out for all daily subjects. During follow-up, rows 1-3 should be filled out for the subjects placed on the conventional arm of the study. Rows 1-6 should be filled out for subjects placed on the daily dialysis arm of the study. Try to leave this form in a place where the subject will remember to fill it out each dialysis session such as in the front of the chart or attached to the flow sheet. Of course, if you can be present at the clinic you can give the subject this form. If you are not there, call the patient and remind him/her to fill this form out. If you can not do this, ask the nurse to remind the subject. Specify (Q.7) how this form was filled out.

Kinetic Modeling Form 273

This form is to be filled out and entered into the FHN database every time a kinetic modeling session is completed. It should be done twice, separated by at least one week, during baseline (the time from which a patient has signed a consent form and Form 110 has been entered into the database through 12 weeks), Follow up (week 2), and monthly. Kinetic modeling will include pre-post BUN, creatinine, phosphate, and pre-albumin. Dialysate concentrations for the Kinetic Modeling day can be found on the flow sheet near the dialysis order. These will include initial sodium, potassium,

magnesium, calcium, bicarbonate and final sodium (if applicable). Ask for help from the dialysis staff ONLY when necessary. It is important to keep the burden placed on the clinical staff to a minimum. Most of the information required on this form can be found on the patient flow sheet. Do not complete this form during an ultra filtration session.

Q1-4 Study coordinator enters data

1. Enter participant ID #
2. Enter alpha code. This is extremely important for the DCC to identify the subject.
3. a. Visit type = enter **B** if you are completing this form during baseline. Enter **F** if you are entering this form during follow-up
   b. Visit number = Choose the visit number from the pull down bar menu.
4. Enter the date at which this assessment was completed. This is not necessarily equivalent to the day you enter the data into the system.
5. If the dialysis treatment day, time, and prescription remain as scheduled, this is defined as a routine treatment. If a patient has a problem that leads to an incomplete treatment, do not enter the incomplete treatment kinetic modeling data. Enter the kinetic modeling data on the rescheduled treatment. To signify this change, enter #2 or "Redo" as the type of session. Code 3 is anything else that does not fit in code 1 or 2. You should be able to find the information to help you figure this out on the flow sheet.
6. Enter the dialysis machine code that matches the code on the dialyzer list attached to this form.
7. The reuse number can be defined as the number of times the subject's dialyzer has been used in a dialysis treatment **prior** to the present treatment. It is important to note that the reuse number and the use number are different. The reuse number and the use number both can be found on the subject's dialyzer. Only enter the reuse number in the database for question number 7. The use number includes the empty run whereas the reuse number does not. Refer to the flow sheet or dialysis log book if it is not available.

Weight

8. Enter patient estimated dry weight (EDW) in kg as found on the subject's flow sheet. Pre-dialysis weight is the weight that the subject weighed when he/she came into the treatment clinic that day. It will be labeled pre-dialysis weight or pre- (under weight) on the flow sheet. At the end of a patient treatment the dialysis staff will record the patient weight as "post weight". It can be found on the patient flow sheet.

Access

9a. Enter the type of access the patient has used during this treatment. This information can also be found on the subject's flow sheet. Do not assume that this is the same access as used previously in the study. Although uncommon, if a subject needs to utilize two different accesses in one treatment, e-mail the DCC @ fhn-dcc@bio.ri.ccf.org for an additional code to reference the subject's accesses in use.

9b. If the access has changed, enter 1 and fill out form 271. If it has not changed since the previous kinetic modeling session, enter 0.

10. The type of needle used for this subject's hemodialysis can be found on the flow sheet. Single needles are generally used with a higher blood flow and dialysate flow.

Double needles are generally used with lower blood flow and dialysate flow. Note: needles are not used with catheters.

11. Enter the subject's prescribed treatment time. This is the treatment time goal that the subject's doctor has set to ensure health and safety of the patient. Nurses and techs use this prescription as a target time length for each treatment. This can be found on the subject's flow sheet as well as in the MD orders section of the chart. This does not always match how long the patient actually runs on treatment. For example, if the patient has to get off treatment to go to the bathroom or shows up late to treatment, he/she may be taken off treatment when scheduled to be taken off. Many clinics will not push the next patient's treatment start time later just to accommodate the present patient.

12a. Enter the exact time the subject's dialysis treatment began on the day of the kinetic modeling session that you are capturing. This can be found on the flow sheet.

12b. Enter the exact time the subject's dialysis treatment ended on the day of the kinetic modeling session that you are capturing. This can be found on the flow sheet.

13. Interruption time is defined as the amount of time that the patient was not receiving treatment for any reason i.e. bathroom break, patient or machine complications etc. Most machines will stop running while the machine alarms. This can add up quickly. If the interruption is greater than 15 minutes, it is considered a serious interruption. If this occurs, enter 1. If not, enter 0.

14. Look on the flow sheet for the total minutes patient dialyzed.

15. Enter the number that the dialysis machine provides as the average blood flow during a treatment. If it does not give you this information, record the subject's blood flow 30 minutes after the patient starts the treatment. Do not record blood flow in the first 15 min or the last 15 min of the subject dialysis treatment. Often the first 15 min and the last 15 min of a subject's dialysis session are slower than the average blood flow.

16. Record dialysate flow. This is *generally* 800 ml/min and remains the same throughout every treatment. This information can be found on the subject's dialysis machine and flow sheet abbreviated as dialysis flow.

17a. Did the patient experienced cramping during treatment?

- Enter 1 if the patient did experience cramping, but not requiring saline, lowering of UF, or reducing blood flow.
- Enter 2 if the patient did experience cramping, requiring either saline, lowering of UF rate, or reduced blood flow.
- Enter 0 if the patient did not experience cramping.

17b. Did the patient experienced nausea or vomiting (N/V)

- Enter 1 if the patient did experience N/V, but not requiring saline, lowering of UF, or reducing blood flow.
- Enter 2 if the patient did experience N/V, requiring either saline, lowering of UF rate, or reduced blood flow.
- Enter 0 if the patient did not experience N/V.

17c. If the patient experienced chest pain

- Enter 1 if the patient did experience chest pain, but not requiring saline, lowering of UF, or reducing blood flow.
- Enter 2 if the patient did experience chest pain, requiring either saline, lowering of UF rate, or reduced blood flow.

- Enter 0 if the patient did not experience chest pain.

17a,b,c information should be available on the pt flow sheet.

18. Refers to subject blood pressure information

18a. Pre-dialysis blood pressure (BP) can be found on the flow sheet

18b. Post-dialysis BP can be found on the flow sheet

19a-f Enter the concentrations of the following substances in the dialysate. This information should be available on the patient flow sheet. If the dialysate concentrations are modified during the patient treatment, that information can also be found on the flow sheet. Note: it is only essential to enter the pre and post concentration for dialysate sodium. If the dialysate concentration changes for potassium, magnesium, calcium, or bicarbonate, record only the initial concentration.

19a. Enter initial dialysate sodium (Na) concentration provided during dialysis.

19b Enter the final dialysate sodium (Na) concentration provided to the patient during the last 30 min of treatment. ENTER THIS DATA ONLY IF THE CONCENTRATION VARIED FROM THE BEGINNING. This is generally the same sodium level as given to the patient in the beginning of the treatment but varies with some patients. If it has not changed from the beginning to the end of the treatment, leave this section blank.

19c. Enter the INITIAL level of potassium (K) provided to the patient via dialysate. This is found on the flow sheet.

19d. Enter the INITIAL concentration of Magnesium (Mg) in the dialysate provided to the patient.

19e. Enter the INITIAL concentration of dialysate calcium (Ca).

19f. Enter the INITIAL concentration of dialysate bicarbonate (Co3).

Patient's Lab Measurements

Enter these lab results as they appear on the patient lab result page. This page is generally referred to as the "monthly lab" or "kinetic lab" page and can be found in a lab section of the subject dialysis electronic or paper chart. Verify that the lab draw date is the same date as the kinetic modeling date.

20h. Enter the date these samples were drawn. Be careful not to enter the date these sample values were printed.

200. Enter the date you completed this form.

201. Enter the name of the person completing this form.

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202. If the person entering the form is different than the person completing this form, enter the name of the person entering the form. If it is not a different person, enter the same name as entered in 201.

203. Enter the date that this form was entered into the database.

Retrospective Kinetic Modeling Date Form 274

This form captures information concerning treatment times, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during the one week period

proceeding the B-01 kinetic modeling session. In order to find all the information to be entered in this form, refer to the flow (run) sheet during this period. The 1-week period for retrospective data collection ends on the day prior to the kinetic modeling session. A "hypotensive episode" can be defined as any low blood pressure that leads to a lowering of the UF rate or a reduced blood flow. A "significant interruption" qualifies as any interruption in a subject's dialysis session lasting 15 min or greater.

Co-Morbidity Assessment and Medical History Form 104

This form can be provided to the physician to fill out during baseline, after subject consent. Alternatively, the physician can provide the study coordinator with a list of the subject's medical history leaving the form to be filled out by the study coordinator. When the list is completed, have an MD associated with FHN sign off on it. In the case that the subject's physician does not contribute in any way to this form, the corresponding FHN physician, associated with that clinical center, needs to review the subject's medical chart(s). One suggestion is to send this form along with a letter to the subject's physician notifying him/her that the patient has signed the consent form and verify that he/she may be randomized to FHN.

Baseline Demographics, Employment, and Income- Form 105

This form should be completed at baseline and records all subject's self-reported demographic, employment, and income information.

Local Biochemistry Laboratory Data Form 207

This form records the local dialysis clinic lab values for each subject. Form 207 should be completed at baseline and monthly for follow-up lab values (Local iron and PTH profiles should be done at baseline but a lab draw from up to 4 months prior to baseline can be used.). Follow up labs must be after a participant's randomization. Use the most recent lab values available. It is recommended to have a hard copy of labs available in your source document before entering information into this form and study database.
In order to obtain this information, contact the local lab department working with the dialysis clinic during baseline and continue to check in with them monthly. This will keep you updated on any changes occurring in each local lab. It is possible that HD clinic may change the lab it uses during the duration of our study. Also, the lab may switch assays used for some measures (for example: iPTH -> bioPTH). Thus, it is important that coordinators note this change. Ask if the lab department can fax you a copy of your subject's lab results each month.
Note: the post treatment lab values are not entered on this form but on the kinetic modeling form #273. Urine data will be recorded on the residual renal form # 206.

Biological Specimen Repository Mailing Form 255(U.S.), 256 (International)

Make sure that a subject consents to have a sample of his or her blood sent to the repository before filling out this form, drawing additional blood samples, and shipping any blood samples to the repository. If a subject has consented, obtain extra blood samples, spin the blood tubes, and fill out this form - see Chapter 22 of the MOP because Canadian centers have to follow a different procedure for collection and shipping of repository samples.

After a copy of this form has been made, pack the blood tubes on cold packs inside the packing box supplied. Place the original copy of this form inside the package and the copy in the source document. Ship samples to the NIDDK address supplied on the top of the form Mondays through Thursdays. Notify the repository of shipments by e-mail (at bio-niddkrepository@fishersci.com) or by facsimile on the day the package is picked up by FedEx. Do not ship on Fridays. Also, be aware of any major holidays that may occur during a week. This form is completed after the Biological Specimens for repository are collected at Baseline, 4 months, and 12 months.

Access Used For Chronic Hemodialysis Form 271

This form is completed at baseline and whenever changes in the subject's access occur. This form might be completed on multiple occasions. If the subject has more than one access, make sure that the access entered at randomization is the one the subject is presently using. Make sure to check with your local IRB whether or not you need to enter an access change as an AE or an SAE, i.e., if a subject is hospitalized for greater than 24 hours for access surgery. A subject's access information can be found in the "access section" of a participant's medical/HD clinic charts. Enter the date when this access was placed (Q5). If this information is not available, enter the date when it was first used. This information should be found in the access section of a subject's chart. Also you may find related information in the subject's "medical history" and/or "progress note" parts of participant's HD clinic chart. Verify this information by asking the subject directly and reviewing subject's flow sheets during at least the previous week of HD.

Medications

IV Iron Therapy Form 203

Record any IV iron given to a subject within the last month. Include the dose and frequency of IV iron supplied to the subject. IV iron use can be found in the subject's flow sheet or an IV medication record kept at the dialysis clinic and/or in a computer system. Have a calculator handy to verify that all calculations are correct. Complete this form at baseline and monthly during follow-up.

Injectable Medications Form 204

Record synthetic intravenous (IV) and subcutaneous (SC) erythropoietin, darbepoietin, and vit D analogues given to the subject. IV and SC medications used can be found in the subject's flow sheet or an IV medication record kept at the dialysis clinic and/or in a computer system. Have a calculator handy to verify that all calculations are correct. Medication codes for this form can be electronically found on the code list in the study database. This form should be filled out at baseline and follow-up months 4, 8, and 12.

Medications and Supplements Form 205

Record any prescription and OTC medications excluding IV Iron, synthetic IV and SC erythropoietin, darbepoietin, and vit D analogues. Prescription and over the counter (OTC) medications should be in a subject's chart under a medication tab or nursing notes tab. Generally, these medications are recorded by a dialysis nurse monthly. This form should be filled out at baseline and follow-up months 4, 8, and 12.

QOL FORMS

Feeling Thermometer Form 230

On page 2 of Form 230, a script is provided at the top of the page. Follow this script when administering the test. Have a pen or pencil available to do this test as well as the paper form the patient will complete.

Make sure the subject draws a line from the dot to the number that represents his/her imaginable health state TODAY. Circling the number that represents the subject's health state does not count!

The coordinator may split up the bedside tests onto 2 or more separate days but this needs to be the 1st test administered.

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) Modified Mini Mental Status (3MS)
3) Trailmaking B
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

Modified Mini Mental Status Form 231

It is essential to read the MOP before administering the Mini Mental cognitive function test. This test needs to be administered in the middle of the week pre-dialysis in a quiet place, with minimal distractions, at a desk or table the participant can use as a writing table. Have a pen or pencil, a stop watch, at least 2 blank sheets of paper, and the flash cards (of the pentagons and "close your eyes") available to do this test. It is recommended that this test be administered following the Feeling Thermometer test. Note that the scoring of each question is reviewed in full in section 11.5 of the MOP. Follow all scripts provided for the Examiner. Some questions are more challenging to administer or score than others. These questions are discussed below.

Question 6- "Where were you born?"

Record the subject's answer but do not score this until later when the subject answers question 23. Question 23 asks the same question again to ensure that Q6 is correct.

Question 7-

Make sure the subject is attentive before you state the 3 words that must be repeated. They will be asked to recall these 3 words later in the exam.

When the subject has difficulty recalling the words, repeat the items up to six times until they are all learned. (Total of seven presentations.)

Be sure that the correct suffix of the word is repeated. For example, do NOT accept "shirts" for "shirt" or "honest" for "honesty". The exact form of the word must be repeated.

Question 8-

If the participant cannot count forward to 5, prompt with "Say 'one, two, three, four, five'" at the rate of 1.5 seconds per digit.
Note 8a is the only section of this question which the study coordinator will need to score. 8b receives a score by the DCC after being entered into the database. Enter the numbers as they are told to you with an X in the spaces where a number is not provided.

Question 9-

If the participant cannot spell "world" forward, prompt with "It is spelled W O R L D (sounding out each letter)" at the rate of 1.5 seconds per letter.
Note 9a is the only section of this question which the study coordinator will need to score. 9b receives a score by the DCC after being entered into the database. Enter the letters as they are told to you with an asterisk in the spaces where a letter is not provided. (The asterisks help to identify that no response was forthcoming from the participant and the coordinator did not accidentally forget to write in a response.)

Question 10 - What three words did I ask you to remember earlier?
1) The words may be repeated in **any** order.

2) For each word not readily reported, provide the category (for instance, **"it is something to wear" "it is a color" "it is a good personal quality"**) followed by multiple choices when necessary. Do not wait more than 3 seconds for spontaneous recall and do not wait more than 2 seconds after giving the category before providing the next level of help.

3) If the participant gives an incorrect answer in the correct category (e.g., says "socks" or "coat" instead of "shirt"), provide the three alternatives for them to choose from, and score 1 when the choice is correct. For example; **"Was it shirt, shoes, or socks?", "Was it blue, black or brown?" or "Was it honesty, charity or modesty?"**

Question 11e-

Since distinctions between seasons can be difficult during certain months, the following schedule has been created. For months with two seasons listed, either answer is correct.

Month	Correct Response
January	Winter
February	Winter
March	Winter or Spring
April	Spring
May	Spring
June	Spring or Summer
July	Summer
August	Summer
September	Summer or Fall (Autumn)
October	Fall (Autumn)
November	Fall (Autumn)
December	Fall (Autumn) or Winter

Question 12d-

This question assumes that the test is being administered in a clinic setting. When the correct answer is not among the three alternatives (e.g., test is being conducted in a hospital or nursing home), substitute the correct response for the middle alternative (store).

Question 13f- - What animals have four legs? Tell me as many as you can.
Record the total number of correct responses. A set of abbreviations may be helpful for writing the animal names quickly.
Discontinue after 30 seconds.
***** If the participant gives no response in 10 seconds and there are still at least 10 seconds remaining, gently remind them (once only): "What (other) animals have four legs?"
* The first time an incorrect answer is provided, say, "I want four-legged animals." Do not correct for subsequent errors.

• Score one point for each correct animal.
• Different names for the same animal of different age or sex count as one animal. For example:
- kitten/cat
- puppy/dog
- deer/doe
• Those animals with similarities but true technical differences may be counted as two separate animals; e.g., pony and horse may be counted as two; mule and donkey may be counted as two; but ass and donkey are the same animal and must be counted as one.

Question 14-
This question evaluates the subject answers as being either concrete or abstract. The abstract thinker scores a 2 whereas the concrete thinker scores a 1.

Question 17-
a-c. Check "Correct" for each part (e.g., *ifs, ands, buts)* correctly repeated; give no credit if the participant misses the "s".
d. Hold up Card # 1 and say, "**Please do this**."
1) If the participant does not close their eyes within 5 seconds, prompt by pointing to the sentence and saying "**Read and do what this says**".
2) If the participant has already read the sentence aloud spontaneously, simply say, "**Do what this says**." Allow 5 seconds for the response.
3) As soon as the participant closes their eyes, say: **"Open".**

Question 18-
Right- or Left-Handedness
Observe which hand the participant uses to write and record on the form. You will need this information later in Question 16. If this task was not performed due to a functional disability, ask the participant if they are right- or left-handed.

Question 20-
NOTE: If the participant is still working at the end of one minute, allow them to complete the task for the sake of maintaining rapport and morale. Mark the 1 minute point on the product and do not credit for parts finished after 1 minute.
• Each pentagon is scored as follows: Check appropriate box:
- 5 approximately equal sides.
- 5 unequal sides, and the longest:shortest side ratio is > 2:1.
- non-pentagon enclosed figure is drawn.
- 2 or more lines, but it is not an enclosed figure.
- less than 2 lines or the participant refuses to do the task.

- participant does not attempt the task due to a functional disability such as visual impairment or severe arthritis, etc.

• The intersection is scored as follows:
- 4-cornered enclosure.
- not a 4-cornered enclosure.
- no enclosure or the participant refuses to do the task.
- participant does not attempt the task due to a functional disability such as visual impairment or severe arthritis.

Question 22-
Note: The words may be repeated in **any** order.

Trail Making B Form 232

This test should be completed at Baseline, F4, and F12. It should be administered mid week, prior to the subject's dialysis treatment, and following the Modified Mini Mental test in a quiet place, with minimal distractions, at a desk or table the participant can use as a writing table.
Have available:
• #2 pencils with eraser
• Stop watch
• Trails B sample form
• Trails B test form
Use only the script provided when giving this test to a subject. When the subject does an incorrect line, use the script provided and cross out the incorrect line. It may be helpful to use a red pen when marking the incorrect line done by a subject.

Clinical Center Miscellaneous Form 233

This form allows the database to identify those study participants that did and did not consent to provide linkage information to the USRDS. The database can not assume a subject did not consent because there is no form 108 or 109 in the system. If a patient willingly provides USRDS data (Forms 108/109) at baseline but then decides they do not want their information shared during follow-up, then the study will need to address it. If a patient withdraws consent, we would not expect to collect this information.

Instructions: Note Q4 refers to baseline data. Q5-6 apply only to nocturnal trial. Q7-11 should be entered at the end of the study. Review the Patient Future Linkage form 108 and Demographic, Employment, and Income form 105 before completing this form.

For all patients at baseline:
The United States Renal Data System (USRDS) is funded by NIDDK to collect information on all patients undergoing dialysis in the US. If the patient agrees to provide health insurance identification numbers the subject can be linked to USRDS and the repositories. In the case the patient does agree to this enter 1 and Complete form 108. In the case that the patient does not agree to provide health ID numbers, enter 0 only and d*o not complete Form 108.* (See section 9 of the MOP for further detail).

For Canadian centers, you will need to complete a Form 109 to obtain linkage information. This form is under development.

For All Patients at End of Trial

Employment Status Change

This section of the form is attempting to find out if, during the course of the study, the patient's job status and health insurance status has changed and why the changes were made (i.e. due to their medical condition versus their place of employment closing down). Enter patient employment status, whether or not it has changed since baseline, and if the subject employment status changed, explain why.

FHN Combination Physical Function Tests, Form 234

Make sure to review the MOP before administering the physical function test. These tests are completed at baseline, 4 months, and 12 months. Have a stop watch, pen, pencil, measuring tape, chair (without wheels), and a 4 meter space available before beginning these tests. It is important to demonstrate all tests before you ask the subject to do them. Once you have demonstrated the test, ask the subject if he or she feels safe doing the test. It is okay to give a subject your arm to help with balance before any of the tests start. Once the subject begins a test, he or she should not have contact with you unless he or she needs the physical support. It is essential to stand or walk beside them in case they have difficulty completing the tests. Follow the scripts exactly as they are written on form 234 while administering these physical function tests. The FHN Database will calculate individual scores and the total score of the physical function testing.

BIOIMPEDANCE TEST

Form 242 – Single Frequency Bioelectric Impedance (BIA) Assessment

This test is administered pre -dialysis, mid-week at baseline, follow-up visits 1, 4, and 12 months. Section 6.2.8 of the FHN protocol states that a subject should be lying down during the BIA test. Specify on the form if the subject was not lying flat. Record the subject's weight, height, resistance, and reactance on this form. Following the assessment, enter all the data in the Cyprus software on your computer.

Form 250 – Dialysis Session Before MRI

This form is completed after the MRI is performed. Data is obtained from the last dialysis treatment before MRI. Refer to the subject's flow sheet from the treatment date preceding the MRI.

MRI Mailing Form # 251

Complete questions 1-4 on this form and then send it to the MRI technician. Double check that the MRI technician has this form and 2 CDs, one for the Cardiac MRI Core Laboratory and one for the clinical center, prior to the subject arriving at the MRI testing site. This form records the subject's MRI images. Questions 7-35 should be completed by the MRI technician at the time of the MRI. Once the form is completed, the technician should send it back to the study coordinator to fill out questions 5-6 & 200-201. Upon completion of this form, the study coordinator or data entry person should enter the data into the database. This notifies the database that the Central MRI results will be supplied by the CICL. The database keeps track of whether a participant has received an MRI and whether the results have been received from CICL before a participant is randomized.

Presented for information purposes only:

MRI Central Data Entry Form # 252

This form will be completed by a member of the Cardiac MRI Core Laboratory in New York. The calculated information recorded on this form will be reported back to the clinical centers through the database.

Heart Rate Variability Mailing Form # 253

This form records whether or not the Holter Test, otherwise known as the Heart Rate Variability Test, was completed. Heart rate variability will be measured at baseline and at the F12 visit using 24-hour Holter measurements from KCl. Refer to MOP chapter 16. Holter monitoring will be done on the first dialysis day following the weekend. Each 24-hour Holter analysis period will commence immediately after placement of the Holter equipment, which will take place at any point in time in the hour preceding the start of dialysis. Record the time that the Holter test was started and stopped, the name of the person administering the test, and the time that Dr. Chan was notified that the test was done. You will need to download the data onto two CDs: 1)for transmission to the Central Holter Facility and 2) one CD for the study files. Make sure to record the KCI transmission file number associated with the transmission of the Holter data so that you can alert Dr. Chan that it was sent. Although there is a diary card in the Holter packaging, the FHN trial does not require this to be filled out.

Presented for information purposes only:

Center Holter Reading Facility Data Transmission Form # 254

This form is completed by the Central Holter Reading Facility once they have received a subject's Holter test. The data on this form is transmitted electronically to the DCC and will be available through the database. In addition, DCC will send each clinical center a report of these results.

FORMS COMPLETED BY THE QOL INTERVIEWING CENTER

QOL Assessments: Administered pre- dialysis, mid- week

Review Chapter 8 of the MOP for information regarding these forms which are completed by the central interview facility located at the University of Pittsburgh. Double-check that the patient's information appearing on the website (https://surveyweb2.ucsur.pitt.edu/DialysisQOL/patient.php), is current. Do not attempt to enter any data into the database form as only data provided by the Central QOL facility will be allowed. You will be able to view the participant's data by querying up the individual form. For technical questions contact the central interview facility @ *survey@pitt.edu or* `https://surveyweb2.ucsur.pitt.edu/DialysisQOL/`.
The following tests will be administered through the Central Telephone Interview:

Form 220 - SF-36
Form 221 - Beck Depression Inventory
Form 222 - Cousineau Self-Perceived Burden Scale
Form 223 - Health Utilities Index
Form 224 - Special Study Questions
Form 225 - MOS Sleep Scale

ONCE ALL THE AFORMENTIONED PROCEDURES/FORMS HAVE BEEN COMPLETED **AND** PARTICIPANT IS ELIGIBLE:

RANDOMIZE THE PARTICIPANT!!!

***The DCC notifies the HRQOL Interviewing Center as to whether the participant has been randomized or not. The HRQOL Patient Tracking Database is updated with randomization status (i.e. randomized, not randomized).

The HRQOL patient tracking database is updated with date of baseline HRQOL Interview completion and projected dates for follow-up HRQOL interviews.

***Two weeks prior to the scheduled date for the HRQOL interview, the HRQOL sends a standardized email to the study coordinator as a reminder to complete the web-based HRQOL Interview Follow-up Contact Form, which includes the following fields:

a) participant ID#
b) status (i.e. still participating in the trial, withdrew from trial but interview, withdrew from trial and don't interview, deceased), and
c) contact information

Following is the link to the HRQOL follow-up form:
https://surveyweb2.ucsur.pitt.edu/DialysisQOL/index.php

CARDIAC MRI

Dialysis Session Before MRI, Form 250

This form is completed after the MRI is performed. Data is obtained from the last dialysis treatment before the cardiac MRI.

MRI Mailing Form 251

Items 1-6 completed by Study Coordinator
Items 7-35 completed by MRI technician

Participant In-Center Log Sheet Form 208

For conventional participants, dialysis sessions 1, 2, and 3 will need to be captured on this form. The study coordinator may either pick up the completed form at the dialysis center or provide a self-addressed stamped envelope for the completed form to be sent back to him or her.

Attendance at In-Center Dialysis Sessions Form 275

This form is to be completed by the study coordinator or dialysis unit technician at the start of each calendar month, following randomization, in order to document missed dialysis treatments during the prior calendar month. Do not count those treatments completed for ultra filtration only. The information needed to complete this form can be found on a subject's flow (run) sheet or medical chart.

ACCESS REPAIR PROCEDURE - FORM #276

This form is completed whenever an access procedure is done to help maintain or restore function of the access that is currently being used for HD. Wait until at least one dialysis procedure is done after the access placement before you complete this form (Otherwise you will never be able to answer "yes" to the question about the success of the repair.)
On this form you will need to enter what type of access was repaired and how it was repaired. You will also be asked to explain whether an MD or a non-MD did the repair procedure.
For access failure or removal, complete Form 277. For placement of a new access, complete Form 278. *If you only wish to indicate that a new access is being used for hemodialysis, fill out Form 271*.
The following do not count as FHN access repair procedures and do not merit a Form 276, so do NOT complete this form if:
• the patient only had diagnostic venogram without any other procedures.
• the patient only had one or more dwells of TPA
• the only procedure done was banding
• the procedures was done within a dialysis unit. This form is intended for procedures done in a vascular access center or in a hospital
• there is angioplasty of a central vein or stent placement on a central vein

Term defined:
Angioplasty: Alteration of the blood vessel

Permanent Access Failure or Removal Form 277

This form is completed whenever an access that is currently being used for HD is removed or otherwise can no longer be used (defined as "permanent failure.") On this form you will need to state when and why the access failed. You will also need to record when the failed access was first placed in the subject, the type of access it was, and whether it was removed.

New Access Placement Form 278

This form is completed at any time a new access is placed. If two accesses are placed on one day, complete this form twice. You will need to record the type of access that was placed, the reason it needed to be placed, and whether or not the new access is being used.

Patient Event Forms

Patient Management Forms

Consent for Repositories Form 406

This form should be completed at baseline for all individuals who were asked to participant in the Repository collections, **even if they refused**. If a participant was asked to participate in the Repository collections and refused, complete questions 1, 2, 3, 200 and 201. This form is completed at baseline or following the time when a subject is initially asked to participate in the Repository collections. It informs the DCC whether or not a subject agreed to have a biological specimen collected

Patient Transfer Form 400

A subject that chooses to dialyze at an alternative clinic can do so and remain in the FHN trial only if he or she transfers to a clinic participating in the FHN trial. When a subject chooses to transfer, fill out this form. Record where the subject is transferring to and when he or she transferred. This is to ensure that the DCC and anyone else who needs to know, is aware of the site transfer.

Re-enrollment of a previously enrolled patient Form 401

Once a subject has been randomized, it will be necessary to follow-up with that subject for an entire year. If he or she chooses to no longer be involved in the study at any point, he or she will be excluded from the study. A patient that has been randomized can re-enroll in the FHN trial if the subject's nephrologist, PI, DCC, and Study Coordinator agree that it is medically safe for him to re-enroll. This form should be filled out if the subject is going to re-enroll. read below:

a) Provided the subject does not withdraw consent and is not lost to follow-up, data collection and follow-up will continue for all subjects meeting any of the following stop-points. The treating physician determines that the subject

requires more frequent or less frequent dialysis for reasons including, but not limited to, the following: uremic symptoms, uncontrolled hypertension, patient fatigue/burnout, etc.

b) The subject changes from in-center hemodialysis to home hemodialysis. Where possible, recommendations will be made to continue the subject on their assigned treatment frequency (i.e., in-center daily will change to home daily HD; in-center conventional will change to home conventional HD).

Efforts will be made to follow all randomized subjects for 12 months, irrespective of their adherence to the randomized therapy. However, certain situations may preclude complete data collection for the full 12 months (losses to follow-up).

The randomized therapy and routine data collection will be discontinued in the following situations:

a. Subject withdraws consent for study participation
b. Subject changes to peritoneal dialysis
c. Subject receives renal transplant
d. Subject relocates to a non-study center.
e. Subject changes to home HD and further follow-up not possible.

For patients who are lost to routine follow-up for reasons b – e above, all attempts will be made to collect vital status, the primary and main secondary outcomes, and other centrally administered quality of life questionnaires at the 12-month visit.

All losses to follow-up with reason will be reported to the DCC (discontinuation of therapy form). The Adherence Committee will review all losses to follow-up on a monthly basis.

Post Randomization Withdrawal, Lost To Routine Follow Up On Treatment, Patient Refusal For Patient Contact Data Collection Form 402

This Form should be completed by a study coordinator

A) When a patient becomes unable to provide some study data

B) When a patient is lost to follow up due to transplantation or a switch to PD

C) When a patient is truly lost to follow-up and all efforts to keep the patient in the study have been exhausted. (If a lost to follow-up patient comes back to the studycontact the DCC.)

D) When a patient refuses to provide some study data

E) When a patient absolutely withdraws from the study, refusing consent even for passive data collection regarding his hospitalizations

Note that this form is not completed when a patient stops following his frequent dialysis prescription. This is an adherence issue, and a different form (form xxx) is used .

Questions 17 – 21 refer to withdrawal post randomization as a result of a subject refusing to provide some data. If a subject does not adhere to the 12 month MRI test, phone interviews, mental status tests, functional status tests you will need to fill out this form. Note that a physician should speak to the patient before this section may be completed. The physician should explain that the data is valuable whether the patient is adhering to his or her randomized treatment group or not. That physician could be the PI, a Co-PI or the patient's primary nephrologist. Question 21 refers to the last date which the study team was able to collect full data. For example; if you put a 4 (refuses to provide some data) in Q19 (mental status) you will need to write the date in which you last completed a full mental status assessment on the subject. If you mark each question 17-20 as “refuses to provide data”, record the most recent date in which a subject refused to provide the data. Enter the last date that you were able to collect partial data for the MRI test, phone interviews, mental status tests, and functional status tests for question 20.

4. Ready to Randomize

4.1 Eligibility for Randomization: Daily Study

Frequent Hemodialysis Network (FHN) Clinical Trial
Eligibility Report for the Daily Study

07/30/2008 11:12 AM
Page 1 of 3

PID: 900XXX **Alpha Code:** ML **Screening Date:** XX-JUN-2008 **Last Day:** XX-SEP-2008

Is this patient eligible to be randomized to the Daily Study?
1 Is this patient eligible?

Form 110: Daily Trial Eligibility Confirmation Form available and supports eligibility?
1 100% of items have valid answers (refused is a valid answer for Race/Ethnicity)
2 Patient is eligible based on the data on this form?

Form 104: Comorbidity Assessment Form Available?
1 100% of items have valid answers?

Form 105: Basic Demographic Form Available?
1 100% of items have valid answers?

Form 111: Documentation of Six Consecutive Days Form Available?
1 100% of items have valid answers?

Form 202: Amputation Form Available?
1 100% of items have valid answers?

Form 203: IV Iron Therapy Form Available?
1 100% of items have valid answers?

Form 204: Injectable Medications Form Available?
1 100% of items have valid answers?

Form 205: Medications and Supplements Form Available?
1 100% of items have valid answers?

Form 206: Residual Renal Function Acceptable?
1 Form 206 entered into the database?
2 Has the residual renal function been calculated?
3 Residual renal urea clearance less than or equal to 3 ml/min/35 L?

Form 207: Local Laboratory Test Results Form Available?
1 All items except sodium (optional) have been answered and are within a valid range?

Form 220: SF-36 Form Available?
1 100% of items have valid answers?
2 SF-36 date within 15 weeks?

Form 221: Beck Depression Inventory Form Available or Not Applicable?
1 At least 75% of questions completed?
2 All completed items have valid answers?

PID: 900XXX Alpha Code: R9 Screening Date: XX-JUN-2008 Last Day: XX-SEP-2008

Form 223: Health Utilities Index 3 Available?
1 Enough of the items are completed such that the index can be calculated. Note that responses of don't know or refused can't be used in calculations - they are missing data?

Form 230: Feeling Thermometer Results Form Available?
1 100% of items have valid answers?

Form 231: Mini Mental Status Available?
1 100% of items have valid answers?

Form 232: Trailmaking B Score Sheet Available?
1 Form available?
2 100% of items have valid answers?

Form 233: Clinical Center Miscellaneous Questions Form Available?
1 100% of items have valid answers?

Form 234: FHN Combination Physical Function Tests Form Available or N/A?
1 100% of items have valid answers?

Form 250: Dialysis Session prior to MRI Available?
1 100% of items have valid answers?

Form 251: MRI Mailing Form Available?
1 100% of items have valid answers?
2 MRI date within 15 weeks?

Form 252: Central MRI Results Form Available?
1 100% of items have valid answers?

Form 271: Details on Patient's Access at Start of Trial Form Available?
1 Q4: Non-tunneled catheter?
2 100% of items have valid answers?

Kinetic Modeling Criteria:
1 At least two valid KM sessions with corresponding forms 273 and 274?
2 Baseline eKt/V of >= 1.0?
3 Kinetic volumes of two baseline KM sessions have a CV no more than 20%?
4 No more than six KM sessions have been performed?

Form 406: Consent for Repositories Form Available?
1 100% of items have valid answers?

Form 113: Ready For Randomization Confirmation Form Available?
1 100% of items have valid answers?
2 Form confirms ready to randomize?
3 Form completed within 2 weeks?

PID: 900XXX **Alpha Code:** R9 **Screening Date:** XX-JUN-2008 **Last Day:** XX-SEP-2008

Within 15 weeks of patient's screening date?

1 Within 15 weeks of the screening date on Form 110?
The last day to randomize this patient is 18/SEP/2008

4.2 Eligibility for Randomization: Nocturnal Study

Frequent Hemodialysis Network (FHN) Clinical Trial
Eligibility Report for the Nocturnal Study 07/30/2008 11:22 AM

Pid: 900XXX **Alpha Code:** 7S **Screening Date:** XX-MAY-2008 **Last Day:** XX-SEP-2008

Is this patient eligible to be randomized to the Nocturnal Study?
1 Is this patient eligible?

Form 100: Nocturnal Trial Eligibility Confirmation Form available and supports eligibility?
1 100% of items have valid answers (refused is a valid answer for Race/Ethnicity)
2 Patient is eligible based on the data on this form?

Form 101: Nocturnal Trial Evaluation of Home Environment Form Available?
1 Q14a Are there plans to make the recommended modifications?
2 100% of items have valid answers?

Form 102: Nocturnal Trial Evaluation of Patient and Caregiver Form Available?
1 Q12 - Is this patient capable of performing the necessary procedures to conduct his/her dialysis at home if randomized to the nocturnal arm?
2 Q13 - Will this patient have remote monitoring and/or a partner living in the home that is willing to help the patient?
3 100% of items have valid answers?

from 104: Comorbidity Assessment Form Available?
1 100% of items have valid answers?

Form 105: Basic Demographic Form Available?
1 100% of items have valid answers?

Form 202: Amputation Form Available?
1 100% of items have valid answers?

Form 203: IV Iron Therapy Form Available?
1 100% of items have valid answers?

Form 204: Injectable Medications Form Available?
1 100% of items have valid answers?

Form 205: Medications and Supplements Form Available?
1 100% of items have valid answers?

Form 206: Residual Renal Function Acceptable?
1 Form 206 entered into the database?
1 Has the residual renal function been calculated?
2 Baseline GFR less than or equal to 10 ml/min/1.73m2?

Form 207: Local Laboratory Test Results Form Available?
1 All items except sodium (optional) have been answered and are within a valid range?

Pid: 900XXX **Alpha Code:** 7S **Screening Date:** XX-MAY-2008 **Last Day:** XX-SEP-2008

Form 211: Nocturnal Study v3.0 Results Of Baseline Home Training Form Available?
1 100% of items have valid answers?
2 Successfully able to complete Phase I of home training?

One Form 215 for MID WEEK: Nocturnal Study 2-Day Home Blood Pressure Form Available?
1 100% of items have valid answers?

One Form 215 for Weekend: Nocturnal Study 2-Day Home Blood Pressure Form?
1 100% of items have valid answers?

Form 220: SF-36 Form Available?
1 100% of items have valid answers?
2 SF-36 date within 18 weeks?

Form 221: Beck Depression Inventory Form Available?
1 At least 75% of questions completed?
2 All completed items have valid answers?

Form 223: Health Utilities Index 3 Available?
1 Enough of the items are completed such that the index can be calculated.
Note that responses of don't know or refused can't be used in calculations
- they are missing data?

Form 230: Feeling Thermometer Results Form Available?
1 100% of items have valid answers?

Form 231: Mini Mental Status Available?
1 100% of items have valid answers?

Form 232: Trailmaking B Score Sheet Available?
1 Form available?
2 100% of items have valid answers?

Form 233: Clinical Center Miscellaneous Questions Form Available?
1 100% of items have valid answers?

Form 234: FHN Combination Physical Function Tests Form Available or N/A?
1 100% of items have valid answers?

Form 250: Dialysis Session prior to MRI Available?
1 100% of items have valid answers?

Form 251: MRI Mailing Form Available?
1 100% of items have valid answers?
2 MRI date within 18 weeks?

Form 252: Central MRI Results Form Available?
1 100% of items have valid answers?

Pid: 900XXX **Alpha Code:** 7S **Screening Date:** XX-MAY-2008 **Last Day:** XX-SEP-2008

Form 271: Details on Patient's Access at Start of Trial Form Available?

1 Q4: confirm that they don't have Non-tunneled catheter?
2 100% of items have valid answers?

Kinetic Modeling Criteria:

1 At least two valid KM sessions with corresponding forms 273 and 274?
2 Baseline eKt/V of >= 1.0?
3 No more than six KM sessions have been performed?

Form 406: Consent for Repositories Form Available?

1 100% of items have valid answers?

Within 18 weeks of patient's screening date?

1 Within 18 weeks of the screening date on Form 100?
The last day to randomize this patient is 17/SEP/2008

5. Guidelines for Study Coordinators

5.1 Introduction

The study coordinator plays an integral role at each clinical center of the FHN Study. He/she, along with the Principal Investigator and Co-Investigators, keeps the study running smoothly at the clinical center level, with the assistance of the dialysis unit technicians.

The study coordinator must work closely with the physician at the clinical center to screen and enroll patients, to make sure patient information is gathered, recorded, entered and verified correctly, and to ensure that the FHN Study protocol is followed. He/she must coordinate the patients' visits with the physicians and the dialysis unit. He/she will work closely with the Consortium Centers, to help resolve problems that arise with patient data.

All FHN study coordinators must attend central training in order to be certified to participate in the FHN Study. Central training of the study coordinators will help enhance compliance with the protocol and will help in the development of uniform procedures for data acquisition. At the central training session, the study coordinators will learn about the FHN Study and be certified to complete forms, enter data into the Oracle database, and correct errors. If a study coordinator must leave his/her position at the clinical center, he/she should help train his/her replacement.

Each study coordinator will have a copy of and familiarize himself/herself with the protocol, the manual of operations (MOP) and data collection forms. These can be found on-line at the FHN website. The coordinator should make sure to keep all study documents up to date. The DCC staff welcomes questions about the protocol, MOP and Forms.

The most current version of address directory can be reviewed on the FHN website.

5.2 General Instructions for Completing Forms

Follow these instructions when completing FHN data forms.

- Use a black or blue ballpoint pen (Flairs, Pentel pens, etc. will smear). Write legibly so that data entry is accurate. You will keep all forms at your Clinical Center.

- Print and capitalize all letters.

- Make corrections as follows: put a line through the incorrect value; write the new value either above or next to the old value; write your initials and the date of the correction in the margin.
  bw 01/31/2006

  Example: 1 ~~2~~ 2

- Any forms that a patient completes must be reviewed before entry into the study database. Examine these forms to ensure they have been completed properly and that the writing is legible.

- Enter only one character or number on each dash.

- Each categorical data item has an assigned code. Be sure to enter the coded response.

  Example: Given 0=No, 1=Yes and the answer to the question on the form is **no**, the code should be transcribed on the form as: 0

- Round off values after a decimal point to fit into the given space. Do not add dashes or move a decimal point.

  Example: Given four dashes, a decimal point, and one dash, the value 123.57 should be entered as:

  1 2 3. 6

- The decimal point is always assumed to be at the far right if it is not included on the form. Do not add a decimal point.

- If a value is too large to fit in the provided spaces, notify the DCC that a larger field needs to be placed in the database.

- Dates should always be entered as dd/mon/yyyy. (e.g., 09/SEP/2005).

  * *When entering a birth date, be careful not to enter the current year.*

Patient Identification Number Assignment And Alpha Code

If a participant consents, each subject will be assigned a six-digit ID number. It will be made up of the dialysis unit number (4 digits) and a 2-digit number assigned by the coordinator. It is recommended that these 2-digit numbers be assigned sequentially so as not to run out of unique numbers (i.e., xxxx01, xxxx02, xxxx03, etc.). Once an ID number has been assigned to a specific participant, this participant CANNOT be assigned a different number throughout the study. This number CANNOT be reused for another participant in the study.

When entering Form 100/110 into the database, the box at the left will be used to enter and establish the participant's ID number. The dialysis unit will be selected with the dropdown list into the field labeled "dialysis unit". The key entry person will then enter the coordinator assigned 2-digit number into the field that is labeled "sequence" (01, 02, 03, etc.). Once they hit enter, the participant ID number will be displayed in Item #1-Patient ID field and the database will automatically move the cursor to the "visit date". The Alpha Code will be automatically assigned once the form has been entered and saved to the database. Be sure to document this alphanumeric code since the combination of the participant ID and the alphanumeric code is used to uniquely identify each participant in the study.

Visit Types

Visit types will appear on almost every form. The choices are:

S = Screening (will only be used on Forms 100/110)
B = Baseline
F = Follow-up

5.3 Site Registration

The FHN Study address book lists all Core Consortia, and Clinical Centers, and gives their study identification numbers. Clinical Centers, Dialysis Units, MRI Facilities, Lab Facilities and study personnel become registered when their data are entered in the Form 600 System: Form 600, 601, 602, 603, and 604 in the FHN Study Database.

Consider Dialysis Unit 2304, El Camino Rose Garden. This dialysis unit is part of Clinical Center 23-Peninsula Satellite that is part of Core Consortium 2-UCSF. It is likely that the first three patients enrolled in baseline at this site will have ID numbers: 230401, 230402, and 230403. Data for the dialysis unit itself, unit 2304, would be key entered into Form 603.

A patient can be enrolled at one of the study clinical centers when the dialysis unit where the patient is treated has met all of the criteria enumerated in the Ready to Enroll report. . At this point, the unit becomes ready to enroll patients and the study coordinator will be able to key in and save a Form 100 (Nocturnal Study) or a Form 110 (Daily Study) enrolling its first patient.

5.4 Monitoring Site Registration

Progress in site registration will be summarized on the Ready-To-Enroll Report which are updated daily, and will be discussed on Steering Committee conference calls. Summaries of which sites are ready to enroll and which criteria are keeping other sites from becoming ready to enroll will be developed over the course of the study. These reports can be accessed on the FHN website.

5.5 Completing Baseline

Once a patient has enrolled in baseline with a Form 100 (Nocturnal Study) or a Form 110 (Daily Study), baseline procedures are performed as efficiently as possible. All baseline requirements must be met within 12 weeks from the visit date on Form 100/110 in order for a patient to be randomized.

Data to be collected during baseline are shown in MOP Chapter 2 for the Daily Study and in MOP Chapter 3 for the Nocturnal Study.

5.6 Checking Eligibility

At any point after a patient has been enrolled in baseline (i.e., Form 100/Form 110 in the database), anyone from the clinical center who has a database account can run a patient eligibility report for the patient by logging into the study database and selecting Reports>Patient Eligibility Report from the Menu. The Eligibility Report will show which required baseline forms and procedures have been done and which are still outstanding. The report will check if the data in the database support patient eligibility. If the report shows that a patient is not eligible, the reason(s) will be provided.

5.7 Randomizing Patients

When a patient's Eligibility Report shows that the patient is eligible to be randomized, the study team at the clinical center should meet to confirm that all staff members agree that the patient should

be randomized. The PI, Study Coordinator and others who have worked with the patient during baseline, should feel confident that the patient would come in six times a week for 12 months (if randomized to daily dialysis in the Daily Study) or that the patient would pass home nocturnal training and do home dialysis six nights a week for 14 months (if randomized to home dialysis in the Nocturnal Study). The PI, Study Coordinator and others who have worked with the patient during baseline, should feel confident that the patient will continue to participate in the study, perform needed tests and provide required data, whether he is randomized to the conventional group or the six-times a week group.

If the eligibility Report shows the patient to be eligible and the study team feels the patient will fully participate in the follow-up protocol, if randomized, the Study Coordinator or anyone from the clinical center who has a database account can randomize the patient by logging into the study database and selecting Reports>Randomize a Patient from the Menu.

5.8 Scheduling Follow-Up Visits

During follow-up, visits are scheduled on a calendar month system. Suppose a patient is enrolled in Baseline in October 2006 and randomized in December 2006. For that patient, Follow-up month 0 is December 2006. Month 1 is January 2007, Month 2 is February 2007, and so on, until Month 12 (when the patient has had 12 months of post randomization or follow-up data) is December 2007.

The database will accept data that are done outside of its recommended visit month. Even if the protocol says a measurement is done at F8, the database will accept it any month. Some data summaries will only consider the data to have been completed if it was done right in month 8, but it is anticipated that most data summaries will consider the data to have been completed if it is collected in the plus or minus one month visit window. Data required for F8 can be completed in months F7, F8, or F9.

Whenever possible, patient visits should be scheduled early in the month that they are required, so that there is time to complete the visit in the window even if the patient misses the first scheduled visit.

The study coordinator or her designee should schedule the visit. She should make sure the patient has any needed supplies (log forms, urine containers.) She should make sure that the patient receives a reminder call prior to the visit.

It is useful to have a graphic display of your clinical center's enrolled patients and where they are in follow up for each calendar month.

5.9 Coding Medications

The study has three medication-related forms, Form 203 for IV Iron, Form 204 for Injectable Medications, and Form 205 for all other medications (including over-the-counter meds). Medication will be coded by the data entry person during key entry by using the WHO Drug medication code

database. The data entry person enters characters in the drug's trade name or generic name, and then the data entry form displays a variety of drug codes with specific names. The key entry person selects and confirms the appropriate drug code, and saves it on the medication data form.

5.10 Coding and Reporting Adverse Events, Severe Adverse Events and Hospitalizations

Adverse Events (AE's) are coded and reported on Form 307 and Severe Adverse Events (SAE's) are coded and reported on Form 308. All hospitalizations are by definition SAE's and full details of hospitalizations are collected on Form 303. Refer to the individual forms for more details.

Diagnoses and symptoms will be coded by the data entry person during key entry by using the MedDRA database. The data entry person enters characters in the diagnosis or description of the symptom and then the data entry form displays a variety of diagnosis/symptom codes with specific names. The key entry person selects and confirms the appropriate code, and saves it in the database.

Note that Manual of Operations Chapter 25 describes the system for Outcome Committee review of hospitalizations.

5.11 Coding Deaths

Form 305 is completed to notify the database when a patient expires, and full details of the death are reported on Form 306. See the form for more information.

Table 5.1, Parts 1, 2 and 3 What makes a dialysis unit Ready to Enroll patients?

Part 1. We must know the following about the Clinical Center that the dialysis unit is under

• Consortium number (1, 2, or 3) • Clinical Center number • Name of the Clinical Center
Clinical Center Principal Investigator Name
Federal Express Shipping Address of the Clinical Center PI • Address Line 1 • City/Town • State/Province • Zip/Postal Code • Country • Telephone Number
Email address of Clinical Center Principal Investigator
Clinical Center Study Coordinator Name
Federal Express Shipping Address of the Clinical Center Study Coordinator • Address Line 1 • City/Town • State/Province • Zip/Postal Code • Country • Telephone Number
Email address of **the clinical center study coordinator**
One staff member trained in BIA
One staff member trained in Modified Mini-Mental
One CC staff trained in Trailmaking B
One CC staff trained in Feeling Thermometer
One staff member trained in Physical Function test
One staff member has successfully sent in a test repository kit
For Nocturnal Study: One staff member has been trained in Home Blood Pressure measures

Part 2. What do we need to know about the Dialysis Unit itself?

Item
Name of the dialysis unit
Mailing address of the dialysis unit
First name, last name of the medical director physician in charge of this dialysis unit
For U.S. Centers only: CMS (old HCFA) number for this dialysis unit
IRB Assurance number for IRB
Date main protocol submitted to this IRB
Date of IRB approval of main protocol
Date repository submitted to IRB (may be part of the main protocol)
Date of IRB approval protocol VERSION 2.1
Rural, suburban or urban status known

Part 3. What do we need to know about the MRI unit this dialysis center is linked to?

Item
a. Name of the supervising MRI physician in charge of the MRI unit
b. First Name, Last Name of the MRI tech
c. Federal Express Shipping Address of the MRI tech
• Address Line 1
• City/Town
• State/Province
• Zip/Postal Code
• Country
• Telephone number
d. Email address of the MRI tech
e. We need to know that one Staff Member of this MRI unit has done two test cardiac MRI's and submitted them to Sanjay and Sanjay approved both of them

Table 5.2 Summarizing "ready to enroll"

How the DCC will report summaries of "Ready to Enroll"

February 15, 2006

This is a page from the Ready to Enroll **Summary**. This report runs nightly and is automatically updated on the FHN website. Each clinical center will be able to review its status on any of its dialysis units at any time. This is a sample taken from the Daily Study Ready to Enroll Report.

Ready to Enroll Report - Daily Study	**11 RRI New York City (RRINY)**		
Questions	**1106 Queens Artificial Kidney Center**	**1108 Yorkville Dialysis Center**	**1109 Irving Place Dialysis Center**
Name, Number of Clinical Center----------(f601, q1)	Y	Y	Y
Clinical Center PI Name ----------(f600, q12)	Y	Y	Y
Fedex Address of Clinical Center PI ----------(f600, q10 a,e,f,g,h)	Y	Y	Y
Telephone Number of Clinical Center PI ----------(f600, q5,14)	Y	Y	Y
Email Address of Clinical Center PI ----------(f600, q4,14)	Y	Y	Y
Clinical Center Coordinator Name ----------(f600, q1,2)	Y	Y	Y
Fedex Address of Study Coord ----------(f600, q10 a,e,f,g,h)	Y	Y	Y
Telephone Number of Study Coordinator ----------(f600, q5,14)	Y	Y	Y
Email Address of Study Coordinator ----------(f600, q4,14)	Y	Y	Y
One Clinical Center staff member has done a holter which was approved by Chris Chan ----------(DCC files)	Y	Y	Y
One CC staff trained in BIA ----------(DCC files)	Y	Y	Y
One CC staff trained in Trailmaking B ----------(DCC files)	Y	Y	Y
One CC staff trained in Feeling Thermometer ----------(DCC files)	Y	Y	Y
One CC staff trained in Mod. Mini-Mental ----------(DCC files)	Y	Y	Y
One CC staff trained in Physical Function ----------(DCC files)	Y	Y	Y
One CC staff sent a test repository kit that was approved by NIDDK repository staff ----------(DCC files)	Y	Y	Y
One CC staff trained in Holter placement ----------(DCC files)	Y	Y	Y
Name, Number of the Dialysis Unit ----------(f603, q101)	Y	Y	Y
Local lab has been identified ----------(f602, q1,2)	Y	Y	Y
Name of medical director ----------(f603, q200,202,203)	Y	Y	Y
Dialysis Unit Address ----------(f603, q102 a,e,f,g,h)	Y	Y	Y
CMS (HCFA) number of the dialysis unit ----------(f603, q301)	Y	Y	Y
Assurance # for IRB this unit uses ----------(f603, q301)	Y	Y	Y
Date main protocol submitted to this IRB ----------(f603, q105)	Y	Y	Y
Date of IRB approval of main protocol ----------(f603, q107)	Y	Y	Y
Date of IRB approval protocol VERSION 2.1 ----------(f603, q107b)	Y	Y	Y
Date repository consent submitted to IRB ----------(f603, q108)	Y	Y	Y
Rural, suburban or urban status known ----------(f603, q110)	Y	Y	Y
Flow monitoring status known ----------(f603, q304)	Y	Y	Y
# of stations used at the unit knwon ----------(f603, q305)	Y	Y	Y
# of patients that could be treated known ----------(f603, q306)	Y	Y	Y
Profit, nonprofit, mixed status known ----------(f603, q307)	Y	Y	Y
Water standard status known ---------- (f603, q308)	Y	Y	Y
Ultra filters for pure water on majority known----------(f603, q309)	Y	Y	Y
Dialyzer reuse status known ----------(f603, q312a)	Y	Y	Y
Volumetric control of hyper filtration ----------(f603, q310)	Y	Y	Y
Experience with Frequent In-Center Dx ----------(f603, q311a)	Y	Y	Y
# in-center frequent patients before FHN ----------(f603, q311 a,c)	NA	NA	NA
MRI Facility to be used ----------(f604, q1 & f603 link)	Y	Y	Y

Ready to Enroll Report - Daily Study	11 RRI New York City (RRINY)		
Questions	**1106 Queens Artificial Kidney Center**	**1108 Yorkville Dialysis Center**	**1109 Irving Place Dialysis Center**
Name supervising MRI Physician----------(f600, q14 & f603, q202,203)	Y	Y	Y
Name of at least one MRI Tech ----------(f600, q14 & f603, q202,203)	Y	Y	Y
MRI tech Fedex address ----------(f600, q11 a,e,f,g,h & f603 link)	Y	Y	Y
Telephone # of MRI tech ----------(f600, q5,14 & f603 link)	Y	Y	Y
Email address of MRI tech ----------(f600, q4,14 & f603 link)	Y	Y	Y
2 test case MRIs approved by MRI Core			
"	Y	Y	Y
Reviewed talking points with Core Consortium PI ----------(DCC files)	NA	NA	NA

6. Computing and Data Entry

6.1 Computing systems overview

Computing for FHN can be divided into two broad areas: computing at the Clinical Centers and computing at Data Coordinating Center (DCC). The purpose of this overview is to describe in general terms how these systems are organized.

Each Clinical Center has at least one personal computer. These PC's will be used, for study purposes, to run software for communicating over the Internet to the DCC. They may additionally be used for a variety of tasks useful for the centers' work related to the study, such as word processing.

To connect from your PC to the DCC (located in Cleveland, Ohio, at the Cleveland Clinic Foundation), you will be making use of the Internet, a world-wide network of computers, composed of and supported by primarily academic, governmental, and non-profit institutions. Using the Internet, you will be able to interact with the DCC's computers in Cleveland.

The PC that sits in your office is not directly connected to the Internet. You must first connect from your PC to a nearby computer that is on the Internet, and then from that computer to the DCC. This nearby computer is called an Internet "node." Just what kind of computer each center will connect to in order to access the Internet will vary from center to center. Some centers will be connected to computers at their institution that are an Internet node. This connection might be through a campus network, or it might involve dialing up the institution's computer over a phone line using a modem. Other centers will be utilizing a public provider of Internet access for a small monthly fee. Connecting to such a service will involve making a local phone call to connect using a modem. In either case, this manual will refer to the nearby computer to which the FHN center's personal computer connects to gain Internet access as the Local Internet Provider (LIP).

The DCC's computer is also connected to the Internet. Hence, connecting from your personal computer to your LIP allows you to reach the DCC across the Internet. In fact, you'll be using the DCC's computer directly when you enter data, and receive reports and mail messages from the DCC.

6.2 Your FHN Study personal computer

Each Clinical Center is required to have a minimum of one PC dedicated to the purposes of the FHN Study. The DCC's recommended specifications for your PC are as follows:

PC specification
A 500 Mhz or better PC is required.

Monitor
Color monitor.

Internet connection

A live connection to the Internet.

Browser software
Netscape Communicator 4.77 or Internet Explorer 5.5 or higher. Adobe Acrobat Reader 4.05. Oracle Jinitiator 1.1.8.14. These can be downloaded from the DCC's website.

Web site downloadable utilities

The website https://clinapps.bio.ri.ccf.org/download.html
a number of files needed to fully utilize the FHN Consortium web application. Included are: (1) Netscape Communicator version 4.77 cc32d477.exe (2) Adobe Acrobat Reader version 4.05 rs405eng.exe (3) Oracle JInitiator version 1.1.8.14 jinit11814.exe The following steps must be performed in the order given below: 1) If you do not have Netscape 4.77 already installed, install it by double-clicking on cc32d477.exe This is the latest version in the 4.x series. We've seen numerous problems with the 6.x Netscape and do not recommend it at this time. 2) Double-click jinit11814.exe to install (accept all defaults). This is a thoroughly debugged and Oracle-certified version of Sun Microsystems's Java Plug-In which replaces the browser's built-in Java Virtual Machine when the FHN application is run.
Once these components are installed:
Please go to https://clinapps.bio.ri.ccf.org/ and follow the links to FHN and then log in to the appropriate database.
NOTE: Using Netscape 6.x and Jinitiator
Aside from other directions in the computing section of the MOP and the above, the user still might not be able to run the application and gets the message to 'Get Plug-In' even after JInitiator had been installed. The problem is that the plug-in, NPJinit-11814.dll, may not have been copied to the correct directory. It needs to be in the Netscape Plug-Ins directory along with other Java dlls. This seems particularly true for Netscape 6 and higher especially if there is a previous version of Netscape installed. To do to this, use the Windows 'Search' or 'Find' utility (Depends on which version of Windows OS). Once you have located 'NPJinit-11814.dll' copy it to the Plug-Ins directory under the current version of Netscape if it isn't there already.

6.3 Accessing the DCC website to enter data

See Appendix A for instructions on how to set up your PC to access the DCC's website.

The forms were designed assuming a user desktop area setting of 800 x 600.

There is currently a one hour idle time setting in effect. If the one hour idle time is exceeded, the user will see an error message containing the text "ORA-03114". To fix the problem, please log out and then log in again.

After you have successfully entered the website, you will see a menu titled "FHN Study". At this point, resize the window to the largest that will fit on the screen for optimal

viewing. You can then choose a form or report from the menu, or you can go to the "Query" menu to answer or view your queries.

6.4 Passwords

You will have an Oracle database username and password. The username is the first six characters of your last name followed by the first character of your first name. Please do not share passwords. Passwords will need to be changed every 75 days. Oracle passwords are NOT case sensitive; i.e., it does not matter if the cap lock is on.

Your new password must be at least 6 characters long.
Your password must contain at least two alphabetic characters.
Your password must contain at least one numeric character.
Your password must differ from your old password by at least 3 characters, or not match any of the three past passwords.
Your password cannot contain quotation marks OR ANY OTHER SPECIAL CHARACTERS.
Your password must begin with a LETTER.
Your password should not be a common word, a proper name, or a common phrase.

Selecting a good password

Here are some good references for picking a good password:

http://www.net.berkeley.edu/dcns/faq/good_pw.html

http://www.msc.tamu.edu/services/cops/security/goodpasswd.html and

http://www.cs.umd.edu/faq/Passwords.shtml

Please read them all as they all have good advice

Changing your password

There is a menu option available to change your password.

6.5 Instructions: How to enter study data into the database

Press enter, tab or click your mouse to move from field to field within a form. Note that you will see bubble help when you move your mouse over the top buttons. The upper left button should be the save button. When you are finished entering data for a form, click on the save button, or choose "Save" from the "Action" menu, or press the F10 (Accept or Commit) function key. The F10 key corresponds to the Oracle function "Accept" or "Commit". You will see a message at the bottom of the screen indicating how many new records were added to the database. You can get out of a form by pressing the "Exit" button or choosing "Exit" from the "Action" menu. There is also a speed key for this. If you want to enter another form you should navigate to the top of the form, and press the "Insert Record" button. "Insert" can be selected from the "Record" menu. Unfortunately, you are not permitted to remove records once you have saved/committed them. You will need to send the DCC a query to do that. You are also not permitted to change certain key

fields or fields that determine eligibility. Again, you will need to send a query to the DCC.

Keymappings
Ctrl+F1 means hold down the <Ctrl> key and then simultaneously press the <F1> key. Now release <F1> and then <Ctrl>. Another way to get to the key mappings is to choose "Keys" from the "Help" menu.

List of values (LOV)
Note that you may see messages on the bottom of your screen. If you see "List of Values", that means you can choose "Display List" from the "Edit" menu, or press F9 to retrieve a list of values to your screen which you can scroll through and make a selection.

Editing
If the field is smaller than the text you are typing into it, you can choose "Edit" from the "Edit" menu, or press Ctrl+E when your cursor is in that field. This will open up a pop-up box containing a larger view of that field. Use this also for viewing.

Navigation
Other useful Oracle functions that you can use are "Next Record" and "Previous Record". You can find buttons and speed keys for these and they are also on the "Record" menu. Use these to navigate between forms or detail records (for example, in medication forms).

Error messages
If you skip over a required field, you will see the error message:

Field must be entered.

If you enter a value that is not possible for that field, you will see the error message:

Invalid value for fieldname.

If you enter a non-numeric character in a numeric field, you will see the error message:

Legal characters are 0-9 - + E.

If you try to update previously entered data without using the [Change Value] button, you will see

Field is protected against update.

You will also see other various error messages as well. If you can't figure out why you are getting that particular error message, please write down the complete message, and also choose Help->Display Error while the message is on the screen to see if a further explanation pops up before calling us. If you get stuck, it may help to use [Cancel Query] or Query->Cancel (if you see "Enter-Query" on the bottom of your screen), Action-

>Clear All or Record->Clear

6.6 Instructions: How to change study data in the database

Retrieving data

Once the data has been entered, you can retrieve it to your screen for viewing:

· Access the form # you want to view.
· Press the [Enter Query] key or button.
· Note the hint line will say “Enter-Query”.
· Enter the Patient ID and visit number. Note that visit number is not applicable for some forms.
· Press the [Execute Query] key or button.

Real-time changes

Clinical Centers can change data within 7 days and the new value is acceptable to the database:

Query the data from the appropriate from.
Position cursor on field to be changed, and then press the [Change Value] button.
Type in the new value.
If multiple fields within the same form need to be changed, repeat the above, starting with positioning your cursor in the new field.
You will receive a data change number for each field that you change.
You will need to save (commit) the data before you leave the form.
If a desired change does not pass an edit check, then none of the changes will be saved if you have made multiple changes. If you quit out of the form at this point the data change numbers will be discarded, but before you quit out of the form, you may be able to change the unacceptable value back to its original state, and then save the form again. Otherwise, you may need to quit out of the form and make the (acceptable) changes again, or make the changes one at a time, saving the form in between each change.
See the section entitled "Data Change Within 7 Days But the Database Will Not Accept It" for how to handle the changes that do not pass the edit checks.

Data change within 7 days but the database will not accept it

Retrieve the data.
Position the cursor on the field where changes were rejected.
Press the [Change Value] button.
Press [Enter] only.
A pop-up box will appear asking if you would like to send a query.
Answer “OK” to the popup box.
A new screen will appear that will allow you to enter a requested value and an explanation.
You will receive an inquiry number after you save the request. You can use this number to check to see if the DCC signed off on your inquiry.
After investigating, the DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.

A “DCC Sign-Off to CC Initiated Data Inquiry” will be sent to the DCC and CC. No further action is required.

Clinical Center change to data after 7 days

Retrieve the data.
Position the cursor on the field to be changed (only make one change per each inquiry).
Press the [Change Value] button.
A new screen will appear that will allow you to enter a requested value and an explanation.
Enter the new value as well as text describing the desired change. The DCC will use this response to investigate the request.
You will receive an inquiry number after you save the request. You can use this number to check to see if the DCC signed off on your inquiry. (Also document this number on the hard copy of the form).
The DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.
A “DCC Sign-Off to CC Initiated Data Inquiry” will be sent to the DCC and CC. No further action is required.

6.7 Instructions: How to initiate and respond to queries

Clinical Center Initiation of Queries

Queries can be initiated by the Clinical Center as described in the above section on changing data.

Clinical Center response to a DCC initiated inquiry

You will receive a DCC initiated inquiry report through e-mail, or you can go to the Main menu, choose "Forms" → "Inquiry Forms" → "Center Response to DCC Inquiry" to find unanswered queries.
When the screen appears you can press [Execute Query] to retrieve all unanswered queries, or press [Enter Query] and enter the query # and then press [Execute Query]. If you do not enter an inquiry number all unanswered queries will be retrieved. You need to press [Next Record] to navigate to the other queries. Keep pressing [Previous Record] to get back to a previous query.
Position your cursor on the “DCC text” field.
Choose Edit->Edit if you want to read the entire explanation from the DCC as to why you are being queried.
Navigate to “New Value”.
Type a new value for the field being inquired. If a different field requires changing, leave it blank or enter N/A for not applicable.
Navigate to “CC text”, and enter an explanation for your value. This field must be answered in order for the DCC to take action. Please make sure that your explanation is specific and complete.
The explanation can be up to 2000 characters. Click on the [Save and Exit] button on the bottom of the screen to save the text. Click on [Exit and Don’t Save] if you do

NOT want to save the text.
The DCC will then make the appropriate updates to the database.
It is very important that the CC respond within 3 business days.

6.8 E-mail alias lists

From your center's FHNxxxx study account at the DCC, you will have access to several pre-defined distribution lists. These include:

fhn-steering@bio.ri.ccf.org - lists all Steering members
fhn-steeringplus@bio.ri.ccf.org – lists all Steering Committee members plus key others
fhn-dcc@bio.ri.ccf.org - lists all DCC members
fhn-rri@bio.ri.ccf.org – lists those in the RRI Daily Consortium
fhn-ucsf@bio.ri.ccf.org – lists those in the UCSF Daily Consortium
fhn-wake@bio.ri.ccf.org – lists those in the Wake Forest Nocturnal Consortium
fhn-xxx@bio.ri.ccf.org – lists those in Committee XXX

A complete list of these e-mail addresses can be found in the FHN address directory.

6.9 Retrieving data from forms

Introduction

Data can be retrieved in several ways from the form application. In order to "query" data available in the database for the information on a given form application, the [Enter Query] and [Execute Query] functions can be used. The screen will be populated with the first set of patient data for the form application being accessed. By using the [Next Record] or [Previous Record] functions (record menu or triangular buttons just below the menu), you will have the ability to view the next or previous set of data.

There are different ways to retrieve data. You can execute simple queries that meet specific criteria, as well as complex queries that satisfy several conditions. The following topics are discussed.

· Matching exact values
· Entering variable conditions
· Matching values that meet a specified pattern

Matching exact values

Suppose you want to check on all instances of visits of the follow-up type for a given patient ID (10001 for example). The data entry screens can retrieve the record(s) that contains specifically these values. The following are general steps for retrieving records that match exact values:

1) Access the appropriate form via the menu system.
2) Use the [Enter Query] function.
3) Type the values you want to match into the appropriate fields.
For this example, cursor to the Patient ID field and type 10001.

4) Use the [Execute Query] function.
5) Use [Next Record] or [Previous Record] to view the retrieved data.

NOTE: If no data meet the specified criteria, the following message will be displayed on the status line of your screen:

"FRM-40301: Query caused no records to be retrieved. Re-enter."

You must use [Cancel Query] if you decide not to complete the initiated query.

Entering variable conditions

Sometimes it is not practical to enter the exact values that you want retrieved data to match. For example, you might want to retrieve the following:

· All Form 203's with visit type = F and visit number >6
· All Form 203's after 12/31/2005

Rather than entering an exact data value, you can enter a relational operator before the data values in one or more fields.

The following table shows some relational operators typically used:

Operator	Meaning	Example
=	equal to	= '01/01/2006'
!=	not equal to	!=6
>	greater than	>6
>=	greater than or equal to	>=6
<	less than	<6
<=	less than or equal to	<=6

For example, to select data that have a visit number >6, press [Enter Query] and type >6 on visit number field and press [Execute Query]. To select any Form 203's after 12/31/2005, press [Enter Query], type >=01/01/2006, and press [Execute Query].

Using pattern matching

Pattern matching provides the capability to fetch data where a value for a field fits a certain pattern. This is useful when specifying search criteria on "string" or character value fields.

When specifying a pattern "_" represents any single character and "%" represents any combination of characters. The "_" and "%" symbols are referred to as wild cards.

For instance, suppose you are interested in all patients that have the letter “A” in their Alpha Code.

1) Access any data entry screen containing Alpha Code.

2) Use the [Enter Query] function.
3) Place your cursor on a blank Alpha Code field.
4) Type %A% (case sensitive).
5) Use the [Execute Query] function.
6) Use the [Next Record] and [Previous Record] functions to view the retrieved data.

To further refine the search, to find all patients with an “A” and a “B” (“A” is before “B”, but not necessary beside “A”), restart the process by using [Enter Query], type %A%B in the alpha code field, and then use [Execute Query}.

Count query hits

If you are interested in simply a count of how many records meet your search criteria, use the [Count Query Hits] function in place of the [Execute Query] function. Rather than having a screen full of data returned to your screen, you will receive a message indicating the number of "records" that meet the search criteria. For example, you will see something such as the following:

"FRM-40355: Query will retrieve 3 records"

This function can be helpful if you are interested in determining a count of patients that meets some specific criteria.

Notes:
Queries can be issued in the first block of multi-block forms.

7. CARDIAC MAGNETIC RESONANCE IMAGING (CMRI)

FREQUENT HEMODIALYSIS NETWORK

CARDIAC MAGNETIC RESONANCE IMAGING (CMRI)

MANUAL OF OPERATIONS

Version 3.1
June 10, 2011

Cardiovascular Imaging Core Laboratory (CICL)
for the Daily Hemodialysis Trial and the Nocturnal Hemodialysis Trials

Table of Contents

A. INTRODUCTION

A.1 Overview

This document is the manual of operation for the cardiac magnetic resonance imaging (CMRI) in the Daily Hemodialysis (DHD) Trial and the Nocturnal Hemodialysis (NHD) Trial. This manual is provided by the Cardiac Imaging Core Laboratory (CICL) to standardize the CMRI procedures among the clinical sites participating to the DHD and NHD trials. In particular, this manual of operation describes the procedures for CMRI scan execution, image acquisition, image submission, and image analysis.

A.2 Rationale for a Cardiac Imaging Core Laboratory (CICL)

As part of the DHD and NHD Trials, measurements obtained from CMRI scans in two separate intervals will be used to provide information on the efficacy of frequent dialysis on left ventricular mass regression (primary end-point) and in improvement of left ventricular volumes, functional indices and aortic stiffness (secondary end-points). These end-points (for CMRI, in particular) although highly reproducible and applicable to the clinical trial context are still subject to performance and measurement variability. The purpose of this manual is therefore to ensure a standardized approach to image acquisition and analysis.

A.3 Location and function of the CICL

The core lab is located in the OSU Division of Cardiovascular Medicine in Cardiac MR/CT Section
The primary goal of the CICL is to assist for the acquisition of the data related to the primary and secondary end-points for both the trials. In brief, as part of this process the CICL will accomplish the following: 1. Determination of appropriate image acquisition parameters and scanning protocol; 2. Establishment of standards for the submission of images and data; 3. Assessment of the eligibility of sites to perform studies; 4. Certification of each site's readiness to begin imaging studies; 5. Training of participating sites in implementation of appropriate protocols for consistency; 6. Establishment of quality control measures; 7. Performance of studies in patients enrolled in investigator sites located in the CICL area; 8. Data analysis; 9. Quality Control; 10. Transmission of final results to the data-coordinating center.

A.4 Contact Information at the CICL

Cardiac Imaging Core Laboratory (CICL) Coordinator
Floor 3, Room 398 Biomedical Research Tower
Ohio State University
460 West 12th Avenue
Columbus, OH 43210-1252
Tel: 614-247-7760
Fax: 614-688-4233
Email: sanjay.rajagopalan@osumc.edu

B. PRELIMINARY SITE QUALIFICATION

Prior to enrolling any study subjects into the imaging study section of the trials, the appropriate CMRI hardware and software specifications should be confirmed as being acceptable. For CMRI, the magnet will need to have the following minimum gradient performance characteristics: peak strength ≥ 12 mT/m, slew rate ≥ 40 mTm/s (ideally ≥ 20 mT/m and ≥ 100mT/m/s, respectively). The pulse sequence employed for evaluation of ventricular mass and volumes will be steady state free precession (SSFP). This goes by a variety of proprietary names depending on the vendor: TrueFISP® (Siemens, Erlangen, Germany), FIESTA® (General Electric,Milawaukee, USA), BFFE® (Philips Medical Systems, Best, Netherlands). All images will need to be retrospectively triggered.
All candidate sites are required to submit test cases and Scanning parameters forms (Appendix 1 and 2) to the CICL to obtain site qualification.

B.1. Training Sessions

The CICL will conduct online training sessions on multiple occasions for sites on the protocol requirements and scanning procedure for Cardiac MRI in the trials. The tests will be provided based on demand (rate of inclusion of new imaging centers in the trial). The training sessions are designed by Drs. Rajagopalan and Sanz, and lead by Dr. Sanz. Multiple training sessions are held because of the different availability of the imaging centers, and the core lab. This is individualized with each imaging center(s). The success of the training will be determined by the test cases that each imaging center needs to submit to the core lab before certification for participation in the trial. These studies must be acquired and submitted according to the MOP specifications.

B.2 Test cases

The test cases should include CMRI images as specified in this manual. The submission of 2 CMRI test cases is required for inclusion as a CMRI site.
The images for these cases should be acquired in the format recommended in this manual. CMRI studies should be performed following the protocol specifications. The test cases submitted to the CICL can be past exams from your institution, as long as these cases have been performed in conformity with the required procedures. The instructions for test-cases image submission to the CICL are reported in section E (Images submission).
The Quality Review Laboratory of the CICL will process the images and the study site notified of the results. After the notification, the site may begin submitting CMRI from enrolled patients as specified in the study protocol. If the test images are not initially acceptable, the CICL will work with the site to identify solutions to improve image quality and protocol conformity (additional test cases will likely be requested). Specific training from the CICL is available for candidate centers.
Once two designated technicians have completed training in protocol specified image acquistion at each site, those persons can supervise other technicians in collecting scans according to the study protocol. The additional technicians are not required to go through the CICL training.

B.3 Scanning parameters form

Specific imaging parameters are required in this study. To assess the technical adherence of the candidate site to the prescribed parameters (see Sections C and D). CMRI Scanning Parameters Form (Appendix 1) should be completed for each of the test cases. These parameters will be updated on a yearly basis to ensure adherence to the protocol.

C. CMRI EXAMINATION

C.1 PATIENT PREPARATION FOR CMRI

This is detailed in Appendix 2, which also includes a list of contraindications for the procedure. As a general rule, subjects in whom CMRI studies are contraindicated will not be included in the trials. During the enrollment process, patients will be screened for the presence of such contraindications and an informed consent will be obtained. The imaging sites are however expected to perform a brief survey of contraindications (i.e. presence of metallic objects), following standard MRI safety procedures. Please also note the recommendations regarding patients with atrial fibrillation outlined in Appendix 2.

C.2 CMRI SCANNING PROTOCOL

The appropriate imaging hardware and software specifications should be confirmed as being acceptable and the designated imaging pulse sequence needs to be available on the CMRI scanner. Cross Vendor Lexicon reference is available at the website http://www.scmr.org/technologists/crossvendorlexicon.pdf. If it is necessary to deviate from the protocol due to equipment or software issues, the local investigators should contact the CICL prior to imaging a study patient.

Entry of patient ID number on the scanner: Enter the patient's Study Identification Number in the 'Last Name' and `Patient ID' fields on the scanner. The patient's Study Identification Number is the number that has been assigned to the patient when initially enrolled in the trial. If you do not know the patient's Study Identification Number, please contact your local study coordinator. In addition to the patient's Study Identification Number, please enter the date of the CMRI scan. All clinical (underlying diseases) and/or demographic data, such as age, gender or ethnicity, should be specifically excluded from the images.
ATTENTION: DO NOT ENTER INFORMATION THAT MAY DISCLOSE PATIENT IDENTITY.

Patient Positioning and ECG Gating (for patient preparation and scan time sequence see Appendices 2 and 3): Position the patient on the table with ECG leads applied and a phased-array receiver coil placed correctly on the chest for highest signal intensity cardiac imaging. It is crucial to achieve a high quality ECG signal to ensure accurate cardiac triggering and optimum image quality. If it is not possible to obtain adequate ECG gating, peripheral pulse gating with an appropriate plethysmographic device will be accepted as an alternative. This would need to be documented in the CMRI Mailing Form 251 (see Appendix 6).
THIS PROTOCOL DOES NOT REQUIRE IV ACCESS.

Breathing instructions: The patients should be advised to hold their breath at a relaxed point in end-expiration. The patients should not be instructed to "blow all the way out" or to hold their breath after forced end-expiration as this curtails the breath hold time. Test breathing instructions before starting the examination may be useful to confirm that the subjects understand what they are expected to do.

Brief protocol synopsis

Standard scout images leading to double oblique horizontal long axis (4-chamber view) of the heart

1. Cine images of the horizontal long axis view of the heart (4-chamber view)
2. Prescribed double oblique short axis view of the heart with the first slice above the insertion point of the mitral valve.

3. Cine images of the short axis of the left ventricle (LV) from the position in 3 (copy image position) extending proximal to this portion, to the apex to allow full and complete coverage of the LV.
4. Prescribed remaining long-axis views of the heart (2-chamber view, LV outflow tract view) and cine images from these positions.
5. Cine image of the LV outflow tract perpendicular to the 3-chamber view.
6. Cine image perpendicular to the ascending aorta for the evaluation of aortic stiffness.

Recommended sequence parameters and tips for optimal image quality
(for the complete list of scan parameters see Appendices 4 and 5)

Ventricular function (Appendix 4)

1. Steady state free precession (SSFP) imaging sequences [True-FISP (Siemens); FIESTA (GE); Balanced FFE (Philips)] should be retrospectively ECG-gated and performed in end-expiration.
2. Slice thickness of 8 mm with 2-mm gap between slices.
3. Temporal resolution <45 ms.
4. Flip angle maximized (>60°).
5. On obtaining the first short axis on a double oblique cut begin basally to the mitral valve (atrial level) to ensure full coverage of the LV for mass calculations.
6. Proceed to obtain sequential short axis cine loops of the entire LV all the way to the apex until the apex cannot be seen.

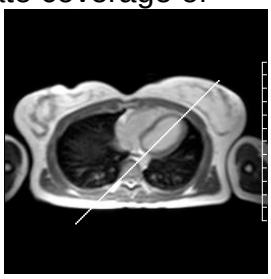
Aortic stiffness (Appendix 5)

1. Steady state free precession (SSFP) imaging sequences [True-FISP (Siemens); FIESTA (GE); Balanced FFE (Philips)] should be retrospectively ECG-gated and performed in end-expiration.
2. Slice thickness of 8 mm.
3. Temporal resolution ≤30 ms.
4. To ensure an adequate perpendicular orientation to the ascending aorta, prescribe your plane using both LV outflow tract cine views as references.
5. Check that the imaging plane remains above the sinotubular junction at all times during the cardiac cycle.

C.3 CMRI SCAN SEQUENCE

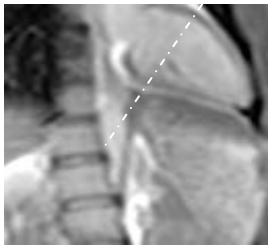
- Localizers and Cardiac Scout Images

Obtain initial multiplane thoracic localizer images (sagittal, coronal and transverse) with the heart at the center of the magnet bore. For higher accuracy it is preferable to have the localizer images acquired during a breath-hold. Confirm that all your coils are turned on and appropriate coverage of the area of interest is obtained. If not, reposition the coils and/or patient.

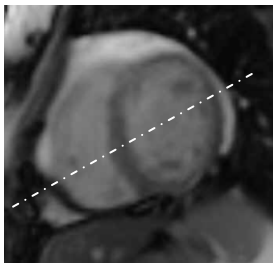


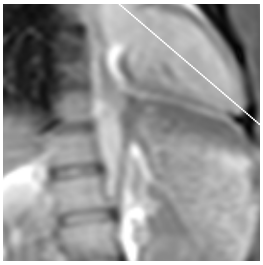
Two-Chamber Scout: Using the best axial (pseudo-4 chamber) localizer image, prescribe an imaging plane that bisects the LV taking care to ensure that the plane traverses the apex.

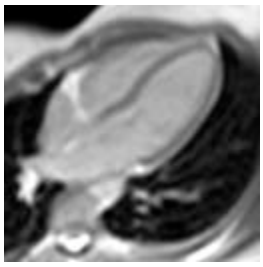
Short-axis Scout: Using the 2-chamber scout prescribe a plane parallel to the mitral plane and perpendicular to the LV long axis.



Four-chamber Scout. From the short-axis and two chamber scouts, prescribe a plane that transverses through the center of both ventricles, center of the mitral valve and the LV apex, to generate a double oblique horizontal long axis view (4-chamber).





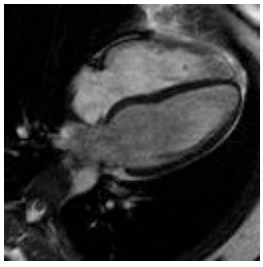


- ***Cine Images***

The sequence used for the cine mages is SSFP [True-FISP (Siemens); FIESTA (GE); Balanced FFE (Philips)] with retrospective ECG gating and breath-hold imaging. Prior to obtaining the cine images, the scan parameters should be checked on the scanner (see Appendix 4). It is recommended that once the participating sites have been certified by the CICL after submission of the test images, the imaging parameters are saved as a separate identifiable protocol on the scanner (e.g. frequentdialysis_CMRI). This will help minimize operator-dependent variability should different technologists perform the studies in various time-points.

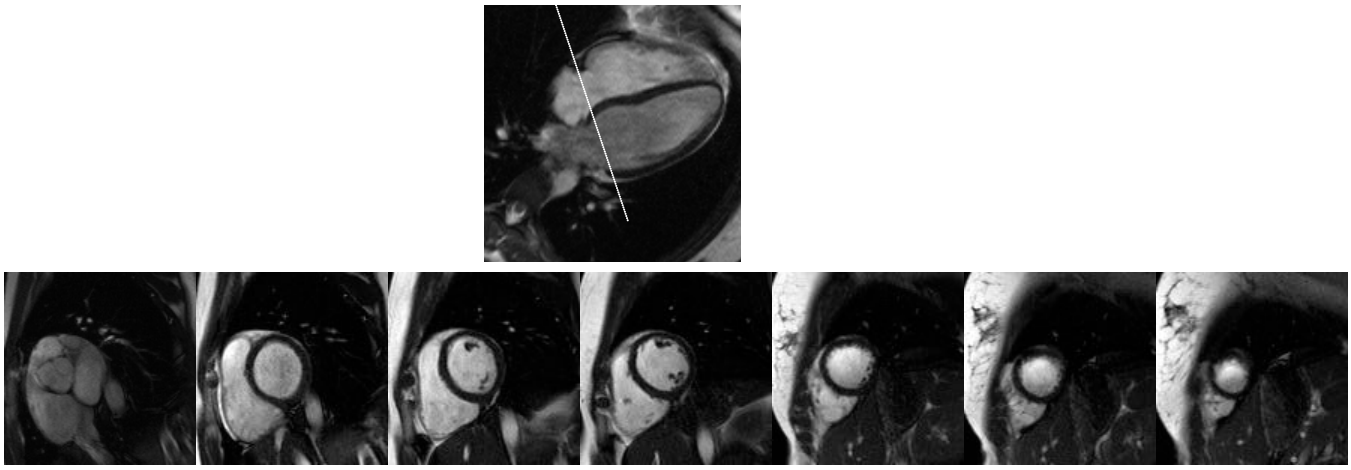
Cine images are acquired once the desired 4-chamber localizer displayed above is obtained.

Four-Chamber Cine: This is acquired by copying the image position from the 4-chamber scout image and running the cine sequence using the parameters outlined in Appendix 4.



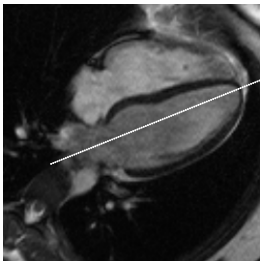
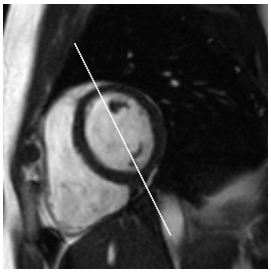
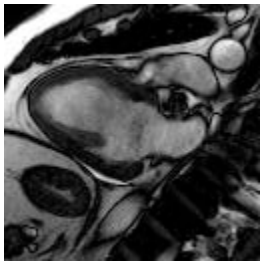
Short-axis cines: These are prescribed from the 4-chamber cine images. The short-axis images are to be correctly acquired as improperly oriented images may result in errors during analysis. A plane perpendicular to the interventricular septum is chosen. The short axis stack should begin above the level of the insertion points of the mitral valve (atrial level) and proceed towards the apex. Confirmation of the “double oblique” orientation as well as perpendicularity to the septum/anterior wall is recommended by simultaneously comparing the orientation on the 4-chamber and 2-chamber scouts. Once a single short axis cine-loop has been obtained at the most basal level, you may

proceed from this level in 8 mm (2-mm gap) intervals to the apex, ensuring complete ventricular coverage.

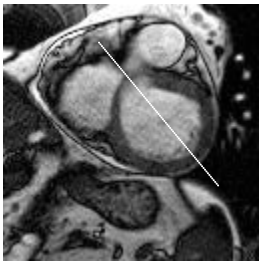
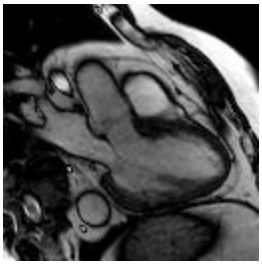


It is vitally important to provide complete anatomic coverage of the ventricle from the base to the apex. It is good idea to get images all the ways through till you do not see any apex. If one or more of the short axis slices are of sub optimal quality (due to motion artifacts, gating problem) please repeat the acquisition until adequate images are obtained. Indicate in the CMRI Data Acquisition Form (see Appendix 6) which series number is the “best” acquisition for a certain slice position.

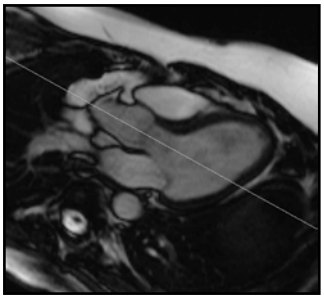
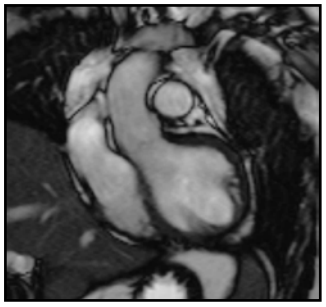
Two-Chamber Cine: This can be obtained from the 4-chamber view by drawing a line that passes between the mitral valve leaflets and extending to the apex of the LV. On the short axis images this plane should pass through the anterior and inferior walls and should pass right through the apex. The orientation when correctly placed should not include the right chambers.

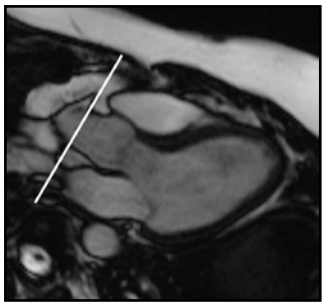
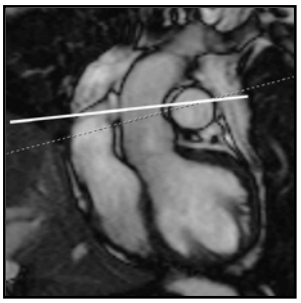
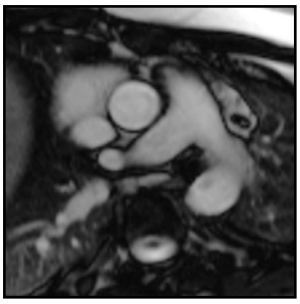
LV outflow tract view: This should be obtained by prescribing a plane that passes through the outflow tract on a short-axis cine movie-loop where one visualizes the outflow tract. The plane should pass through the apex and this can be confirmed in other views.

Cine image of the LV outflow tract: Obtain a cine loop perpendicular to the 3-chamber view, aligning your plane along the LV outflow tract and ascending aorta.

Ascending aorta: Prescribe a cine loop parallel to the plane of the aortic valve annulus and perpendicular to the ascending aorta using both LV outflow tract views as references. Ensure that this plane remains above the level of the sinotubular junction (defined as the junction between the sinuses of Valsalva and the tubular ascending aorta; dashed line on the image) at all times during the cardiac cycle. Remember that the scanning parameters for this acquisition differ from the prior cine loops (see Appendix 5). Because of more prolonged imaging time for this specific acquisition, it is a good idea to warn the patient that this breath-hold will be longer. If the subject cannot complete the breath-hold, repeat the acquisition using some of the tips outlined in Appendix 5 to reduce scanning time.

C.4 CMRI SAFETY GUIDELINES

Dialysis patients undergoing CMRI do not require specific safety measures above and beyond routine precautions that apply to the performance of CMRI in general. Updated information about biomedical devices that may impose a risk to patients undergoing MRI is available on the Internet at www.MRIsafety.com. Each clinical site should have written safety guidelines, practices and policies previously established for patients undergoing CMRI as well as for the personnel participating in patient care in the MRI department. All study patients should undergo the routine screening process for the presence of contraindications to MRI that is routinely used by the local department. In addition to the exclusion criteria specified in the protocol, patients with implanted biomedical devices that are not MRI safe or that may result in imaging artifacts are to be excluded. In addition, patients who have a history of claustrophobia who are unable to lie flat, hold their breath for at least 12 seconds or who are too large to fit in the bore of the scanner are to be excluded. General guidelines and standard practices should be followed. This would include institution of oxygen if needed, monitoring of heart rate and blood pressure.

D. IMAGES SUBMISSION

(See also section B.2)

The same protocol should be followed every time during submission of CMRI cases to the CICL.

Data Archiving and Submission: The complete CMRI studies (including scout images, repeated acquisitions for CMR) should be copied to a CD or DVD in DICOM compatible format. The only unique identifiers that should be included in this DICOM header are the center number, the patient ID number (will be assigned by the DCC) and the date of the scan. Prior to saving the DICOM file it is important to ensure that the patient name, social security number and hospital related identifiers are completely removed in order to protect patient confidentiality. In addition, there should be no other information contained in the DICOM header of the image or written on the CD/DVD that would disclose the identity of the patient for HIPAA compliance reasons (According to the United States Department of Health and Human Services, a covered entity [e.g. a hospital] may always use or disclose for research purposes, health related information which has been de-identified (in accordance with 45 CFR 164 502(d) and 164.514(a)-(c) of the rule; for more information visit www.os.dhhs.gov/ocr/hipaa/guidelines/research.pdf).
A copy of the CD should be maintained at the site.

CD/DVD Labeling: The CD/DVD should be labeled on the non-recording surface with a pen that has indelible ink. The data that should be included on the label is: center number, patient ID number and date of CMR scan.

Data Forms: Complete the CMRI Mailing Form 251 (Appendix 6). This Form will be provided to you by the local study coordinator. Return the CMRI Mailing Form 251 and the 2 CDs to your local study coordinator. The study coordinator will fax the CMRI Mailing Form 251 with the Data Submission Form (Appendix 7) to the CICL at 888-362-0639. This notifies the CICL coordinator that CD's from the site are to be expected soon.
In addition, the study coordinator will need to mail the CMRI Mailing Form 251 and the CD of the patient's study to the CICL.

Test cases: The images acquired for the initial test cases need to be sent using the same protocol described above. Each test case should be sent in DICOM format on a separate CD/DVD. The CD/DVD should be appropriately labeled with the patient's Study Identification Number (for the test cases: TEST-1 and TEST-2), Center Number and the date of study. A CMRI Mailing Form 251 should accompany each CD/DVD. In addition to the CD/DVD and CMRI Mailing Form 251, each test case must be accompanied by a CMRI Scanning Parameters Form (Appendix 1). The CMRI Scanning Parameters Form provides the CICL with technical data regarding the imaging protocol to ensure adherence to the Trial standards and reproducibility of imaging techniques amongst centers. The local study coordinator will mail the CD, CMRI Mailing Form 251 and the CMRI Scanning Parameters Form to the CICL for each test case. Prior to shipping the CD/DVD's and forms, the local study coordinator will also fax a copy of each Data Submission Form and CMRI Mailing Form 251 to the fax number above. These forms are identical to those that will be used for actual data submission and would provide a trial run for appropriate form submission as well

E. ANALYSIS PROTOCOLS FOR CARDIAC MR IMAGES
E.1 PRE-ANALYSIS LOGISTICS

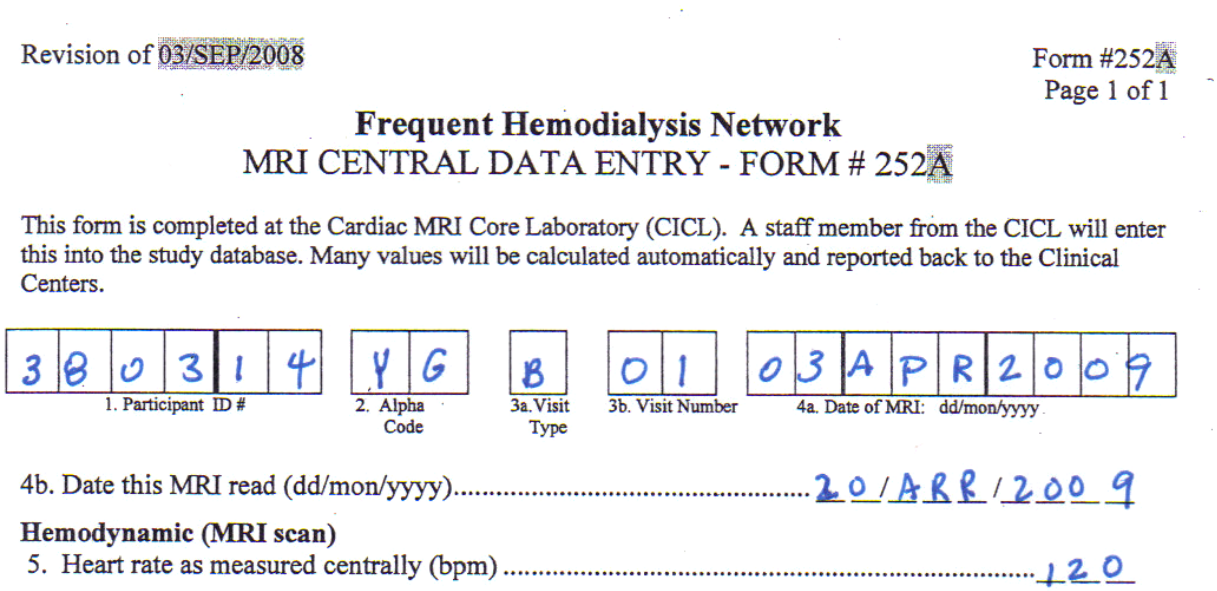
MRI PERFORMANCE AND SHIPPING
On performance of an MRI, an email is sent to the core notifying that the CD was sent.

Pick up the mail package from the front desk of DHLRI room 110. Whitney Works is normally the receptionist who will inform you via email of when the package(s) would be available. The normal time for a package to come in is around 10 AM.

Confirm that envelope from site contains the following items:
- CMRI Mailing Form 251filled out, 2 pages.
- CD of exam that could be in DVD or CD format

Review the CMRI Mailing Form 251to make sure that the dates written on it are correct.
Fill out a 252A form with the corresponding information from the 251 Form, see Figure 1 below for a visualization of these entries:

1. Participant ID#
2. Alpha Code
3a. Visit Type
3b. Visit Number
4a. Date of MRI: dd/mon/yyyy
5. Heart rate as measured centrally (bpm)



Revision of 03/SEP/2008 Form #252A
Page 1 of 1

Frequent Hemodialysis Network
MRI CENTRAL DATA ENTRY - FORM # 252A

This form is completed at the Cardiac MRI Core Laboratory (CICL). A staff member from the CICL will enter this into the study database. Many values will be calculated automatically and reported back to the Clinical Centers.

3	B	0	3	1	4		Y	G		B		0	1		0	3	A	P	R	2	0	0	9
1. Participant ID #							2. Alpha Code			3a. Visit Type		3b. Visit Number			4a. Date of MRI: dd/mon/yyyy									

4b. Date this MRI read (dd/mon/yyyy)..... 20/APR/2009

Hemodynamic (MRI scan)
5. Heart rate as measured centrally (bpm) 120

Figure 1: 252A Form basic entries.

Take the CD along with Form 251 and 252A to the Argus Workstation located in the Ross Heart Hospital.

E.2 ARCHIVAL PROCEDURE

Make a copy of the CD/DVD of the exam. One copy of the CD/DVD is to be mailed out to Dr. Javier Sanz for wall motion reads. The original after below is saved in a folder for safekeeping. The CD/DVD's that are sent to Dr. Sanz at Mount Sinai will be stored in a locked cabinet, located in a locked office, located in secured area of the Mount Sinai Hospital Cardiovascular MR/CT Laboratory. They are organized in order of receipt. Dr. Sanz keeps a separate database that details the date each study was read, whether clinical findings were present, and if so, what findings were noted.

Import the study via the 'Import Function' on a SIEMENS ARGUS Workstation.

Once the study is imported, check to make sure that the study is de-identified. All studies should have the following format:

Patient's Name: 123456 (Participant ID#)
Patient's ID#: 123456 (Participant ID#)
Date of Exam: 12/22/2008 for example. Should match up with Question 4a from Form 252A

Remove any information on the MRI header that may identify the patients such as referring physician, date of birth, gender, etc.

Once the naming convention of the imported study is accomplished; push the study to WebPAX storage system. WebPAX is our centrally located server where we are able to store images for safe keeping.

Select study that you want to send to WebPAX.
Go to "Send" on the menu and select it.
In the pop-up window, select WebPAX destination and click the Send button.
The study should be sent to WebPAX, it may take 1 to 2 minutes to send all of the study to WebPAX. The duration depends on the size of the study. Be patient.

<u>DETAILS ON WEBPAX AND BACK-UP FOR WEBPAX</u>

The images for the Daily Dialysis and Nocturnal Dialysis trials are saved on a centralized web-based PACS system called WebPaxTM. WebPax has over 40TB of space currently available and is backed up regularly.

WebPAX stats as of April 27th 2009:
Storage Used (GB): 4096.000
Storage Available (GB): 4096.000

E.3 READING PROTOCOL

When the images are received in the Core Lab, they will be checked for quality and consistency, including appropriate anonymization, compliance with the imaging protocol and completeness of study. A scan may not be evaluable for measures due to a number of foreseeable circumstances:

- Damage of the images physical support (CD or DVD). The research coordinator at the original imaging center will be notified to submit another copy of the study
- Major violation of image protocol that precludes evaluation of the primary endpoint (LV mass), such as missing images, inadequate gating (prospective), gross motion or other artifacts. The imaging center will be immediately notified and the Core Lab will discuss the reason for failure with the imaging technologist. If the problem can be addressed, the Core Lab will request that the patient be called back for re-evaluation as soon as possible (within the enrollment window).
- Minor violations of imaging protocol that do not preclude evaluation of the primary endpoint (LV mass) will prompt notification to the imaging center but the images will be analyzed for the available parameters.

In all cases software-generated contours will not be accepted and that only hand-drown contours will be used.

<u>Procedure to be followed for reading</u>

Select the loaded exam. Look for the Short Axis cine series (SAX for short). Highlight the series and load them into Argus. The Patient Browser should look similar to Figure 2 below.

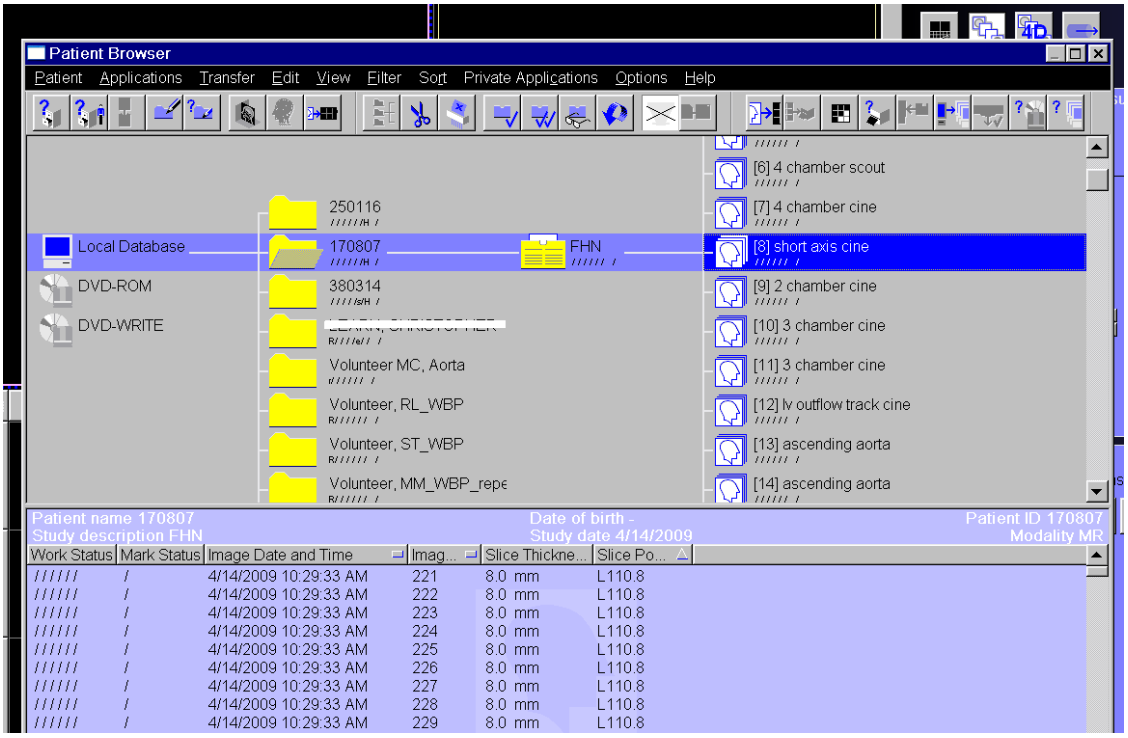


Figure 2: Siemens Workstation Leonardo Patient Browser window.

Make sure to check the slice location for all of the loaded series to see if there are any discrepancies. Sometimes there are multiple series that covered the same location of the heart (for example, the MRI technician repeated a series to try to obtain better image quality). Sometimes there is a skip in slice position. Note that the slice position should be 10 mm apart (8 mm thick slices with 2 mm gap). If there are repeat series that are loaded, unload the first series in that particular slice. If there are skipped slices Notify the imaging center in order to check whether not all images were sent to the Core Lab, or if not all slice positions were acquired (protocol violation)

Ensure that all of the requisite slice positions and aortic compliance was performed

Check Image quality and rate image quality on Form. The criteria for image quality are qualitative. The image quality is rated as excellent (3), acceptable (2) (for the purposes of contour analysis) and unacceptable (1).

Depending on the MRI system and/or protocol that was used to acquire the MRI images, you may or may not have to worry about loading multiple series into Argus. For example, GE Scanners typically acquire all short axis slices of the heart into one large series. In contrast, on the Siemens scanner it is typical to acquire each short axis slice as one series. It is also possible to acquire all of the short axis cuts in one series.

Select all of the images then zoom in and window the image. Figure 3 shows the icon where you can click to select all images (shown in red). Please note that the image selection functions like Microsoft Excel. Figure 4 shows the Zoom and Pan function.

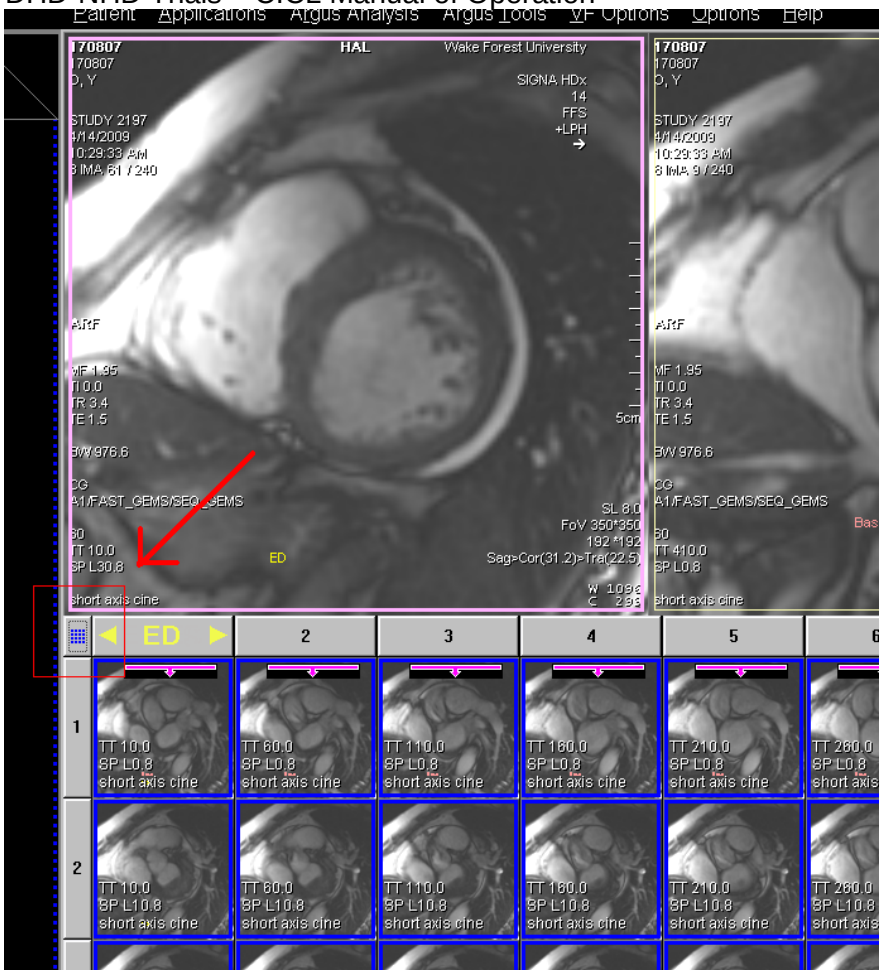


Figure 3: Select all images from Argus.

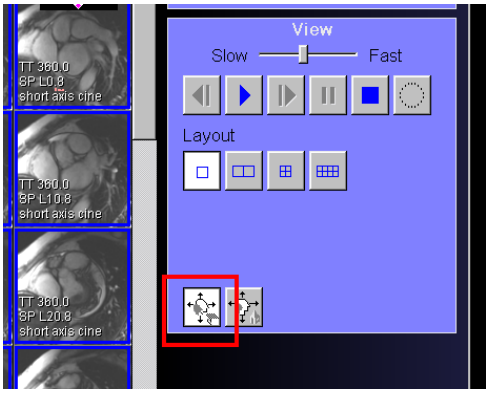


Figure 4: Zoom and Pan function.

Window-level settings

Brightness and contrast of the images are dependent, amongst other factors, on the type of magnet employed for the acquisition. Window settings will be manipulated manually and repeatedly to achieve, in every frame traced, good contrast between the LV cavity and the endocardial border, or between the epicardial border and surrounding fat/fluid.

Determining the Correct Phase for End-Diastole (ED) and End-Systole (ES)

Definition of ED: ED is defined as the phase corresponding to when the blood pool is largest (blood pool have brighter intensity than the bordering myocardium).

Definition of ES: ES is defined as the phase when the blood pool is smallest.

- ED and ES is defined visually based on:
    - Maximum (ED) and minimum cavity volume (ES) of the LV on playing the phases.
    - Valve position: mitral closes in ED, aortic closes in ES.
    - ED is in the vast majority of cases corresponds to the first or last phase in Argus.

Once you are able to determine which phases are ED and ES. Move the corresponding ED/ES tag like the one shown in Figure 4 to their corresponding columns.

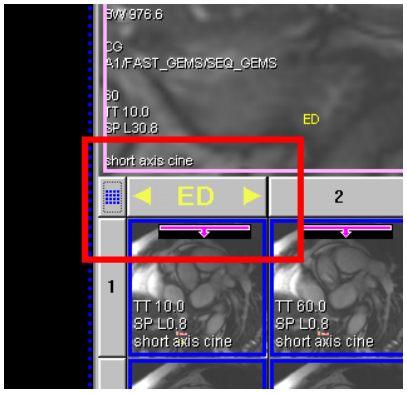


Figure 2: ED designation.

Tracings LV Epicardial and Endocardial Contours

- *Endocardial tracing*: Papillary muscles and trabeculations will be considered part of the ventricular cavity as a general rule (both in ED and ES). If a prominent trabeculation (as dense as the wall myocardium) is in contact with the wall both during ED and ES, it will be considered part of the wall.
- *Epicardial tracing*: Do NOT include epicardial fat. (lobulated, change the windowing)

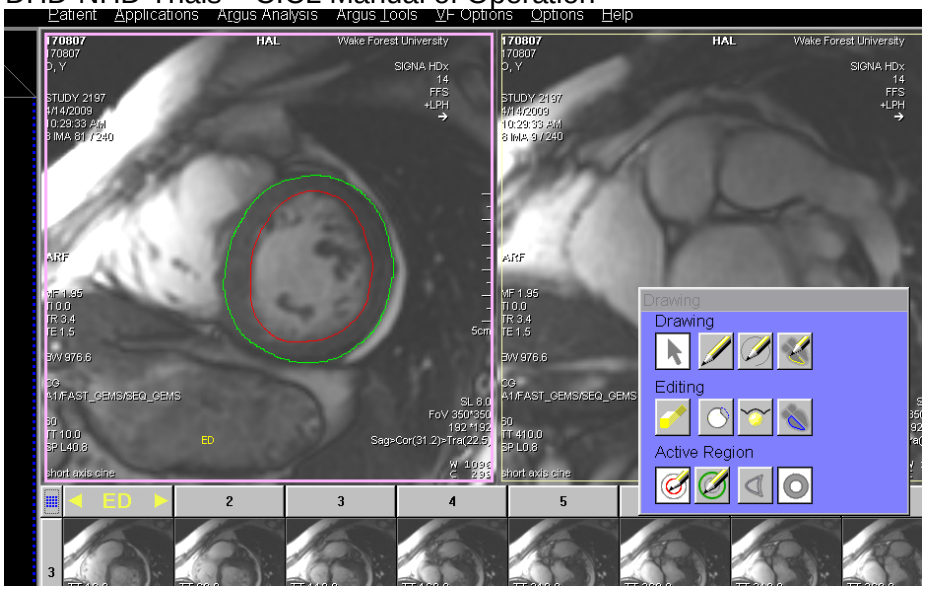
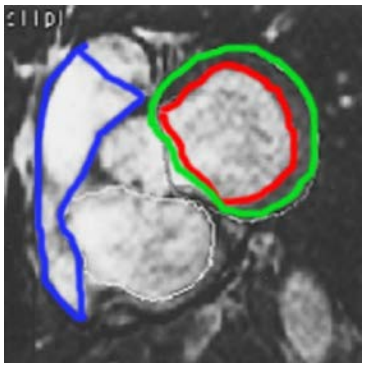


Figure 5: Typical contour tracings.

- Valves: For LV and RV, anything below the aortic/pulmonary valve is ventricle.
- Base: For both ventricles it is defined based on wall thickness (higher for the ventricles than the atria), the motion of the wall (ventricles contract while atria dilate, and vice versa) and, in case of doubt, the position of the slice in the 4 chamber cine. The base in ED is usually one level higher than in ES.



- For the **LV**, the first slice will be considered to be part of the LV if surrounded by ≥ 50 of ventricular myocardium. If the basal slice contains both ventricular and atrial myocardium, the contours will be drawn up to the junction and joined by a straight line (Figure).
- For the **RV**, the outflow tract is often seen in the base together with the atrium (Figure).

- Apex: For both ventricles it is the last image where cavity can be identified.

Click on the Volume box in the Result tab as seen in Figure 6 to get the results.

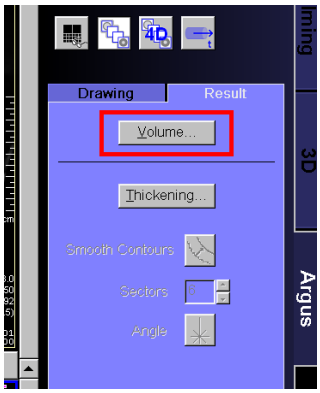


Figure 6: Volume and Mass Result.

The ARGUS workstation provides two LV Mass measurements: end-diastolic and average (representing the mean of end-diastolic and end-systolic measurements). For consistency, only the measurement at end-diastole will be recorded. This is because this is the common approach in clinical practice and it appears that end-systolic measurements overestimate LV mass with the 2D analysis method used in these trials (Swingen et al. J Cardiovasc Magn Reson 2004;6:829-35)

Determination of Systolic thickening

1. Eliminate slices where there is not a complete LV wall circumference.
2. There should be the same number of slices in ED and ES.
3. Go to the “thickening” card in Argus and do the analysis of 2 segments per slice. Add up all results and average them.

Click on the Thickening box in the Result tab as seen in Figure 7 to get the results.

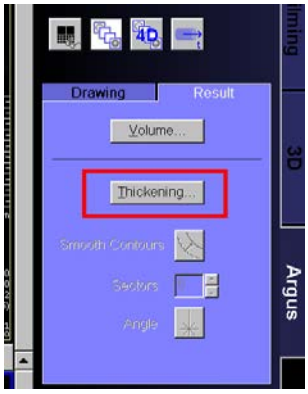


Figure 7: Thickening Result.

Aortic stiffness

1. Aortic series Images are loaded to Argus function.
2. Automatic contour detection is propagated.
3. The maximum and minimum areas are determined visually (ensure reasonable contours) and with Argus “volumes” results.
4. These 2 frames are loaded to Viewing, where diameters and areas are traced.

Both diameters and areas are luminal, NOT wall-to-wall. The diameters are antero-posterior.

LV Thickening and Wall motion score index (to be performed Dr. Javier Sanz)

WMSI = ∑ scores 16 segments:

1. Normal wall motion.
2. Hypokinesia.
3. Akinesia.
4. Dyskinesia.

Dr. Sanz will determine the wall motion score index by adjudicating a category for contractility (1. normal wall motion, 2. hypokinesia, 3. akinesia, and 4. dyskinesia) to each of the standard 17 myocardial segments, as detailed in the MOP. Dr. Sanz will also review the studies for the presence of incidental findings that may pose significant risk to the patient and that may otherwise go undetected, including but not limited to cardiac or extracardiac tumors, aortic dissection, severe pericardial or pleural effusions, or wall motion abnormalities compatible with myocardial infarction/ischemia. These results are currently emailed to the core and then manually entered into the FHN database.

Dr. Sanz will proceed to the clinical reading of the studies within 3 working days upon receipt of the copies of the CD’s from the Core Lab. If incidental findings considered to be of clinical relevance are noted, Dr. Sanz will immediately notify the Core Lab research coordinator, who in turn will fax a brief clinical report to the DCC.

F. RECORDING RESULTS INTO 252A FORM

Record the data obtained in the steps above into Form 252A like the one seen in Figure 8 below.

4b. Date this MRI read (dd/mon/yyyy)..... 20/APR/2009

Hemodynamic (MRI scan)

5. Heart rate as measured centrally (bpm) 120

Global Left Ventricular Function

6. Left ventricular end-diastolic volume: (ml)..... 76.5
7. Left ventricular end-systolic volume: (ml) 44.3

Left Ventricular Mass

8. Left ventricular mass: (gr) 89.2

Global Right Ventricular Function

9. Right ventricular end-diastolic volume: (ml)..... 66.0
10. Right ventricular end-systolic volume: (ml)..... 44.9

Segmental Left Ventricular Function

11. Absolute systolic thickening: (mm)..... 2.6
12. Relative systolic thickening: (%)..... 32.45

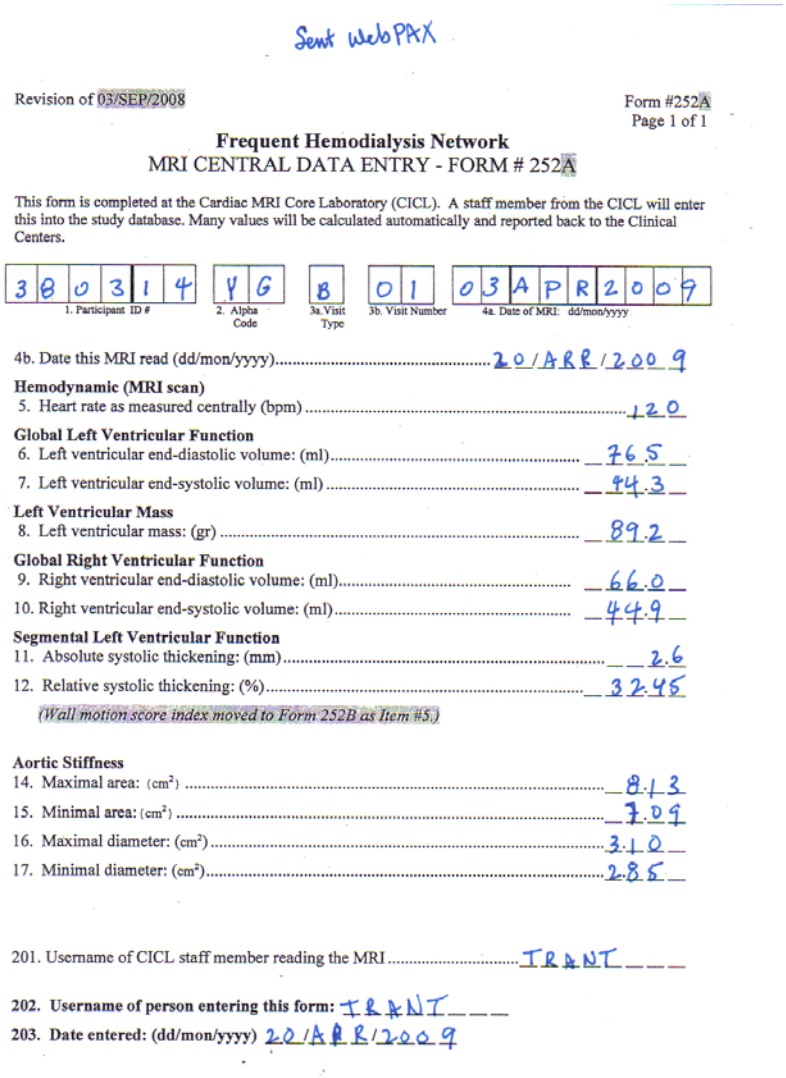
(Wall motion score index moved to Form 252B as Item #5.)

Aortic Stiffness

14. Maximal area: (cm^2) 8.13
15. Minimal area: (cm^2) 7.09
16. Maximal diameter: (cm^2)..... 3.10
17. Minimal diameter: (cm^2)..... 2.85

Figure 8: 252A Form measurement values.

Figure 9 shows a completed 252A Form with all of the patient information, recorded measurements, and person entering the data into the database.



Sent WebPAX

Revision of 03/SEP/2008

Form #252A
Page 1 of 1

Frequent Hemodialysis Network
MRI CENTRAL DATA ENTRY - FORM # 252A

This form is completed at the Cardiac MRI Core Laboratory (CICL). A staff member from the CICL will enter this into the study database. Many values will be calculated automatically and reported back to the Clinical Centers.

1. Participant ID #	2. Alpha Code	3a. Visit Type	3b. Visit Number	4a. Date of MRI: dd/mon/yyyy
38031	YG	B	01	03APR2009

4b. Date this MRI read (dd/mon/yyyy)..... 20/APR/2009

Hemodynamic (MRI scan)
5. Heart rate as measured centrally (bpm)..... 120

Global Left Ventricular Function
6. Left ventricular end-diastolic volume: (ml)..... 76.5
7. Left ventricular end-systolic volume: (ml)..... 44.3

Left Ventricular Mass
8. Left ventricular mass: (gr)..... 89.2

Global Right Ventricular Function
9. Right ventricular end-diastolic volume: (ml)..... 66.0
10. Right ventricular end-systolic volume: (ml)..... 44.9

Segmental Left Ventricular Function
11. Absolute systolic thickening: (mm)..... 2.6
12. Relative systolic thickening: (%)..... 32.46

(Wall motion score index moved to Form 252B as Item #5.)

Aortic Stiffness
14. Maximal area: (cm^2)..... 8.13
15. Minimal area: (cm^2)..... 7.09
16. Maximal diameter: (cm^2)..... 3.10
17. Minimal diameter: (cm^2)..... 2.85

201. Username of CICL staff member reading the MRI..... TRANT

202. Username of person entering this form: TRANT

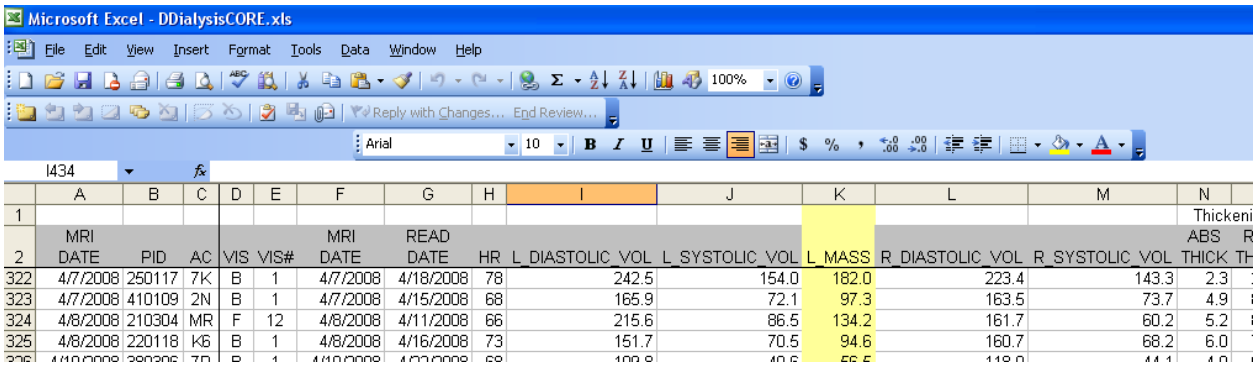
203. Date entered: (dd/mon/yyyy) 20/APR/2009

Figure 9: Completed 252A Form.

G. ENTERING DATA INTO INTERNAL CORE DATA BASE

Enter Results from 252A Form into Core Database (Excel)

Fill in the corresponding values from the 252A Form into the Core Spreadsheet called DDialysisCore.xls. Figure 10 shows the fields that must be filled in. Please take extra care to make sure that you enter the number correctly from the 252A Form to the Excel Spreadsheet.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1														Thickeni
2	MRI DATE	PID	AC	VIS	VIS#	MRI DATE	READ DATE	HR	L_DIASTOLIC_VOL	L_SYSTOLIC_VOL	L_MASS	R_DIASTOLIC_VOL	R_SYSTOLIC_VOL	ABS THICK
322	4/7/2008	250117	7K	B	1	4/7/2008	4/18/2008	78	242.5	154.0	182.0	223.4	143.3	2.3
323	4/7/2008	410109	2N	B	1	4/7/2008	4/15/2008	68	165.9	72.1	97.3	163.5	73.7	4.9
324	4/8/2008	210304	MR	F	12	4/8/2008	4/11/2008	66	215.6	86.5	134.2	161.7	60.2	5.2
325	4/8/2008	220118	K6	B	1	4/8/2008	4/16/2008	73	151.7	70.5	94.6	160.7	68.2	6.0

Figure 10: DDialysisCORE.xls spreadsheet.

H. QUALITY CONTROL MEASURES

The CICL has established quality assurance at multiple levels that will serve as a safeguard against error/bias in the trial.

1. Sequence/protocol fidelity through the trial: This will be ensured at sites prior to study initiation by requiring that the sequence for CMRI (SSFP) be saved as a separate identifiable protocol on the scanner.

2. Scanner and site of performance: The same scanner and site where the original MRI was performed will be adhered to through out the protocol for all patients. If any change is contemplated the site will contact the MRI core to approve any changes.

3. Periodic surveillance of sites by CICL: Sequence parameters specified in the MOP will be surveyed routinely during the review of the images. This will ensure uniformity of study performance at sites. In addition if there has been a change at a site with regards to hardware, software or technician at a site this will be required to be relayed to the CICL.

4. Analysis of data in the trial: Dedicated CMRI specialists will analyze CMRI end-points in the trial. The analysis of CMRI measurements will be performed for the most part by the same reader to reduce inter-reader variability. However in the event that the primary reader becomes unavailable, there will be a replacement reader who will take on the responsibility. The training of the reader has to fulfill the following criteria.

5. Certification of New Reader

The number of readers will be maintained at a minimum to reduce inter-reader variability. If a new reader needs to be introduced they will have the meet the following criteria.

- The new reader goes through an exhaustive introduction and training of cardiac MR physics, scanning protocol (at the scanner) and exhaustive training on the workstation for analysis of cardiac MRI images over the course of 3 months. In the event of substantial cardiac MRI experience (>12 months experience scanning or /PhD level training in MR Physics with at least 6 months of scanning experience) this requirement for training in cardiac MR physics, on-scanner and workstation training may be waived
- Approximately 60 unique cases will be read and verified over a period of 2 months. These cases will correspond to cases that have been previously read and will be assigned randomly so that the trainee is unaware of the previous results. The cases may be divided into phases that corresponds to the progression in skill set required for interpretative skills over a 2 month period (20 days each). In the event of substantial prior cardiac MRI experience the number of review cases will be limited to 20 over the course of 30 days. The original contours for these cases
- The mean absolute difference between readers for LVMass (Reader 1 and Reader 2) will be estimated for these cases
- Over the first 40 cases (20 in each set), the contours and volume analysis will be examined by a senior reader (Dr Rajagopalan or Dr. Sanz) and corrected resulting in an iterative learning process for the new reader
- The final 20 or so cases will be interpreted with the assumption that these measurements would be as close as possible to the expected mean absolute difference as determined by published criteria.[†]

- If this assumption was not met (that is, if mean absolute LV mass difference is >5% in any of the 20 cases), additional sets of 20 cases will be analyzed till satisfactory agreement is accomplished

† Grothues et al [Am J Cardiol. 2002 Jul 1;90(1):29-34] showed that the mean absolute difference between scans for a "normal" population was 1.1± 4.2 grams. In the same study a hypertensive or heart failure population the variability was far more with a mean absolute difference ± SD of 2.4 ± 9 grams between measurements. When expressed as a % of the mean LV mass in this published study for the two populations this works out to 3% and 5% respectively.
In our preliminary analysis of over 300 cases for which we repeated measurements on 2 occasions, we established that the mean absolute difference was 2.8 ± 6 g. Based on this data and when expressed as a percent of the mean LV mass in the frequent dialysis population we estimated that a 5% variation between measurements would be an optimal trigger for review.

Quality control of data at CICL

The following procedures will be implemented on a periodic basis to ensure accuracy of data.

Parameter	Frequency	Procedure
CMRI Data Entry		
Lab Meetings	Every other week	Cases Reviewed; Contour Analysis reviewed in the event a new reader is introduced
Reproducibility of LV Mass and LVEDV	On every case Typically Done 1-2 months after initial tracing	Contours for LV Mass redrawn by same individual without knowledge of prior contours (not saved)
Reproducibility of LVESV and LVEF	Not recorded on all cases but on ≥5 % of cases	End-systolic contours redrawn

Lab meetings: Cases for review or where there is a question regarding analysis will be presented to the senior reader as and when these issues arise.

Protocol for Repeat Studies

A repeat LV Mass and LVEDV will be done for all cases. This step was implemented in June 2008 to ensure fidelity of measurements of the primary end-point LV MASS and LVEDV. This step is meant to reduce bias and will ensure reproducibility and performance measures to be derived.

- The repeat measurement will be typically done 30-60 days after the first measurement to ensure that there is no bias from the initial reading to the second reading. In addition, because traced contours are save only temporarily (for approximately 30 days), the second reading is repeated as if it is a brand new study. This reduces the bias of comparing first and second tracings by the reader and ensures independent analysis. The second reading will involve tracing contours in end-diastolic phases only, as these are the only ones needed to derive LV Mass.

- Cases requiring a repeat measurement are identified from the Case Log spreadsheet and pulled up on Webpax. The case-log sheet does not contain information on results of the MRI scans.

- Once cases have been identified they are then pushed to an Argus workstation where repeat measurements are done.

- The data ensuing from the second read will be entered into the corresponding fields in the Core Spreadsheet as seen below in Figure 11.

U	V	W	X	Y	Z	AA	AB	AC	AD
	QC Repeat					Adjudicate			
EAD_USER	LVM Repeat	Repeat Date	Read User	Delta LVM	Delta %	Adj Date	Adj Reader	Adj Final Value	Reason
KARIISM	246.1		KARIISM	-6.2	-2.6%				
KARIISM	128.3		KARIISM	3.7	2.8%				
KARIISM	108.3		KARIISM	2.3	2.1%				
KARIISM	125.1		KARIISM	1.3	1.0%				
KARIISM	89.2		KARIISM	43.8	39.4%		KARIISM	89.2	Measurement Error

Figure 11: Quality Control fields in Core Spreadsheet.

Handling Of Discordant Values On Quality Control

- In the event that the first and second measurements (repeat) for LV Mass differ by more than 5%, this will trigger an evaluation by a senior reader. The contours are only temporarily saved and most tracings will be unavailable for review. Thus a third measurement will be made. In cases where the contours are available (<5% of cases) on ARGUS, then this second set of contours will be reviewed (in almost all cases only the second contour is available). If the second set of contours are unacceptable, the senior reader may request a third contour tracing. Although LVEDV is always measured twice in every patient (as its calculation is needed for the quantification of LV Mass), LVEDV will not be subject to the 5% criterion because it is not a primary endpoint in the trials.

- The third contour analysis will be reviewed by the senior reader (Dr. Sanz or Dr. Rajagopalan) in conjunction with the technician (for didactic purposes).

- The results on this analysis will be compared with the preceding measurements. There are several case scenarios.

o Scenario A. In the event that the third measurement of LVM (M3) varies by <5% from M1. M1 measurements will be retained.
o Scenario B. In the event that the third measurement of LVM (M3) varies by <5% from M2. M2 measurements (EDV, ESV and LVM)
o Scenario C. In the event that the third measurement of LVM (M3) varies by >5% from M1 and M2. M3 measurements will be used ((EDV, ESV and LVM)

- The new “adjudicated” values based on above will be recorded into the ‘Adjudicate’ fields of the Core Spreadsheet as seen in Figure 11.

- The QC procedure of LVESV will involve analysis of contours in 5% of cases to ensure internal consistency. In cases where the LVESV or LVEF vary by more than 10% a third measurement will be made. Cases for LVESV/LVEF reproducibility will be selected as the twentieth case of each set of 20 consecutive studies.

Appendix 1

CMRI Scanning Parameters Form
(To be filled out at study qualification)

FREQUENT DIALYSIS INVESTIGATORS

TEST CASE #:	SITE NUMBER:	DATE OF STUDY

Ventricular function

IMAGING PARAMETERS (SSFP)	VALUES	
TR (ms)		
TE (ms)		
Flip angle (degrees)		
Slice thickness (mm)		
Gap (mm)		
Field-of-view (mm)		
Matrix (lines)		
Averages (NEX)		
Lines (views) acquired per segment		
Reconstructed phases		
Bandwidth (Hz/pixel) or MHz		
Parallel imaging	Yes	No
View sharing	Yes	No

Aortic stiffness

IMAGING PARAMETERS (SSFP)	VALUES	
TR (ms)		
TE (ms)		
Flip angle (degrees)		
Slice thickness (mm)		
Field-of-view (mm)		
Matrix (lines)		
Averages (NEX)		
Lines (views) acquired per segment		
Reconstructed phases		
Bandwidth (Hz/pixel) or MHz		
Parallel imaging	Yes	No
View sharing	Yes	No

Please fax the completed form to the Cardiovascular Imaging Core Laboratory together with the CMRI Mailing Form 251 and Data Submission Form: 1-888-363-8923

Appendix 2

Patient Preparation for CMRI

1. A registered nurse or CMRI technician conversant with the procedure will conduct a brief survey of possible contraindications. These will include:
    a. Metallic implants incompatible with the magnetic field (pacemakers, defibrillators, aneurysm clips, etc). Intracoronary stents in particular are not a contraindication.
    b. Pregnancy (known or suspected)*.
    c. Severe obesity (weight > 200 kg)†.
    d. Severe claustrophobia.
    e. Unstable clinical condition or inability to lie flat.
    f. Inability to perform 8-12 second breath-holds
2. The patient will be instructed about the procedure (including purpose, estimated duration, steps and risks).
3. The patient's height and weight will be recorded for standardization of measurements according to the body surface area (BSA).
4. The absence of metallic objects will be confirmed and, if present, transdermal patches (such as those containing nitroglycerine) will be removed.
5. The patient will then be transported to the magnet room.
6. The patient will lie down on the CMRI examination table in the supine position (feet-first or head-first depending on the specific magnet).
7. CMRI-compatible ECG electrodes will be positioned on the precordial region of the chest for ECG monitoring and gating during the procedure. The ECG leads or plethysmography device will be connected to the magnet built-in monitoring system. In the event that the patient has markedly irregular atrial fibrillation (R-R interval variability >400 ms within 20 seconds) that precludes retrospective gating within a satisfactory breath-hold, the patient should be enrolled only after consultation with the CICL.
8. Dedicated surface coils will be placed and secured.
9. Headphones and/or earplugs will be provided for acoustic protection. During the full length of the procedure, visual and/or verbal contact with the patient will be maintained.

* In the event pregnancy is suspected, this will be ruled out by a pregnancy test.

† Maximum possible weight recommended by the manufacturer in a 1.5T *Magnetom Sonata*® magnet (Siemens Medical Systems, Erlangen, Germany). This figure may vary from site-to-site according to specific vendor-related specifications.

Appendix 3

CMRI Scan Time Sequence

• *Pre-scan*	Patient preparation (see Appendix 2)
• *Scan*	
- T=00 min	Patient preparation (see Appendix 2)
- T=10 min	Start scan and acquisition of axial, sagittal and coronal localizer images
- T=12 min	Two-chamber, short-axis and four-chamber localizer images
- T=13 min	Four-chamber cine view (SSFP)
- T=15 min	Short-axis cine sequences to assess ventricular function (SSFP)
- T=24 min	Three-chamber and two-chamber cine imaging (SSFP)
- T=26 min	End of study

Appendix 4

CMRI Parameters for Acquisition of Cine Images (Ventricular Function)

Parameters (SSFP Sequence)	Values
TR – Repetition time (ms)	3.2
TE - Echo time (ms)	1.6
Flip angle (degrees)	60-90
*Slice thickness (mm)**	8
*Interslice gap (mm)**	2
Typical field-of-view (mm) †	Minimal
Typical matrix (lines)	256 x 166
*Typical spatial resolution (mm)**	1.7 x 1.4
Averages (NEX)	1
*K Lines per segment**	11-15
*Typical temporal resolution (ms)**	33-45
Segments (number of heart beats)	11-15
Reconstructed phases	20-25
Bandwidth (Hz/pixel)	900-1000
Parallel imaging techniques	Allowed
View sharing‡	Allowed

The parameters provided in the Table are those typical of an LV function examination performed in the CICL (*TrueFISP*®, *Magnetom Sonata*® 1.5T, Siemens Medical Solutions, Erlangen, Germany).

* The asterisk denotes imaging parameters to be kept within restricted ranges between imaging sites.
  - Both the spatial and temporal resolution of the sequence have significant influence in the measured LV volumes and mass. The temporal resolution is inversely proportional to the number of k-space line acquired per segment and will be required to be < 50 ms. Similarly in-plane spatial resolution, which is determined by the field-of-view and matrix sizes, will be kept ≤ 2 mm.

† Orient the phase encoding axis of the field-of-view in the narrowest anatomic direction (typically anteroposterior for short-axis images). Minimize the field-of-view as much as possible but in the process ensure that you do not get wraparound artifacts, affecting the interpretation of images.

‡ View sharing allows for a decrease in effective temporal resolution, although the “real” temporal resolution of the acquisition may still be suboptimal and result in inaccuracies in volume measurements. Consequently, maintain the acquired lines per segment within the limits established by the CICL to ensure adequate temporal resolution.

Appendix 5

CMRI Parameters for Acquisition of Cine Images (Aortic Stiffness)

Parameters (SSFP Sequence)	Values
TR – Repetition time (ms)	3.2
TE - Echo time (ms)	1.6
Flip angle (degrees)	60-90
Slice thickness (mm)	8
Typical field-of-view (mm)	Minimal
Typical matrix (lines)	256 x 123
*Typical spatial resolution (mm)**	1.9 x 1.3
Averages (NEX)	1
*K Lines per segment**	6-9
*Typical temporal resolution (ms)**	20-30
Segments (number of heart beats)	18-28
Reconstructed phases	40
Bandwidth (Hz/pixel)	900-1100
Parallel imaging techniques	Allowed
View sharing†	Allowed

The parameters provided in the Table are those typical of an aortic stiffness examination performed in the CICL (*TrueFISP*®, *Magnetom Sonata*® 1.5T, Siemens Medical Solutions, Erlangen, Germany).

* The asterisk denotes imaging parameters to be kept within restricted ranges between imaging sites. In-plane spatial resolution, determined by the field-of-view and matrix sizes, will be kept ≤2 mm. Maintaining adequate temporal resolution is crucial when analyzing dynamic changes in aortic dimensions. The temporal resolution for this acquisition and will be required to be ≤30 ms (≤9 lines per segment or views per segment). This will result in a longer scanning (and breath-hold) time than for other cine images (12-25 s). Some tips for reducing scanning time without compromising the protocol requirements include:
  - Use parallel imaging if your scanner has that capability.
  - Orient the phase encoding axis of the field-of-view in the narrowest anatomic direction (typically anteroposterior). Minimize the field-of-view in this direction as much as possible, enabling wraparound artifacts. Make however sure that the artifact does not involve the ascending aorta.
  - Decrease slightly your matrix size, without violating the spatial resolution requirements.
  - Precede the breath-hold with a brief period of hyperventilation.
  - Oxygen supplementation may help some patients.

† View sharing allows for a decrease in effective temporal resolution, although the “real” temporal resolution of the acquisition may still be suboptimal and result in inaccuracies in volume measurements. Consequently, maintain the acquired lines per segment within the limits established by the CICL to ensure adequate temporal resolution.

Appendix 6 Frequent Hemodialysis Network
CARDIAC MRI MAILING FORM # 251

No technician may do an MRI on an FHN study patient until they have submitted two test case MRI's to the Cardiac MRI Core Laboratory (CICL) and received feedback that the test MRI's were performed and processed correctly. MRI's are assumed to have been done at the MRI site associated with the patient's participating dialysis unit as recorded in the study database. This form should be completed at the time of the MRI or (if *the MRI is not done*) at the end of the visit window for the MRI (if the MRI is not done, use the end date of the visit window as Date of MRI). If an MRI is done but is clearly of inadequate quality, repeat the MRI. Do not submit the MRI to the CICL and/or key enter a mailing form. When this form has been completed, it should be photocopied. The copy should be sent with the MRI images to the CICL; make sure it is a clear, clean copy. The original should be entered by a Clinical Center data entry person and kept with the patient's other completed study forms.

TO BE COMPLETED BY STUDY COORDINATOR:

														•									

1. Participant ID # | 2. Alpha Code | 3a. Visit Type | 3b. Visit Number | 4a. Date of MRI dd/mon/yyyy

5. Was the MRI done during the visit window? .....___

1=Yes
2=No, patient refused
3=No, logistic problem related to the patient
5=No, logistic problem related to the FHN site
6=No, logistic problem related to the MRI site

If MRI done, continue. If not done, skip to item 200.

6. Type of study.....__
   1=Routine (in window)
   2=Make up for missed routine (in next window)
   3=Repeat

TO BE COMPLETED BY MRI TECHNICIAN:

Heart rate

7. Heart Rate Measured at the Time of MRI (bpm).....___ ___ ___

MRI

8. Time of MRI .....(military) __ __ : __ __

9. Was there sinus rhythm? (0 = No, 1 = Yes).....__

10. What was the gating? (1= ECG, 2 = pulse).....__

Left ventricular function

11. Position: 4-chamber view ..... a. Series Number ____ ____ b. Slice position _____

Cine Short Axis

12. Position: Proximal to base ..... a. Series Number ____ ____ b. Slice position _____

13. Position: Base ..... a. Series Number ____ ____ b. Slice position _____

14. Next ..... a. Series Number ____ ____ b. Slice position _____

15. Next ..... a. Series Number ____ ____ b. Slice position _____

16. Next ..... a. Series Number ____ ____ b. Slice position _____

17. Next ..... a. Series Number ____ ____ b. Slice position _____

18. Next ..... a. Series Number ____ ____ b. Slice position _____

19. Next ..... a. Series Number ____ ____ b. Slice position _____

20. Next ..... a. Series Number ____ ____ b. Slice position _____

21. Next ..... a. Series Number ____ ____ b. Slice position _____

22. Next ..... a. Series Number ____ ____ b. Slice position _____

23. Position: Apex ..... a. Series Number ____ ____ b. Slice position _____

24. Position: Distal to Apex ..... a. Series Number ____ ____ b. Slice position _____

Cine Long Axis

25. Position: 3-Chamber View ..... a. Series Number ____ ____ b. Slice position _____

26. Position: 2-Chamber view ..... a. Series Number ____ ____ b. Slice position _____

Aortic stiffness

27. Position: LV outflow tract ..... a. Series Number ____ ____ b. Slice position _____

28. Position: Ascending aorta ..... a. Series Number ____ ____ b. Slice position _____

---

29. Username of certified MRI tech who did this MRI. .....__ __ __ __ __ __ __ __

TO BE COMPLETED BY STUDY COORDINATOR:

30. Date shipped to CICL (dd/mon/yyyy)..... __ __ /__ __ __ /__ __ __ __

200. Date this form completed (dd/mon/yyyy)……... __ __/__ __ __ /__ __ __ __

201. Username of person reviewing this form prior to data entry……__ __ __ __ __ __ __ __

FOR CLINICAL CENTER USE ONLY:

202. Username of person entering this form: __ __ __ __ __ __ __ __

203. Date Entered: (dd/mon/yyyy) __ __/__ __ __ /__ __ __ __

Appendix 7

Data Submission Form

FREQUENT DIALYSIS INVESTIGATORS

CENTER NUMBER

PATIENT STUDY IDENTIFICATION NUMBER

DATE OF CMRI

(DD-MM-YYYY) **TIME OF SCAN**

DATE SCAN SENT TO CORE LAB

: :

STUDY COORDINATOR SIGNATURE/DATE

Please fax the completed form to the CICL together with the CMRI Mailing Form 251: 888-362-0639

PID: [redacted] AC: [redacted] MRI Date: 28/JAN/2009

Global left ventricular	**Left venticular end-dialstolic volume**	**LVEDV**	**155.90**	mL
	Left ventricular end-diastolic volumne index	LVEDVI	66.06	mL/m^2
	Left ventricular end-systolic volume	**LVESV**	**54.90**	mL
	Left ventricular end-diastolic systolic index	LVESVI	23.26	mL/m^2
	Left ventricular stroke volume	LVSV	101.00	mL
	Left ventricular stroke volume index	LVSVI	42.80	mL/m^2
	Left ventricular ejection fraction	LVEF	64.79	%
	Left cardiac output	LCO	8,484.00	$L/m/m^2$
	Left cardiac index	LCI	3,595.14	L/m
Left ventricular mass	**Left ventricular mass**	**LVM**	**139.50**	g
	Left ventricular mass index	LVMI	59.11	g/m^2
Global right ventricular function	**Right ventricular end-diastolic volume**	**RVEDV**	**94.00**	mL
	Right ventricular end-diastolic volume index	RVEDVI	39.83	mL/m^2
	Right ventricular end-systolic volume	**RVESV**	**33.00**	mL
	Right ventricular end-diastolic systolic index	RVESVI	13.98	mL/m^2
	Right ventricular stroke volume	RVSV	61.00	mL
	Right ventricular stroke volume index	RVSVI	25.85	mL/m^2
	Right ventricular ejection fraction	RVEF	64.89	%
	Right cardiac output	RCO	5,124.00	$L/m/m^2$
	Right cardiac index	RCI	2,171.33	L/m
Segmental left ventricular	**Absolute systolic thickening**	**AST**	**6.9**	mm
	Relative systolic thickening	**RST**	**88.97**	%
	Wall motion score index	**WMSI**		
Aortic stiff	**Maximal area**	**MAXA**	**5.18**	cm^2
	Minimal area	**MINA**	**4.64**	cm^2
	Maximal diameter	**MAXD**	**2.350**	cm
	Minimal diameter	**MIND**	**2.130**	cm
	Compliance	C	0.0057	$cm^2/mmHg$
	Distensibility	D	0.0012	
	Elastic modulus	EM	833.33	
	Stiffness index	SI	6.81	
	Stiffness index (area method)	SIAREA	6.69	

Note: **Bold text** indicates measured value.

8. Health Related Quality of Life (HRQOL)

Archive Note: All HRQOL data collected by the University of Pittsburgh Central Quality of Life Center during the course of the FHN Trials and Extension Studies will be destroyed in December, 2014.

Only participant response data, identified by FHN study id (unique 6-digit FHN number/ alphacode), was transmitted securely to the DCC. Data received from the Central Quality of Life Interview Center was downloaded into individual HRQOL instrument data collection tables.

8.1 Introduction to Health-Related Quality of Life: A Critical Outcome for the FHN Study

What is health-related quality of life (HRQOL)?

The current definition of HRQOL reflects the World Health Organization's definition of health as "a complete state of physical, mental, and social well-being and not merely the absence of disease and infirmity". Health-related quality of life refers to a subset of quality of life endpoints related to the health of the patient[1]. Most HRQOL instruments used in dialysis patients are multi-dimensional instruments that assess physical, mental, and social domains. If the treatment options for ESRD are potentially similar, such as the decision regarding using HD or PD, nephrologists may wish to discuss HRQOL issues as a part of the decision-making process. In FHN, HRQOL is a co-primary outcome and the collection of this data is crucial to the success of the trial. The collection of the HRQOL data will allow the investigators to examine differences in physical well-being due to the study interventions and describe the experiences of the study participants.

<u>Why health related quality of life is important to FHN</u>

HRQOL measurements are based on a patient's "subjective" sense of well-being and are commonly used as an important clinical measure for beneficial extent of medical treatments for patients undergoing maintenance hemodialysis [2-4]. While the questionnaires are subjective and represent the patients own perspective, they are highly reproducible and the reliability of HRQOL domains used in FHN compare favorably with the reliability of blood pressure measurements. Furthermore, among those with ESRD, HRQOL has been shown to change over the first several months of dialysis, to improve with erythropoieitin therapy[5-7] and exercise[8-11], and to be an independent predictor of survival[12-14]. However, recent investigation has revealed that HRQOL is not effected by hemodialysis dose or flux[15]. The value of HRQOL measurement as a tool to improve clinical care has been recognized by many in the research community [12, 18-21] and both the National Kidney Foundation and the Centers for Medicare and Medicaid Services (CMS).

THE FHN conceptualization of HRQOL

In the FHN trial, the study group will examine HRQOL as a multi-dimensional concept. The study co-primary outcome is physical-well being as measured by an SF-36 RAND summary score (Physical Health Component). The FHN study will also focus on symptoms of depression,

mental health, health utility, sleep problems, self-perceived burden of care and sexual function. These aspects of health-related quality of life are thought to comprise domains that may be impacted by the study intervention and are valued by patients with ESRD.

Telephone administered QOL surveys

Because self-administered questionnaires may be more difficult to complete for the elderly, minority groups, and those with high comorbidity from trial participation [Unruh, 2003], all questionnaires will be administered by trained interviewers using computer-assisted telephone interviewing (CATI). HRQOL will be assessed at baseline, 4 months and 12 months after randomization in the daily study and at baseline, 5 months and 14 months after randomization in the nocturnal study. The telephone interviewers will be blinded to treatment allocation and will conduct the interviews through a central telephone service by the University Center for Social and Urban Research at the University of Pittsburgh.

8.2 Protocol for Transfer of Information To and From HRQOL Central Interviewing Center

1. The patient is recruited as a potential study participant at dialysis clinic.

2. The study coordinator at the dialysis clinic completes and submits the web-based Direct Patient Contact Form. The form includes the following fields:

a. patient study ID #,
b. current date,
c. patient's last name,
d. patient's first name and middle initial,
e. patient's state or province of residence,
f. patient's phone number (including area code and country code if patient is Canadian) and best time to reach patient at given number (x 3),
g. patient age indicator (minor (less than 18 years of age) or adult indicator)
h. trial indicator (Nocturnal or In-Center Daily),
i. language preference indicator (English or Spanish), and
j. site indicator.

Data from the form are appended to the HRQOL Central Interviewing Center's HRQOL Patient Tracking Database.

3. The study coordinator at the dialysis clinic notifies the Data Coordinating Center (DCC) that the patient has been recruited.

4. Study personnel complete the Core and Participating Site Data Form (Form 600). Data from the form are appended to the HRQOL Central Interviewing Center's HRQOL Patient Tracking Database.

5. The baseline HRQOL Interview is conducted as soon as possible after the nephrologist contact information has been obtained by the HRQOL Central Interviewing Center. The nephrologist's contact information is needed to ensure that if certain questions (e.g., suicidal thoughts) are answered in the affirmative by the patient, that the patient's physician can be notified promptly.

6. The participant will be contacted during a best time to call. The telephone administered HRQOL survey should take approximately 45 minutes to complete. The interview will include the following survey instruments, which are described in detail below:

a. SF-36
b. Health Utilities Index
c. Beck Depression Inventory
d. The Medical Outcomes Study (MOS) Sleep Problems Index (SPI)
e. Caregiver Burden
f. Dialysis specific questions

7. If the patient endorses suicide during administration of the Beck's Depression Inventory (Beck Item 13 responses: I would like to kill myself or I would kill myself if I had the chance), the FHN HRQOL Central Interviewing Center will alert the responsible investigators identified in Form 600.

8. HRQOL Central Interviewing Center's HRQOL Patient Tracking Database is updated with date of Baseline HRQOL Interview completion and projected dates for follow-up HRQOL interviews.

9. Baseline HRQOL Interview data are transferred within 24 hours of interview completion to the DCC. An adequate response rate as defined as a Physical Health Composite Score will be required for randomization.

10. The DCC computes scores based on HRQOL interview data and determines if the patient is eligible to participate in trial. If eligible, patient is randomized.

11. The DCC notifies the HRQOL Central Interviewing Center as to whether the patient has been randomized or not. The HRQOL Central Interviewing Center's HRQOL Patient Tracking Database is updated with randomization status (i.e., randomized, not randomized).

12. Two weeks prior to the scheduled date for HRQOL Interview Follow-up 1, the HRQOL Central Interviewing Center sends a standardized email to the study coordinator at the dialysis clinic to remind him/her to complete the web-based HRQOL Interview Follow-up Contact Form which includes the following fields:

a. patient ID #,
b. status (i.e., still participating in trial, withdrew from trial but interview, withdrew from trial and don't interview, deceased), and
c. contact information.

13. Two weeks prior to the scheduled date for HRQOL Interview Follow-up 2, the HRQOL Central Interviewing Center sends a standardized email to the study coordinator at the dialysis clinic to remind him/her to complete the web-based HRQOL Interview Follow-up Contact Form as described above.

Frequent Hemodialysis Network
"Patient Contact Form"

Core Consortium #0 Test
Test Center

Logout

Patient Contact Form 107

Patient ID:	12345 Find Patient Form
Alpha Code:	
Last Name:	
First Name & Middle Initial:	
Trial:	○ Daily Study ○ Nocturnal Study
Visit:	○ Baseline ○ First Follow-up (F4 or F5) ○ Final Follow-up (F12 or F14)
Status:	○ Baseline ○ Still in Trial ○ Withdrew from Trial, agreed to be contacted for QOL interview ○ Withdrew from Trial, do not contact for QOL interview ○ Deceased
Age:	○ Adult 18 years old and over ○ 17 years old and younger
Preferred Interview Language:	○ English ○ Spanish
Best Times to Call:	Phone 1: [ ] Time 1: Phone 2: [ ] Time 2: Phone 3: [ ] Time 3:
	Save Reset «Delete»

University of Pittsburgh
University Center for Social and Urban Research
Technical Questions: survey@pitt.edu
https://surveyweb2.ucsur.pitt.edu/DialysisQOL/patient.php 10/12/2005

8.3 HRQOL Measures in FHN

SF-36 *[Archive note: This instrument was completed in English and Spanish. It required a licensing agreement because of the Spanish component]*

The World Health Organization characterizes health as a state of mental, physical and social well-being. Consistent with this construct of health, the SF36, a short-form HRQOL scoring system with 36 items, is a self-administered questionnaire that was constructed to fill the gap between much more lengthy surveys and relatively coarse single-item measures of the HRQOL [2, 12, 20]. It consists of 36 questions, 35 of which form into eight multi-item scales:

(1) Physical functioning is a ten-question scale that captures abilities to deal with the physical requirement of life, such as attending to personal needs, walking, and flexibility;

(2) Role-physical is a four-item scale that evaluates the extent to which physical capabilities limit activity;

(3) Bodily pain is a two-item scale that evaluates the perceived amount of pain experienced during the previous 4 wk and the extent to which that pain interfered with normal work activities;

(4) General health is a five-item scale that evaluates general health in terms of personal perception;

(5) Vitality is a four-item scale that evaluates feelings of pep, energy, and fatigue;

(6) Social functioning (SF) is a two-item scale that evaluates the extent and amount of time, if any, that physical health or emotional problems interfered with family, friends, and other social interactions during the previous 4 wk;

(7) Role-emotional (RE) is a three-item scale that evaluates the extent, if any, to which emotional factors interfere with work or other activities; and

(8) Mental health is a five-item scale that evaluates feelings principally of anxiety and depression.

The RAND Physical Health Composite (PHC) from the SF-36 will be used to define the second of the two co-primary outcomes for the trial. The short-form 36 (SF-36) is one of the most commonly used instruments to measure patient-reported health related quality of life in the world, and its 36 items making 8 subscales and 2 summary scales (physical and mental components) have been tested extensively for reliability, validity, and responsiveness in HD patients. [Allen, 2002;Beusterien, 1996;Cagney, 2000;DeOreo, 1997;Diaz-Buxo, 2000;Edgell, 1996;Levin, 1993;Merkus, 1997;Meyer, 1994;Rettig, 1997] The survey is well accepted by HD patients, taking only 5 to 10 minutes to complete. [Kurtin, 1992;Rettig, 1997]. Studies in nocturnal hemodialysis patients have shown an improvement in both PCS and MCS scores from baseline [Brissenden, 1998;Kooistra, 1998;Lockridge, 1999;McPhatter, 1999;Mohr, 1999]. The minimal clinically important difference for a change in each of these scores has been suggested to be 3 to 5 points. [Hays, 2001;Samsa, 1999]

The RAND PHC score is used as a component of a co-primary outcome rather than one of the SF-36 summary scales (PCS, MCS) because the PCS and MCS can in some cases produce

distorted results. [Simon, 1998] In one study, for example, the MCS failed to detect major clinical differences associated with disease progression, despite significant differences in its component subscales. [Norvedt, 2000] The RAND PHC is based on the same SF-36 scales as the PCS score (physical function, role-physical, pain, general health perceptions). Unlike the PCS, however, the scoring algorithm used to calculate the PHC is based on non-orthogonal factor rotation. [Hays, 1998] This allows the PHC to correlate with mental health, unlike the PCS.

Health Utilities Index (HUI) *[Archive note: This instrument was completed in English and Spanish. It required a licensing agreement.]*

The Health Utilities Index, Mark 3 (HUI3) is a 21-item generic health instrument for determining the overall utility associated with particular health states. The HUI questionnaire is composed of eight attributes of high importance to members of the general population: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. A preference-based scoring function, based on multi-attribute utility theory, allows one to convert questionnaire responses into a measure of overall health utility, which can then be used to calculate quality-adjusted life years (QALYs) in clinical trials. In the London study, the HUI showed differential responsiveness to change in nocturnal versus conventional HD patients during longitudinal follow-up. Test-retest reliability at 4 weeks was a 0.77. HUI scores will be used for quality-adjustment of survival time in the economic evaluation of this trial. *[Archive note: 'HUI scores will be used for quality-adjustment of survival time in the economic evaluation of this trial' was not done during the course of the trials.]*

Beck Depression Inventory *[Archive note: This instrument required a licensing agreement and the data collection form was not permitted to be displayed on the FHN website. This instrument was completed in English and Spanish.]*

The Beck Depression Index (BDI), a 21-question validated survey presented in multiple-choice format, measures the presence and degree of depression in adults. Each of the answers is scored on a 0 to 3 scale, and inventory items correspond to a specific category of depressive symptom and/or attitude. BDI results are highly correlated with psychiatrists' ratings using the Hamilton Rating Scale (0.75-0.80). Based on a pooled analysis of studies in primary care, the sensitivity and specificity of the BDI in detecting moderate-severe depression are approximately 90 and 56%, respectively. Depressive symptoms are frequently encountered in patients with ESRD. The BDI has been frequently used to assess depression in patients with ESRD [14, 31-33]. High scores on the BDI are associated with mortality in this patient population.

The Medical Outcomes Study (MOS) Sleep Problems Index (SPI)

The Medical Outcomes Study (MOS) Sleep Problems Index (SPI) is a 12-item measure that includes items on sleep initiation and maintenance, sleep adequacy, daytime somnolence, and respiratory disturbance; 10 items of the SPI are summed to obtain an overall sleep score [34]. Subjects are instructed to relate responses to sleep habits over the previous month. The SPI showed good internal consistency reliability (Cronbach's alpha = 0.70) and discriminative validity, with lower (worse) overall sleep scores in HD patients versus patients without known kidney disease [34].

Caregiver Burden

The self-perceived burden scale is a measure to identify patients in emotional distress due to feelings of being a burden on others, and as an outcome measure in intervention studies. The conceptual framework and scale items were derived from previous literature and from qualitative interviews with patients and health professionals. This survey was administered in a construct validation to 100 outpatients undergoing hemodialysis. A 10-item abbreviation of the survey had an alpha = 0.85 [Cousineau, 2003] and this abbreviated version will be used in the FHN study.

Dialysis Specific Questions

There will be eight items specifically related to the frequent dialysis outcomes including time to recovery after dialysis, preference for dialysis modality, global quality of life, and three of the items regarding sexual function. The questions on sexual function will not be administered to minors enrolled in the study.

8.4 Script For the Telephone Administration Of The FHN HRQOL Survey

Hi, my name is ____ and I'm calling you from the University of Pittsburgh. I am calling on behalf of the Frequent Hemodialysis Study to conduct an interview with you. As you may recall, you recently agreed to participate in a randomized clinical trial evaluating the quality of life of dialysis patients. The survey will take about 40 minutes and your answers will be kept completely confidential. It's important that you answer as honestly and as accurately as possible.
1. YES
2. CALL BACK
3. TERMINATE CALL

Q:GENINTR
The following questions ask your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

If you are unsure about how to answer a question, please give the best answer you can. You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

Q:SFINTRO
These first questions are about your health now and your current daily activities. Please try to answer every question as accurately as you can.

Q:SF5
In general, would you say your health is….?
1. Excellent
2. Very good
3. Good
4. Fair
5. Poor
8. DON'T KNOW
9. REFUSED

Q:SF6
Compared to one year ago, how would you rate your health in general now? Would you say it is:
1. Much better now than one year ago
2. Somewhat better now than one year ago
3. About the same as one year ago
4. Somewhat worse now than one year ago
5. Much worse than one year ago
8. DON'T KNOW
9. REFUSED

Q:SF7a
Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities.
First, vigorous activities such as running, lifting heavy objects, or participating in strenuous sports. Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7b
. moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7c
. lifting or carrying groceries? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7d
. climbing several flights of stairs? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7e
. climbing one flight of stairs? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7f
. bending, kneeling, or stooping? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7g
. walking more than a mile? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7h
. walking several blocks? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7i
. walking one block? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF7j
. bathing or dressing yourself? Does your health now limit you a lot, limit you a little, or not limit you at all?
[INTERVIEWER: IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY, PROBE: "Is that because of your health?"]
1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all
8. DON'T KNOW
9. REFUSED

Q:SF8a
The following four questions ask about your physical health and your daily activities.
During the past 4 weeks, have you had to cut down on the amount of time you spent on work or other activities as a result of your physical health?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF8b
During the past 4 weeks, have you accomplished less than you would like as a result of your physical health?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF8c
During the past 4 weeks, were you limited in the kind of work or other regular daily activities you do as a result of your physical health?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF8d
During the past 4 weeks, have you had difficulty performing work or other regular daily activities, as a result of your physical health? For example, it took extra effort?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF9a
The following three questions ask about your emotions and your daily activities.
During the past 4 weeks, have you had to cut down the amount of time you spent on work or other activities as a result of any emotional problems, such as feeling depressed or anxious?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF9b
During the past 4 weeks, have you accomplished less than you would like as a result of any emotional problems, such as feeling depressed or anxious?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF9c
During the past 4 weeks, did you not do work or other regular daily activities as carefully as usual as a result of any emotional problems, such as feeling depressed or anxious?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SF10
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Has it interfered...
1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely
8. DON'T KNOW
9. REFUSED

Q:SF11
How much bodily pain have you had during the past 4 weeks? Have you had...
1. None
2. Very Mild
3. Mild
4. Moderate
5. Severe
6. Very Severe
8. DON'T KNOW
9. REFUSED

Q:SF12
During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework?
1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely
8. DON'T KNOW
9. REFUSED

Q:SF13INT
The next questions are about how you feel and how things have been with you during the past 4 weeks.

As I read each statement, please give the one answer that comes closest to the way you have been feeling; is it all of the time, most of the time, a good bit of the time, some of the time, a little bit of the time, or none of the time?

Q:SF13a
How much of the time during the past 4 weeks ... did you feel full of pep?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13b
How much of the time during the past 4 weeks ... have you been a very nervous person?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13c
How much of the time during the past 4 weeks ... have you felt so down in the dumps that nothing could cheer you up?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13d
How much of the time during the past 4 weeks ... have you felt calm and peaceful?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13e
How much of the time during the past 4 weeks ... did you have a lot of energy?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13f
How much of the time during the past 4 weeks ... have you felt downhearted and blue?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13g
How much of the time during the past 4 weeks ... did you feel worn out?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13h
How much of the time during the past 4 weeks ... have you been a happy person?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF13i
How much of the time during the past 4 weeks ... did you feel tired?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF14
These next questions are about your health and health-related matters.
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities, like visiting with friends, relatives, etc.?
1. All of the time
2. Most of the time
3. Some of the time
4. A little of the time
5. None of the time
8. DON'T KNOW
9. REFUSED

Q:SF15a
Now I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me.
I seem to get sick a little easier than other people. Would you say that's ...
1. Definitely True
2. Mostly True
3. Don’t Know
4. Mostly False
5. Definitely False
9. REFUSED

Q:SF15b
I am as healthy as anybody I know. Would you say that's...
1. Definitely True
2. Mostly True
3. Don't Know
4. Mostly False
5. Definitely False
9. REFUSED

Q:SF15c
I expect my health to get worse. Would you say that's...
1. Definitely True
2. Mostly True
3. Don't Know
4. Mostly False
5. Definitely False
9. REFUSED

Q:SF15d
My health is excellent. Would you say that's
1. Definitely True
2. Mostly True
3. Don't Know
4. Mostly False
5. Definitely False
9. REFUSED

Q:HUINTRO
The next set of questions asks about various aspects of your health. When answering these questions we would like you to think about your health and your ability to do things on a day-to-day basis, during the past week. To define the past week period, please think about what the date was 7 days ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past week. You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Q:HU5
During the past week, have you been able to see well enough to read ordinary newsprint WITHOUT glasses or contact lenses?
1. YES – SKIP TO HU8
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU6
Have you been able to see well enough to read ordinary newsprint WITH glasses or contact lenses?
1. YES – SKIP TO HU8
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU7
During the past week, have you been able to see at all?
1. YES
2. NO - SKIP TO HU10
8. DON'T KNOW
9. REFUSED

Q:HU8
During the past week, have you been able to see well enough to recognize a friend on the other side of the street WITHOUT glasses or contact lenses?
1. YES - SKIP TO HU10
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU9
Have you been able to see well enough to recognize a friend on the other side of the street WITH glasses or contact lenses?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU10
During the past week, have you been able to hear what is said in a group conversation with at least three other people WITHOUT a hearing aid?
1. YES – SKIP TO HU15
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU11
Have you been able to hear what is said in a group conversation with at least three other people WITH a hearing aid?
1. YES – SKIP TO HU13
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU12
During the past week, have you been able to hear at all?
1. YES
2. NO – SKIP TO HU15
8. DON'T KNOW
9. REFUSED

Q:HU13
During the past week, have you been able to hear what is said in a conversation with one other person in a quiet room WITHOUT a hearing aid?
1. YES – SKIP TO HU15
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU14
Have you been able to hear what is said in a conversation with one other person in a quiet room WITH a hearing aid?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU15
During the past week, have you been able to be understood COMPLETELY when speaking your own language with people who do not know you?
1. YES – SKIP TO HU20
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU16
Have you been able to be understood PARTIALLY when speaking with people who do not know you?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU17
During the past week, have you been able to be understood COMPLETELY when speaking with people who know you well?
1. YES – SKIP TO HU20
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU18
Have you been able to be understood PARTIALLY when speaking with people who know you well?
1. YES – SKIP TO HU20
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU19
During the past week, have you been able to speak at all?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU20
During the past week, have you been able to bend, lift, jump and run WITHOUT DIFFICULTY and WITHOUT HELP OR EQUIPMENT of any kind?
1. YES – SKIP TO HU28
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU21
Have you been able to walk around the neighborhood WITHOUT DIFFICULTY and WITHOUT HELP OR EQUIPMENT of any kind?
1. YES – SKIP TO HU28
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU22
Have you been able to walk around the neighborhood WITH DIFFICULTY but WITHOUT HELP OR EQUIPMENT of any kind?
1. YES – SKIP TO HU28
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU23
During the past week, have you been able to walk at all?
1. YES - SKIP TO HU26
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU24
Have you needed mechanical support, such as braces or a cane or crutches, to be able to walk around the neighborhood?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU25
Have you needed the help of another person to walk?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU26
Have you needed a wheelchair to get around the neighborhood?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU27
Have you needed the help of another person to get around in the wheelchair?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU28
During the past week, have you had the FULL USE of both hands and ten fingers?
1. YES – SKIP TO HU32
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU29
Have you needed the help of another person because of limitations in the use of your hands or fingers?
1. YES
2. NO - SKIP TO HU31
8. DON'T KNOW
9. REFUSED

Q:HU30
Have you needed the help of another person with some tasks, most tasks, or all tasks?
1. SOME TASKS
2. MOST TASKS
3. ALL TASKS
8. DON'T KNOW
9. REFUSED

Q:HU31
Have you needed special equipment, for example special tools to help with dressing or eating, because of limitations in the use of your hands or fingers?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU32
During the past week, have you been able to eat, bathe, dress and use the toilet without difficulty?
1. YES – SKIP TO HU35
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU33
Have you needed the help of another person to eat, bathe, dress or use the toilet?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU34
Have you needed special equipment or tools to eat, bathe, dress or use the toilet?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU35
During the past week, have you been feeling happy or unhappy?
1. HAPPY
2. UNHAPPY – SKIP TO HU37
8. DON'T KNOW
9. REFUSED

Q:HU36
Would you describe yourself as having felt:
1. Happy and interested in life, or - SKIP TO HU38
2. Somewhat happy? – SKIP TO HU38
8. DON'T KNOW
9. REFUSED

Q:HU37
Would you describe yourself as having felt:
1. Somewhat unhappy
2. Very unhappy
3. So unhappy that life was not worthwhile
8. DON'T KNOW
9. REFUSED

Q:HU38
During the past week, did you ever feel fretful, angry, irritable, anxious or depressed?
1. YES
2. NO – SKIP TO HU41
8. DON'T KNOW
9. REFUSED

Q:HU39
How often did you feel fretful, angry, irritable, anxious or depressed?
1. Rarely
2. Occasionally
3. Often
4. Almost always
8. DON'T KNOW
9. REFUSED

Q:HU40
During the past week did you feel EXTREMELY fretful, angry, irritable, anxious or depressed; to the point of needing professional help?
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:HU41
How would you describe your ability to remember things, during the past week:
1. Able to remember most things
2. Somewhat forgetful
3. Very forgetful
4. Unable to remember anything at all
8. DON'T KNOW
9. REFUSED

Q:HU42
How would you describe your ability to think and solve day to day problems, during the past week:
1. Able to think clearly and solve problems
2. Had a little difficulty
3. Had some difficulty
4. Had a great deal of difficulty
5. Unable to think or solve problems?
8. DON'T KNOW
9. REFUSED

Q:HU43
Have you had any trouble with pain or discomfort, during the past week?
1. YES
2. NO – SKIP TO HU45
8. DON'T KNOW
9. REFUSED

Q:HU44
How many of your activities, during the past week, were limited by pain or discomfort:
1. None
2. A few
3. Some
4. Most
5. All
8. DON'T KNOW
9. REFUSED

Q:SD8
How often during the past 4 weeks did you feel that you had enough sleep to feel rested upon waking in the morning?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD9
How often during the past 4 weeks did you awaken short of breath or with a headache?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD10
How often during the past 4 weeks did you feel drowsy or sleepy during the day?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD11
How often during the past 4 weeks did you have trouble falling asleep?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD12
How often during the past 4 weeks did you awaken during your sleep time and have trouble falling asleep again?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD13
How often during the past 4 weeks did you have trouble staying awake during the day?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD14
How often during the past 4 weeks did you snore during your sleep?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD15
How often during the past 4 weeks did you take naps (5 minutes or longer) during the day?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q:SD16
How often during the past 4 weeks did you get the amount of sleep you needed?
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little bit of the time
6. None of the time
8. DON'T KNOW
9. REFUSED

Q: BSINTRO
OK, that's all of the sleep questions. Now I will ask you some other types of questions.
We are interested in how you feel about the relationship that you have with the person or people who help you out with your day-to-day activities. You may need a little bit of help with things like shoveling snow and carrying groceries, or a lot of help, like driving you to dialysis or preparing meals. The person who helps you may be a friend, neighbor, or a member of your family – someone who is NOT paid to help you. We will refer to this person as your caregiver.

For each of the statements that I read, please tell me how often you feel this way. Is it none of the time, a little of the time, some of the time, most of the time, or all of the time?

Q:BS5
I worry that the health of my caregiver could suffer as a result of caring for me.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS6
I worry that my caregiver is overextending him/herself in helping me.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS7
I am concerned that it costs my caregiver a lot of money to care for me.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS8
I feel guilty about the demands that I make on my caregiver.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS9
I am concerned that my caregiver is helping me beyond their capacity.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS10
I am concerned that I am "too much trouble" to my caregiver.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS11
I am concerned that because of my illness, my caregiver is trying to do too many things at once.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS12
I am confident that my caregiver can handle the demands of caring for me.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS13
I think that I make things hard on my caregiver.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:BS14
I feel that I am a burden to my caregiver.
1. None of the time
2. A little of the time
3. Some of the time
4. Most of the time
5. All of the time
8. DON'T KNOW
9. REFUSED

Q:SS5A
Okay, we have one last set of questions to go.
First of all, how long does it take you to recover from a dialysis session and resume your normal, usual activities?
INTERVIEWER: RECORD QUANITY HERE AND UNITS ON NEXT SCREEN.
ENTER 88 FOR DON'T KNOW AND 99 FOR REFUSED.
IF (88 OR 99) SKIP TO SS6

Q:SS5B
Units of measure in previous question:
1. MINUTES
2. HOURS
3. DAYS

Q:SS6
On a scale from 0 to 100, with 0 being "no inconvenience" and 100 being "extreme inconvenience," how inconvenient do you find dialysis?

Q:SS7A
Have you missed any pills in the past week?
1. YES
2. NO – SKIP TO SS8
8. DON'T KNOW – SKIP TO SS8
9. REFUSED – SKIP TO SS8

Q:SS7B
EXCEPT for your phosphate binders, have you missed any pills in the last week?
INTERVIEWER NOTE: PHOSPHATE BINDERS INCLUDE, BUT ARE NOT LIMITED TO: TUMS, OSCAL, CALCIUM CARBONATE, CALCIUM ACETATE (PHOS-LO), RENAGEL, LANTHANUM CARBONATE, ETC. THESE PILLS ARE TAKEN WITH EACH MEAL TO BIND TO THE PHOSPHORUS.
1. YES
2. NO
8. DON'T KNOW
9. REFUSED

Q:SS8
The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.
Have you had any sexual activity in the past 4 weeks?
1. YES
2. NO – SKIP TO SS11A IF FOLLOWUP2; END OF SURVEY IF BASELINE OR FOLLOWUP1
8. DON'T KNOW – SKIP TO SS11A IF FOLLOWUP2; END OF SURVEY IF BASELINE OR FOLLOWUP1
9. REFUSED – SKIP TO SS11A IF FOLLOWUP2; END OF SURVEY IF BASELINE OR FOLLOWUP1

Q:SS9
How much of a problem was each of the following in the past 4 weeks?
Enjoying sex?
1. Not a problem
2. A little problem
3. Somewhat of a problem
4. Very much a problem
5. Severe problem
8. DON'T KNOW
9. REFUSED

Q:SS10
[HOW MUCH OF A PROBLEM WAS EACH OF THE FOLLOWING IN THE PAST 4 WEEKS?]
Becoming sexually aroused?
1. Not a problem
2. A little problem
3. Somewhat of a problem
4. Very much a problem
5. Severe problem
8. DON'T KNOW
9. REFUSED

QUESTIONS SS11A TO SS11C ARE ONLY ASKED IN FOLLOWUP 2

Q:SS11A
There are a number of different treatment options for patients with kidney failure. If you were eligible for all of the following treatments, which would you rank as your 1st preference?
1. Peritoneal dialysis
2. In-center 3 times weekly hemodialysis
3. In-center 6 times weekly hemodialysis
4. Home 6 times weekly daily hemodialysis
5. Home 6 times weekly nocturnal hemodialysis
6. Kidney transplant
7. NO PREFERENCE – SKIP TO FINALQ
8. DON'T KNOW – SKIP TO FINALQ
9. REFUSED – SKIP TO FINALQ

Q:SS11B
Which would be your 2nd preference?
1. Peritoneal dialysis
2. In-center 3 times weekly hemodialysis
3. In-center 6 times weekly hemodialysis
4. Home 6 times weekly daily hemodialysis
5. Home 6 times weekly nocturnal hemodialysis
6. Kidney transplant
7. NO 2^{ND} PREFERENCE – SKIP TO FINALQ
8. DON'T KNOW – SKIP TO FINALQ
9. REFUSED – SKIP TO FINALQ

Q:SS11C
Which would be your 3rd preference?
1. Peritoneal dialysis
2. In-center 3 times weekly hemodialysis
3. In-center 6 times weekly hemodialysis
4. Home 6 times weekly daily hemodialysis
5. Home 6 times weekly nocturnal hemodialysis
6. Kidney transplant
7. NO 3RD PREFERENCE
8. DON'T KNOW
9. REFUSED

Q:FINALQ
That's all of my questions! Do you have any additional comments before we end the survey?

Q: THANKYOU
Thank you for your time!

References:

1. Sloan JA, Cella D, Frost M, Guyatt GH, Sprangers M, Symonds T, Clinical Significance Consensus Meeting G: Assessing clinical significance in measuring oncology patient quality of life: introduction to the symposium, content overview, and definition of terms. *Mayo Clinic Proceedings.* 77:367-370, 2002
2. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *Journal of the American Society of Nephrology.* 12:2797-2806, 2001
3. Kutner NG, Jassal SV: Quality of life and rehabilitation of elderly dialysis patients. *Semin Dial* 15:107-112, 2002
4. Kimmel PL, Emont SL, Newmann JM, Danko H, Moss AH: ESRD patient quality of life: Symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *American Journal of Kidney Diseases* 42:713-721, 2003
5. Laupacis A: Changes in quality of life and functional capacity in hemodialysis patients treated with recombinant human erythropoietin. The Canadian Erythropoietin Study Group. *Seminars in Nephrology* 10:11-19, 1990
6. Evans RW, Rader B, Manninen DL: The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group [see comments]. *Jama* 263:825-830, 1990
7. Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE, Jr.: The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *Journal of the American Society of Nephrology* 7:763-773, 1996
8. Tsai TJ, Lai JS, Lee SH, Chen YM, Lan C, Yang BJ, Chiang HS: Breathing-coordinated exercise improves the quality of life in hemodialysis patients. *Journal of the American Society of Nephrology.* 6:1392-1400, 1995
9. Tawney KW, Tawney PJ, Hladik G, Hogan SL, Falk RJ, Weaver C, Moore DT, Lee MY: The life readiness program: a physical rehabilitation program for patients on hemodialysis. *Am J Kidney Dis* 36:581-591, 2000
10. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL: A randomized trial of exercise training after renal transplantation. *Transplantation* 74:42-48, 2002
11. Iborra Molto C, Pico Vicent L, Montiel Castillo A, Clemente Ramon F: Quality of life and exercise in renal disease. *Edtna Erca J* 26:38-40, 2000
12. DeOreo PB: Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *American Journal of Kidney Diseases* 30:204-212, 1997
13. Lowrie EG, Curtin RB, Lepain N, Schatell D: Medical outcomes study short form-36: A consistent and powerful predictor of morbidity and mortality in dialysis patients. *American Journal of Kidney Diseases* 41:1286-1292, 2003
14. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH: Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients.[see comment]. *Kidney International.* 54:245-254, 1998
15. Unruh M, Benz R, Greene T, Yan G, Beddhu S, DeVita M, Dwyer JT, Kimmel PL, Kusek JW, Martin A, Rehm-McGillicuddy J, Teehan BP, Meyer KB: Effects of

hemodialysis dose and membrane flux on health-related quality of life in the HEMO Study. *Kidney Int* 66:355-366, 2004
16. Edgell ET, Coons SJ, Carter WB, Kallich JD, Mapes D, Damush TM, Hays RD: A review of health-related quality-of-life measures used in end-stage renal disease. [Review] [129 refs]. *Clinical Therapeutics* 18:887-938, 1996
17. Kimmel PL: Just whose quality of life is it anyway? Controversies and consistencies in measurements of quality of life. *Kidney International* 57:S113-S120, 2000
18. Meyer KB, Espindle DM, DeGiacomo JM, Jenuleson CS, Kurtin PS, Davies AR: Monitoring dialysis patients' health status. *American Journal of Kidney Diseases* 24:267-279, 1994
19. Singer MA: Health status instruments as an outcome measure: What role can the individual physician play? *Annales CRMCC* 26:160-164, 1993
20. DeOreo PB: The use of patient-based instruments to measure, manage, and improve quality of care in dialysis facilities. *Advances in Renal Replacement Therapy*. 8:125-130, 2001
21. Callahan MB, LeSage L, Johnstone S: A model for patient participation in quality of life measurement to improve rehabilitation outcomes. *Nephrology News & Issues.* 13:33-37, 1999
22. Ware J, Keller S: Interpreting General Health Measures, in *Quality of Life and Pharmacoeconomics in Clinical Trials*, edited by Spilker B, Second edition ed, Philadelphia, Lippincott-Raven, 1996, pp 445-460
23. Ware J, Snow K, Kosinski M, Gandek B: *SF-36 Health Survey Manual and Interpretation guide*. Boston, The Health Institute, New England Medical Center, 1993
24. Ware JE: The Status of Health Assessment 1994. *Annual Review of Public Health* 16:327-354, 1995
25. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 30:473-483, 1992
26. Ware JE, Stewart AL: Measuring Functioning and Well-Being, in, Durham and London, Duke University Press, 1992, p 449
27. Ware JEJ, Kosinski MA, Keller SD: SF-36 Physical and Mental Health Summary Scales: A User's Manual, in, Boston, The Health Institute, New England Medical Center, 1994, p 7:23
28. Kurtin PS, Davies AR, Meyer KB, DeGiacomo JM, Kantz ME: Patient-based health status measures in outpatient dialysis. Early experiences in developing an outcomes assessment program. *Medical Care* 30, 1992
29. Rettig RA, Sadler JH: Measuring and improving the health status of end stage renal disease patients. *Health Care Financing Review* 18:77-82, 1997
30. Nortvedt MW, Riise T, Myhr KM, Nyland HI: Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. *Medical Care.* 38:1022-1028, 2000
31. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney International.* 57:2093-2098, 2000
32. Kimmel PL: Depression in patients with chronic renal disease: what we know and what we need to know. *Journal of Psychosomatic Research.* 53:951-956, 2002

33. Kimmel PL, Patel SS, Peterson RA: Depression in African-American patients with kidney disease. *Journal of the National Medical Association.* 94:92S-103S, 2002
34. Unruh ML, Hartunian MG, Chapman MM, Jaber BL: Sleep quality and clinical correlates in patients on maintenance dialysis. *Clin Nephrol* 59:280-288, 2003
35. Cousineau N, McDowell I, Hotz S, Hebert P: Measuring chronic patients' feelings of being a burden to their caregivers: development and preliminary validation of a scale. *Med Care*. 41:110-118, 2003.

9. USRDS Data Flow

9.1 Introduction

The United States Renal Data System (USRDS) is funded by NIDDK to collect information on all patients undergoing dialysis in the U.S. Therefore, the USRDS already obtains personal identification data (e.g., Social Security number) on these patients. The FHN clinical centers will provide the USRDS with FHN patient's SSN and Medicare HIC number so that the patient can be linked by matching on the FHN patient ID and alpha code to the deidentified biospecimens of the patient stored in the NIDDK Repository. In addition the USRDS will provide CMS with a list of patients enrolled in FHN trials so that CMS can reimburse the dialysis providers as appropriate (see Section 2.1) for an extra dialysis treatment.

9.2 Procedures and Confidentiality

How to send data – Personal identification data should be sent via the type of courier service that can be tracked and verified for timely receipt. There is no special courier service that must be used. The USRDS office is equipped with a security key entry and the data will be stored in a locked room with restriction access only to key personnel. All USRDS employees have to sign patient privacy confidentiality agreement forms before being allowed to access patient identifiable data.

Who will be receiving the data at the USRDS? – Mr. Shu-Cheng Chen, 914 South 8th Street, Suite D-206, Minneapolis, Minnesota 55404, U.S.A. Phone: 612-347-6332.

Where will the electronic file be stored and with what security? – The electronic file will be stored on a separate external hard drive on a private network and locked with password protection.

How long will this electronic file be kept? – It will be kept indefinitely to allow patients to contact USRDS to request that their stored Repository samples be withdrawn from use in future studies (see Section 9.3). Note that, USRDS already has the SSN of the patient through its own database.

Will the paper copy be shredded or stored? – The paper received from the FHN clinical centers will be shredded by USRDS once it is entered into the USRDS database. The SSN information can also be destroyed by the clinical center once it is successfully sent to USRDS. Although it is recommended that patient personal information be retained at the clinical center until the end of the FHN trials.

9.3 Withdrawal of Patient Consent for Usage of Repository Specimens

Patients who have consented and provided biospecimens (e.g., serum and plasma) to the NIDDK Repository can withdraw their consent for using their samples in research studies. During the study, the patient should make this request to the clinical center that enrolled them, who will then notify the DCC using the patient's ID and alpha code. The DCC will instruct the Repository to destroy this patient's samples. After the study ends

the patient should send a written request to: Mr. Shu-Cheng Chen, USRDS: 914 South 8th Street, Suite D-206, Minneapolis, Minnesota 55404, U.S.A.
and provide their name and SSN. USRDS will use the matched patient ID and alpha code to notify the Repository to destroy this patient's samples.

10. Comorbidity Assessment

10.1 Introduction

The assessment of comorbidity is important to determine as the number and severity of non-renal medical conditions will vary from study patient to study patient. There are a number of comorbidity scales that have been developed. In the HEMO Study, the ICED was used to assess comorbidity; however, this assessment took 30 – 45 minutes to complete for each patient. The Charlson Index was developed in 1987 and has been used in numerous analyses of comorbidity in both non-dialysis and dialysis patients.

The FHN comorbidity assessment (Form 104) includes items from the Charlson Index. This index contains 19 categories of comorbidity, which are primarily defined using ICD-9-CM diagnoses codes (a few procedure codes are also employed). Each category has an associated weight, taken from the original Charlson paper [1], which is based on the adjusted risk of one-year mortality. The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality; the higher the score, the more severe the burden of comorbidity. The original Charlson Index included points for the presence of kidney failure; a modified Charlson score for dialysis patients has been developed and will be used in the FHN trials.

10.2 Data Sources

It is important to have a number of different data sources in order to fully capture the comorbidites for each of the study patients. Key data sources include hospital discharge summaries, physician consultation notes, and the nephrologist's comprehensive clinical assessment of the patient that includes a past medical history. At least one of these documents must be present from within the past 6 months in order to complete the comorbidity profile. Other additional sources that may be used to assess comorbidity include physician progress notes at the dialysis unit, nurses progress notes at the dialysis unit, medical problem lists and the completed HCFA 2728 form that lists comorbidities at the initiation of chronic dialysis therapy.

As many of these data sources as possible should be collected PRIOR to the comorbidity review. Note that these records may be located at a hospital, the nephrologist’s office, or the dialysis unit and that these records could be either paper records or stored electronically.

The study coordinator who is trained by the DCC to use Comorbidity Form 104 (which includes the Modified Charlson Index) will assess comorbidity of patients in the FHN Trials.

10.3 Frequency

The comorbidity assessment will be conducted on each patient at baseline in the Daily Study and Nocturnal Study.

Reference:

1. Charlson ME, Pompei P, Ales KL, McKenzie CR (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis, 40(5), 373-383.

11. Modified Mini Mental

11.1 Rationale for Measuring Cognitive Function in the Frequent Hemodialysis Network

Cognitive impairment is common in hemodialysis patients, and may adversely affect quality of life. Frequent hemodialysis, through its effects on a number of biological and psychosocial factors may positively affect cognitive function.

The Mini-Mental State Examination is a widely used test of cognitive function among the elderly. The 3MS exam, or Modified Mini-Mental State Exam[1] is an expanded 100-point version of the original designed to increase the sensitivity and specificity of the test as a screen for dementia. Compared to the Mini-Mental State Exam, the 3MS covers a wider range of difficulty levels and enhances the reliability and validity of the scores while maintaining the brevity and ease of administration of the original. Individual items on the 3MS will be scored by test administrators; the total score is derived by computer algorithm. The test administrator should not attempt to score the test during the testing of the study participant.

In the Frequent Hemodialysis Network (FHN), the 3MS will be administered at baseline, 4 months, and at 12 months in the Daily Trial and baseline, 5 months, and at 14 months in the Nocturnal Trial. Although there are alternate forms available for repeated administration, a single version of the 3MS will be used in the FHN study.

11.2 Equipment and Supplies

- Number #2 pencils with eraser
- Stop watch
- "Close your eyes" (Card # 1) (See Appendix A)
- Several pieces of blank paper
- Intersecting pentagons card (Card # 2) (See Appendix A)

11.3 Safety Issues and Exclusions

None.

11.4. Participant and Exam Room Preparation

The 3MS should be administered in a quiet place, with minimal distractions, at a desk or table the participant can use as a writing table. If any temporary condition that may detract the participant from their optimal performance cannot be removed, the participant should be moved to another location; if this is not possible, reschedule the exam. Ask the participant if they are comfortable. Reassure them that this is a routine test of concentration and memory that will be done several times during the course of the study.

11.5 Detailed Measurement Procedures

11.5.1 General Issues

Examiners should thoroughly familiarize themselves with the testing procedures and the scoring criteria before using the 3MS test in formal assessment. While the 3MS form contains condensed information from the manual, misunderstandings of this information can easily occur. In the

administration of the 3MS exam, give at least 2 seconds for a response, but do not converse or offer extra help. If the participant says “I don’t know” or is unable to give an answer, the examiner may prompt once with the statement, “Please try,” or “Give it a try.” When a participant gives an incorrect answer the examiner scores accordingly and proceeds to the next item. If the participant asks how they are doing, say, “We appreciate your effort.” Although time limits are set for some items, they are used only for guiding the examiners in pacing the administration and in scoring. The participant should never be told of any time limit on any item. The stopwatch should always be kept out of the participant’s view.

11.5.2 General Scoring Issues

The 3MS examination asks the participants to provide information and to perform specific tasks as instructed by the examiner to assess cognitive function. Based on the response or performance of the task, the interviewer marks the appropriate level of "correctness" of the response.

The 3MS version of the exam broadens the final range of scores from 0-30 to 0-100 and exhibits greater sensitivity in screening participants for dementia. The 3MS scores will be generated by a computer algorithm after data entry.

The test administrator should not attempt to score the exam during the actual patient testing phase.

1) If you cannot determine how to code the response, record notes in the left-hand margin so that the scoring can be reviewed later. Bring ambiguities to the attention of the *clinic quality control officer.*

2) If a task is not attempted due to a physical limitation such as vision or hearing impairment, severe arthritis, or illiteracy, that task is scored "Not Attempted/Disability". If a task is scored “Not Attempted/Disability", the reason the task was not completed must be specified in Item 24 on Form 231. - Special Problems. Please indicate the questions that were affected.

3) Check "error/can't do/refused" if the task is not successfully completed for any other reason. This includes errors due to cognitive dysfunction, refusals when no physical or functional disability is present, lack of response, or the participant says they can’t remember.

4) Let the participant attempt all tasks unless you determine that the participant cannot do the task. In these cases, score the question "Can’t do/refused". This includes instances in which you perceive:

• the participant is unable to do the task;
• the participant appears to be experiencing excess stress; or
• no response is received from the participant after a reasonable time period.

5) If the participant answers the question correctly but not within the specified time limit (if a time limit is given), the question remains incorrect (scored can't do/refused). Quick self-corrections are OK as long as they are within the specified time limit. In these as in all cases, continue on to the next question without delay.

11.5.3 Administration

1) Introduce test to participant.

Examiner Script: "Are you comfortable? I would like to ask you a few questions that require concentration and memory. Some are a little bit more difficult than others. Some questions will be asked more than once."

2) Read each question from the form and mark the appropriate level of response.

3) Always read scripts exactly as written.

4) Give at least 2 seconds for the participant to initiate an answer.

5) Always be discreet with the use of the stopwatch.

11.5.3.1 Date and Place of Birth

Question 5 is a measure of long-term memory. It is assumed that everyone has had repeated opportunities to learn and report their date and place of birth.

Question 5a to 5c - When were you born?

1) Fill in the month, day and year reported by the participant; then in the adjacent space enter a "1" if the answer is correct, and a "0" if the answer is incorrect.

2) If partial or unrelated information is given, clarify the question by telling the participant you are looking for the month, day and year in which they were born.

3) If no response is given, record a "0" in the space provided.

Question 6a to 6b- Where were you born?

1) If the participant gives only a partial answer (e.g., only the city/town), ask for the missing information.

2) If an unrelated answer is given (e.g., hospital name), clarify the question by telling the participant you are looking for the city/town and state or country in which they were born.

Scoring:

• If the participant gives a response, record the city/town and state/country reported by the participant. Since we have no independent source for determining the accuracy of the response, the question is repeated in Question 23. When the participant's responses on both occasions are the same, the answer is considered correct and a "1' is recorded in the corresponding space. This

method assumes that when the participant does not remember, it is unlikely that the two responses will be identical.

11.5.3.2 Registration

Question 7 - "I am going to say three words for you to remember. Repeat them after I have said all three words: **shirt, blue, honesty."**

1) Make sure the participant is attentive when beginning the question.

2) Say the three words distinctly at the rate of 1 to 2 seconds per word.

3) The participant may repeat the words in any order.

4) If the participant repeats after each word is read by the examiner, at the end of your presentation say, "Tell me the three words again" and mark the score according to the responses to this request.

5) Do not repeat the words for the participant until after the first trial. When there are errors on the first trial, repeat the items up to six times until they are all learned. (Total of seven presentations.)

6) Be sure that the correct suffix of the word is repeated. For example, do NOT accept "shirts" for "shirt" or "honest" for "honesty". The exact form of the word must be repeated.

7) Record the number of presentations necessary for the participant to repeat the sequence (up to seven). If still not learned after seven presentations, record “error” for each word not learned and “7” in box 7d.

11.5.3.3 Mental Reversal

This item has two parts: counting backward from 5 to 1 and spelling WORLD backward. For each part, ask the participant to do the forward version first; coach once when needed. Only one attempt per question is allowed.

Question 8:

(first part): “I would like you to count from 1 to 5.” ***Wait as the participant counts.***

(second part): “Now I would like you to count backwards from 5 to 1.”

1) If the participant cannot count forward to 5, prompt with "Say 'one, two, three, four, five'" at the rate of 1.5 seconds per digit.

2) Coach only once, then continue with the second part of Question 8 even when the performance in counting forward is not perfect.

Scoring:

• Write the numbers in the sequence given in the blanks provided. If no response is given, record an '*'(asterisk) for each missed digit. The database will allow you to enter the asterisks and will score this item automatically once the participant's responses are entered.

• The computer will score a “2” if the participant accurately counts backwards, a “1” if the participant has 1-2 errors, and a “0” if the participant has >2 errors. Only question 8b will be scored.

Question 9

(first part): “Spell ‘WORLD’.” ***Wait as the participant spells.***

(second part): “Now spell ‘WORLD’ backwards.”

1) If the participant cannot spell "world" forward, prompt with "It is spelled W O R L D" at the rate of 1.5 seconds per letter.

2) Coach only once, then continue with the second part of Question 9 even when the performance in spelling forward is not perfect.

Scoring:

• Write the letters in the sequence given in the blanks provided. If no response is given, record an '*'(asterisk) for each missed digit. The database will allow you to enter the asterisks and will score this item automatically once the participant's responses are entered.

• The computer will score the number of correct responses in 9b. For example, if the participant names 3 letters in the correct sequent, the score for 9b will be a “3”.

11.5.3.4 First Recall of Three Words

Question 10 - What three words did I ask you to remember earlier?

1) The words may be repeated in **any** order.

2) For each word not readily reported, provide the category (for instance, "it is something to wear") followed by multiple choices when necessary. Do not wait more than 3 seconds for spontaneous recall and do not wait more than 2 seconds after giving the category before providing the next level of help.

3) If the participant gives an incorrect answer in the correct category (e.g., says "socks" or "coat" instead of "shirt"), provide the three alternatives for them to choose from, and score 1 when the choice is correct.

4) If the participant repeats an incorrect form of the correct word, e.g., "shirts" for "shirt" or "honest" for "honesty", a code has been added to reflect this answer ('correct word/incorrect form'). In these cases it is very important to repeat the word with the correct ending back to the participant for the subsequent recall.

Scoring: For each word, provide the response in the space provided:
• spontaneous recall;
• incorrect form of the correct word;
• correct recall after cueing with category;
• correct identification from the three alternatives;
• "unable to recall" when an inaccurate response was given after both prompts, or if the appropriate time limit has elapsed.

Example:
Examiner: "What three words did I ask you to remember earlier?"
Participant: "Shirt....." (3 second pause)

Examiner: "Another word is about a color."
Participant: "Blue!"

Examiner: "Good. Another word is about a good personal quality."
Participant: "Modesty?"

Examiner: "I'll give you three words to choose from - honesty, charity, modesty."
Participant: "Modesty!" (Or: No response for 2 seconds)

Examiner: "No. The word is 'honesty'."
For the above example the scores are “spontaneous recall,” “after ‘a color’’, and “unable to recall” respectively for shirt, blue and honesty.

11.5.3.5 Temporal Orientation

Question 11a through 11c - What is today's date?

1) Ask for the date. Fill in the month, day and year reported by the participant, and enter the corresponding numerical score for each response. For example, if the participant is within 1 month of the correct answer, score a ‘1’ for question 11a.

2) If no response is given, record ‘X' in each space provided.

Question 11d - "What day of the week is it?"

Fill in the day of the week reported by the participant, and enter the corresponding numerical score for each response. If no response is given, record an 'X' in the space.

Question 11e - What season of the year is it?

1) Since distinctions between seasons can be difficult during certain months, the following schedule has been created. For months with two seasons listed, either answer is correct.

Month	Correct Response
January	Winter
February	Winter
March	Winter or Spring
April	Spring
May	Spring
June	Spring or Summer
July	Summer
August	Summer
September	Summer or Fall (Autumn)
October	Fall (Autumn)
November	Fall (Autumn)
December	Fall (Autumn) or Winter

11.5.3.6 Spatial Orientation

1) For **questions 12a through 12c,** Fill in the blanks that were reported by the participant, and enter the corresponding numerical score for each response. If no response is given, record an 'X' in the space.

Question 12a - What state (province) are we in?

Question 12b - What county (parish) are we in?

Question 12c - What (city/town) are we in?

Question 12d - Are we in a clinic, store or home?

This question assumes that the test is being administered in a clinic setting. When the correct answer is not among the three alternatives (e.g., test is being conducted in a hospital or nursing home), substitute the correct response for the middle alternative (store).

2) If the participant responds that neither "clinic", "store" nor "home" is the correct answer, ask them to make the best choice out of the three options.

11.5.3.7 Naming

This set of questions tests whether or not the participant can promptly name the two objects and the five body parts.

Question 13a to 13b - What do you call this part...?

1) Ask each question while pointing to the appropriate part on your own body.

2) Correct responses for each item are:

c. forehead or brow
d. chin
e. shoulder or shoulders
f. elbow or elbows
g. knuckle or knuckles

3) If the participant gives a scientific or medical version of the name for any of the body parts (i.e., 'medicalese'), ask them to provide the common name.

4) If the participant cannot name the item within 2 seconds or gives an incorrect answer, do not help or question again. Check "Error/refused" and continue with Question 14.

11.5.3.8 Four-Legged Animals

Question 14 - What animals have four legs? Tell me as many as you can.

1) Record each animal named in the spaces provided.

2) If the participant says "All animals have four legs", say "tell me their names."

3) Discontinue after 30 seconds. Record the total number of correct responses.

4) If the participant gives no response in 10 seconds and there are still at least 10 seconds remaining, gently remind them (once only): "What (other) animals have four legs?"

5) The first time an incorrect answer is provided, say, "I want four-legged animals." Do not correct for subsequent errors.

Scoring:

• Score one point for each correct animal.

• Different names for the same animal of different age or sex count as one animal. For example:
- kitten/cat
- puppy/dog
- deer/doe

• Those animals with similarities but true technical differences may be counted as two separate animals; e.g., pony and horse may be counted as two; mule and donkey may be counted as two; but ass and donkey are the same animal and must be counted as one.

Example:

Examiner: "What animals have four legs? Tell me as many as you can."
Participant: "Dog....Cat....Bird....."

Examiner: "I want four-legged animals."
Participant: "Oh, OK! Elephant...." Ten seconds pass and there are still ten seconds left of the 30 seconds.

Examiner: "What other animals have four legs?"
Participant: "Hippo....Dog....Kitten....Cow....Pig.... Chicken....Sheep...." Thirty seconds is up.

Score: 7

A set of abbreviations may be helpful for writing the animal names quickly.

11.5.3.9 Similarities

This question is designed to measure abstract or conceptual thinking. In general, 2 points are given for conceptual similarities which are primarily pertinent for both members of the pair. Always accept the first answer given. If two concepts are given simultaneously (i.e., within the first statement provided back by the participant), score the higher value of the two concepts.

Question 15a - In what way are an arm and a leg alike?

If the initial response is scored "Lesser correct answer" or "Error/refused", coach the participant by saying "An arm and a leg are both limbs or extremities" to reinforce the correct answer. ***Coach only for Question 15a.*** No other prompting or coaching is allowed.

Scoring:

• Check "Limbs, extremities, appendages" when the response is that they are both:
- limbs
- extremities
- appendages

• Check "Lesser correct answer" when the response is that both:
- are body parts
- bend
- move
- are long

- have joints
- other similar responses

• Check "Error" when the participant gives an incorrect similarity, tells how they are different, says "They are different" or "I don't know", or refuses to answer. Other examples of "Error" answers:

Question 15b - In what way are laughing and crying alike?

Scoring:

• Check "Expressions of feelings, emotions" when the response is that they are both expressions of:
- feelings
- emotions

• Check "Lesser correct answer" when the response is that both are:
- sounds
- expressions
- both have tears
- both are satisfying to you
- you cry with both
- other similar responses

• Check "Error/refused" when the participant gives an incorrect similarity, tells how they are different, says "They are different" or "I don't know", or refuses to answer.

Other examples of "Error/refused" answers:
- when you laugh, you laugh; when you cry, you cry

Questions 15c - In what way are eating and sleeping alike?

Scoring:

• Check "Necessary bodily functions, essential for life" when the response is that they are both are:
- necessary bodily functions
- essential for life

• Check "Lesser correct answer" when the response is that both are:
- body functions
- relaxing
- good for you
- other similar responses

• Check "Error/refused" when the participant gives an incorrect similarity, tells how they are different, says "They are different" or "I don't know", or refuses to answer.

11.5.3.10 Repetition

Question 16 - Repeat what I say: ***I would like to go out.***

Pronounce the individual words distinctly but with normal tempo of a spoken sentence.

Scoring:

• Check "Correct" when the sentence is repeated exactly.
• Check "1 or 2 words missed" when one or two incorrect words are given.
• Check "3 or more words missed" when three or more incorrect words are given, there is no response or the participant refuses.

Question 17 - Now repeat: ***No ifs, ands or buts.***

Pronounce the individual words distinctly but with normal tempo of a spoken sentence.

• Check "Correct" for each part (e.g., *ifs, ands, buts)* correctly repeated; give no credit if the participant misses the "s".

• Check "Error/refused" when the word is not correctly repeated (including when the "s" is not pronounced), no response is given or the participant refuses.

11.5.3.11 Read and Obey

Question 18 - Hold up Card # 1 and say, "**Please do this**."

1) If the participant does not close their eyes within 5 seconds, prompt by pointing to the sentence and saying "**Read and do what this says**".

2) If the participant has already read the sentence aloud spontaneously, simply say, "**Do what this says**." Allow 5 seconds for the response.

3) As soon as the participant closes their eyes, say: **"Open".**

4) Check "Closes eyes without prompting" when participant performs the command spontaneously.

Scoring:
• Check "Closes eyes after prompting" when participant performs the command only after the prompt: "**Read and do what this says**"

• Check "Reads aloud, but does not close eyes" when participant reads the command aloud either spontaneously or after the prompt, but does not close their eyes.

• Check "Does not read aloud or close eyes" when the participant neither reads the sentence aloud nor closes their eyes, or otherwise does not respond.

11.5.3.12 Writing

Question 19 - Please write the following sentence: ***I would like to go out***.

1) Hand participant a piece of blank paper and a #2 pencil with eraser. If necessary, repeat the sentence word by word as the participant writes.

2) Allow a maximum of 1 minute after the first reading of the sentence for scoring the task.

Scoring:
• NOTE: If the participant is still working at the end of one minute, allow them to complete the task for the sake of maintaining rapport and morale. Mark the 1
minute point on the product and do not credit for parts finished after 1 minute.

• Check "Correct" for each correct word, except "I".

• The following are considered acceptable:
- Printing or cursive writing
- All capital letters
- Self corrected errors

• The following are considered errors:
- Portions of sentence written after the one minute time limit.
- Spelling errors
- Incorrect mixed capitalizations, e.g., I Would Like To Go Out.

• Check "Error/refused" for each word which has any error listed above or if the participant does not respond.

Right- or Left-Handedness
Observe which hand the participant uses to write and record on the form. You will need this information later in Question 21. If this task was not performed due to a functional disability, ask the participant if they are right- or left-handed.

11.5.3.13 Copying Two Pentagons

Question 20 - Here is a drawing. Please copy the drawing onto this piece of paper.

1) Hand participant Card #2. Allow one minute for copying.

2) For right handed participants, present the sample on the left side; for left handed participants, present the sample on the right side.

3) Allow a maximum of 1 minute for response.

4) Do not allow the participant to trace the drawing.

Scoring:

• NOTE: If the participant is still working at the end of one minute, allow them to complete the task for the sake of rapport and morale. Mark the 1 minute point on the product and do not credit parts finished after 1 minute.

• Do not penalize for self-corrected errors, tremors, minor gaps, or overshoots.

• When gaps are found in the drawing, they are permissible if the shape of the pentagon can be perceived.

• Each pentagon is scored as follows: Check appropriate box:
- 5 approximately equal sides.
- 5 unequal sides, and the longest:shortest side ratio is > 2:1.
- non-pentagon enclosed figure is drawn.
- 2 or more lines, but it is not an enclosed figure.
- less than 2 lines or the participant refuses to do the task.
- participant does not attempt the task due to a functional disability such as visual impairment or severe arthritis, etc.

• The intersection is scored as follows:
- 4-cornered enclosure.
- not a 4-cornered enclosure.
- no enclosure or the participant refuses to do the task.
- participant does not attempt the task due to a functional disability such as visual impairment or severe arthritis.

11.5.3.14 Three Stage Command

Question 21 - Hold up a piece of white paper in plain view of the participant but out of their reach and say: "**Take this paper with your left (right for left handed person) hand, fold it in half using both hands, and hand it back to me."**

1) Refer to Question 19f to check whether the participant is right- or left-handed. Ask them to take the paper in their non-dominant hand.

2) After saying the whole command, hold the paper within reach of the participant.

NOTE: - Do not repeat any part of the command.

- If the participant requests the examiner to repeat a portion of the command and it is felt appropriate to oblige for sake of maintaining rapport, score according to the response(s) executed prior to repeating command.

- Do not move the paper toward the participant.

- Do not move your hand toward the participant as a gesture to take the paper back.

3) If the participant reaches for the paper right after hearing the first portion of the command, move your hand away from the participant so that the paper is out of reach and continue to state the next two parts of the command without interruption.

4) The participant may hand back the paper with either hand.

Scoring:

• Check "correct" for each portion of the command completed correctly.

• Check "Error/refused" for each portion of the command incorrectly completed. This includes:
- First portion: Participant uses dominant/preferred hand.
- Second portion: Participant folds the paper more than once.
- Third portion: Participant puts the paper down instead of handing it back to the examiner.
- Participant refuses to do the task.

• Check "not attempted/disabled" when a physical or functional disability (such as severe arthritis) prevents the participant from answering.

11.5.3.15 Second Recall of Three Words

Question 22 - What three words did I ask you to remember earlier?

1) Administer this item even when the participant scored one or more "0's" on Question 5.

2) The words may be repeated in **any** order.

3) For each word not readily given, provide the category followed by multiple choices when necessary. Do not wait more than 3 seconds for spontaneous recall and do not wait more than 2 seconds after category cueing before providing the next level of help.

Scoring:

• If the participant repeats an incorrect form of the correct word, e.g., "shirts" for "shirt" or "honest" for "honesty", a code has also been added to reflect this answer ('correct word/incorrect form').

• If the participant gives an incorrect answer in the correct category (e.g., says "socks" or "coat" when the correct answer is "shirt"), provide the three alternatives for them to choose from, and score 1 if the choice is correct.

• If the participant cannot get the correct answer even after multiple choices, check "unable to recall/refused".

• Check "unable to recall/refused" if an incorrect response is given after both prompts, or when the appropriate time limit has elapsed.

11.5.3.16 Validation of Birthplace

Question 23 - Would you please tell me again where you were born?

1) Ask this question only when a response was given in Question 6a and 6b.

2) Score the response by checking against the response in Question 6a and 6b.

11.5.3.17 Special Problems

Question 24 - If physical/functional disabilities or other problems exist which cause the participant difficulty in completing any of the tasks, mark the box coded 'yes' and record the nature of the problem from the following problems codes:

- vision
- hearing
- writing problems due to injury or illness
- illiteracy/lack of education
- language

• If no special problems were noted, check '0'. The way to determine the above listed disability or problem will be by examiner's observation or participant's self-report. For example, if the participant has an obvious difficulty hearing the examiner, or clearly says, "I can't see," the examiner would mark the appropriate box next to the listed problem.

11.6 Alert Values/Follow-up/Reporting

When the interview is completed, thank the participant and tell them they did well, without offering specific feedback on their performance. You might say, "Thank you for doing this interview. You did just fine."

There are no alert values.

11.7. Quality Assurance

11.7.1 Training Requirements

The examiner requires no special qualifications or prior experience to perform this assessment. Training should include:

• Read and study manual

• Attend FHN training session on techniques (or observe administration by experienced examiner).

• Practice on volunteers

• Discuss problems and questions with local expert or QC officer

11.7.2 Certification Requirements

• Complete training requirements

• Explain how to score a question if:

- • Participant has a physical limitation making task impossible
- • Participant has cognitive limitation
- • Participant does not respond or can’t remember
- • Participant answers correctly but not within time allotted

11.7.3 Quality Assurance Checklist

Exam performed in quiet, private area without interruptions
_ Correct instructions given in clear, slow speaking voice
_ Stopwatch used discreetly
_ Missing parts of dates and birthplace asked for
_ List of 3 objects read slowly and evenly
_ 3 objects repeated until learned, up to 6 times
_ WORLD spelled out slowly, about 1 second per letter
_ Waiting for spontaneous recall no more than 3 seconds
_ Waiting for prompted (w/category) recall no more than 2 seconds
_ Standard pencil used for naming
_ Individual words and "s's" in phrase "NO IFS..." clearly enunciated
_ Pentagon drawing held ON LEFT SIDE for RIGHT-HANDED participant and on RIGHT SIDE for LEFT-HANDED participant
_ Pentagon drawing correctly scored

_ Paper for Three Stage Command Q21 held out in front of participant, NOT TO RIGHT OR LEFT

_ Responses correctly coded (QC officer should independently fill out scoring sheet)

_ Special problems (impairment, illiteracy, etc.) recorded in exam comments

_ Reviews form for completeness

_ Correctly completes form

11.8 References

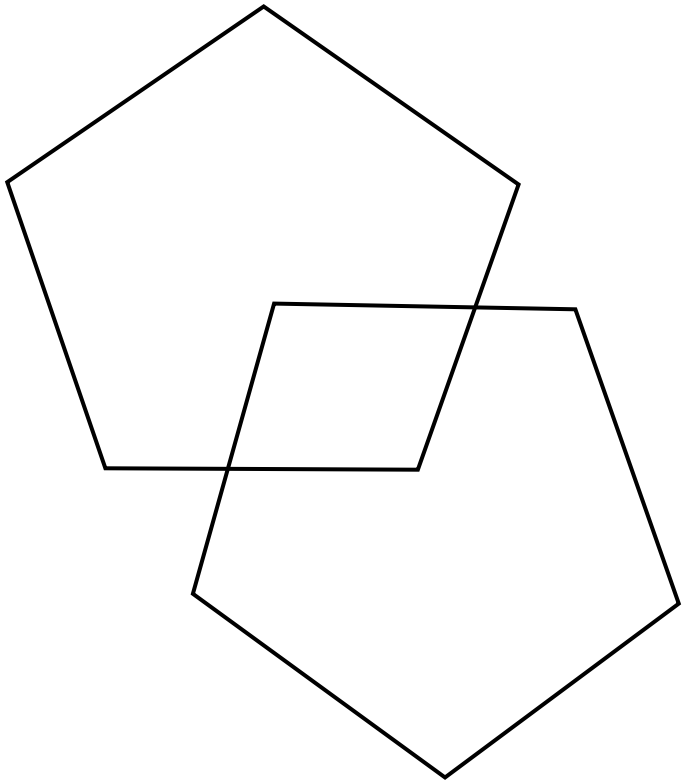
1. Teng, Evelyn Lee, and Helena Chang Chui. 1987. The Modified Mini-Mental State (3MS) Examination. J. Clin. Psychiatry 48:8 pp 314-318.

11.9 Timing of Tests

The coordinator may split up the bedside tests onto 2 or more separate days. Irrespective of whether they are done on the same day or on different days, the order of the tests should be set:

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) MiniMental
3) Trailmaking B
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

CLOSE YOUR EYES



12. Physical Functioning

Short Physical Performance Battery and Score Sheet

All of the tests should be performed in the same order as they are presented in this protocol. Instructions to the participant are shown in bold italic and should be given exactly as they are written in this script.

The participant must be able to stand unassisted without the use of a cane or walker. You may help the participant to get up.

Now let's begin the evaluation. I would now like you to try to move your body in different movements. I will first describe and show each movement to you. Then I'd like you to try to do it. If you cannot do a particular movement, or if you feel it would be unsafe to try to do it, tell me and we'll move on to the next one. Let me emphasize that I do not want you to try to do any exercise that you feel might be unsafe.

Do you have any questions before we begin?

A. Side-By-Side Stand

Script

1. ***Now I will show you the first movement.***
2. (Demonstrate) ***I want you to try to stand with your feet together, side-by-side, for about 10 seconds.***
3. ***You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.***
4. Stand next to the participant to help him/her into the side-by-side position.
5. Supply just enough support to the participant's arm to prevent loss of balance.
6. When the participant has his/her feet together, ask ***"Are you ready?***"
7. Then let go and begin timing as you say, ***"Ready, begin."***
8. Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the participant steps out of position or grabs your arm.
9. If participant is unable to hold the position for 10 seconds, record result and go to the gait speed test.

B. Semi-Tandem Stand
Script

1. ***Now I will show you the second movement***
2. (Demonstrate) ***Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you.***
3. ***You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.***
4. Stand next to the participant to help him/her into the semi-tandem position.
5. Supply just enough support to the participant's arm to prevent loss of balance.
6. When the participant has his/her feet together, ask ***"Are you ready?"***
7. Then let go and begin timing as you ***"Ready, begin."***
8. Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the participant steps out of position or grabs your arm.
9. If participant is unable to hold the position for 10 seconds, record result and go to the gait speed test.

C. Tandem Stand
Script

1. ***Now I will show you the third movement.***
2. (Demonstrate) ***Now I want you to try to stand with heel of one foot in front of and touching the toes of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you.***
3. ***You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.***
4. Stand next to the participant to help him/her into the tandem position.
5. Supply just enough support to the participant's arm to prevent loss of balance.
6. When the participant has his/her feet together, ask "***Are you ready?"***
7. Then let go and begin timing as you say, ***"Ready, begin."***
8. Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the participant steps out of position or grabs your arm.

Scoring

A. Side-by-side stand

Held for 10 sec	☐	1 point
Not held for 10 sec	☐	0 points
Not attempted **(check the reason on Page 4)**	☐	0 points

If 0 points, end Balance Tests

Number of seconds held if less than 10 sec: __ .__ __ sec

B. Semi-Tandem Stand

Held for 10 sec	☐	1 point
Not held for 10 sec	☐	0 points
Not attempted **(check the reason on Page 4)**	☐	0 points

If 0 points, end Balance Tests

Number of seconds held if less than 10 sec: __ .__ __ sec

C. Tandem Stand

Held for 10 sec	☐	2 points
Not held for 3 to 9.99 sec	☐	1 points
Held for < than 3 sec	☐	0 points
Not attempted **(check reason on page 4)**	☐	0 points

If 0 points, end Balance Tests

Number of seconds if less than 10 sec: __. __ __ sec

If participant did not attempt test or failed, check why:

Tried but unable	1	☐
Participant could not hold position unassisted	2	☐
Not attempted, you felt unsafe	3	☐
Not attempted, participant felt unsafe	4	☐
Participant unable to understand instructions	5	☐
Other (specify) _____	6	☐
Participant refused	7	☐

Gait Speed Test

Script

Now I am going to observe how you normally walk. If you use a cane or other walking aid and you feel you need it to walk a short distance, then you may use it.

Gait Speed Test Scoring

1. ***This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the store.***
2. Demonstrate the walk for the participant.
3. ***Walk all the way past the other end of the tape before you stop. I will walk with you. Do you feel this would be safe?***
4. Have the participant stand with both feet touching the starting line.
5. ***When I want you to start, I will say: "Ready, begin."*** When the participant acknowledges this instruction say: ***"Ready, begin."***
6. Press the start/stop button to start the stopwatch as the participant begins walking.
7. Walk behind and to the side of the participant.
8. Stop timing when one of the participant's feet is completely across the end line.

B. Second Gait Speed Test

1. ***Now I want you to repeat the walk. Remember to walk at your usual pace, and go all the way past the other end of the course.***
2. Have the participant stand with both feet touching the starting line.
3. ***When I want you to start, I will say: "Ready, begin."*** When the participant acknowledges this instruction say: ***"Ready, begin."***
4. Press the start/stop button to start the stopwatch as the participant begins walking.
5. Walk behind and to side of the participant.
6. Stop timing when one of the participant's feet is completely across the end line.

Length of walk test course: Four meters ☐ Three meters ☐

A. Time for First Gait Speed Test (sec)

1. Time for 3 or 4 meters __ __ . __ __ sec

2. If participant did not attempt test or failed, check why:

Tried but unable	1	☐
Participant could not walk unassisted	2	☐
Not attempted, you felt unsafe	3	
Not attempted, participant felt unsafe	4	☐
Participant unable to understand instructions	5	☐
Other (specify)_____	6	☐
Participant Refused	7	

Complete score sheet and go to chair stand test

3. Aids used for first walk:

None	☐
Cane	☐

Other (specify)_____

Comments:

B. Time for Second Gait Speed Test (sec)

1. Time for 3 or 4 meters ___ ___ . __ __ sec

2. If participant did not attempt test or failed, check why:

Tried but unable	1	☐
Participant could not walk unassisted	2	☐
Not attempted, you felt unsafe	3	☐
Not attempted, participant felt unsafe	4	☐
Participant unable to understand instructions	5	☐
Other (Specify) _____	6	☐
Participant refused	7	☐

3. Aids used for second walk:

None	☐
Cane	☐
Other (specify)_____	☐

What is the time for the faster of the two walks?
Record the shorter of the two times __ __ **.** __ __ sec
[If only 1 walk done, record that time] __ __ **.** __ __ sec

If the participant was unable to do the walk: 0 points

For 4-Meter Walk:		**For 3-Meter Walk:**	
If time is more than 8.70 sec:	**1 point**	If time is more than 6.52 sec:	**1 point**
If time is 6.21 to 8.70 sec:	**2 points**	If time is 4.66 to 6.52 sec:	**2 points**
If time is 4.82 to 6.20 sec:	**3 points**	If time is 3.62 to 4.65 sec:	**3 points**
If time is less than 4.82 sec:	**4 points**	If time is less than 3.62 sec:	**4 points**

CHAIR STAND TEST

Script

Single Chair Stand

1. ***Let's do the last movement test. Do you think it would be safe for you to try to stand up from a chair without using your arms?***

2. ***The next test measures the strength in your legs.***

3. (Demonstrate and explain the procedure.) ***First, fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest.***

4. ***Please stand up keeping your arms folded across your chest.*** (Record result).

5. If participant cannot rise without using arms, say ***"Okay, try to stand up using your arms."*** This is the end of their test. Record result and to the scoring page.

Repeated Chair Stands

1. ***Do you think it would be safe for you to try to stand up from a chair five times without using your arms?***

2. (Demonstrate and explain the procedure): ***Please stand up straight as QUICKLY as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch***

3. When the participant is properly seated, say: ***"Ready? Stand"*** and begin timing.

4. Count out loud as the participant arises each time, up to five times.

5. Stop if participant becomes tired or short of breath during repeated chair stands.

6. Stop the stopwatch when he/she has straightened up completely for the fifth time.

7. Also stop:
   - If participant uses his/her arms
   - After 1 minute, if participant has not completed rises
   - At your discretion, if concerned for participant's safety

8. If the participant stops and appears to be fatigued before completing the five stands, confirm this by asking ***"Can you continue?"***

9. If participant says "Yes," continue timing. If participant says "no", stop and reset the stopwatch.

Single Chair Stand Scoring

Single Chair Stand Test

		YES	NO
A.	Safe to stand without help	☐	☐

B. Results

- Participant stood without using arms → Go to Repeated Chair Stand Test
- Participant used arms to stand → End test; score 0 points
- Test not completed → End test; score as 0 points

C. If participant did not attempt test or failed, circle why:

Tried but unable	1	☐
Participant could not stand unassisted	2	☐
Not attempted, you felt unsafe	3	☐
Not attempted, participant felt unsafe	4	☐
Participant unable to understand instructions	5	☐
Other (specify)_____	6	☐
Participant refused	7	☐

Repeated Chair Stand Test

	Yes	No
A. Safe to stand five times	☐	☐

B. If five stands done successfully, record time in seconds.

Time to complete five stands __ __ . __ __ sec

C. If participant did not attempt test or failed, check why:

Tried but unable	1	☐
Participant could not stand unassisted	2	☐
Not attempted, you felt unsafe	3	☐
Not attempted, participant felt unsafe	4	☐
Participant unable to understand instructions	5	☐
Other (Specify) _____	6	☐
Participant refused	7	☐

Scoring the Repeated Chair Test

Participant unable to complete 5 chair stands or completes stands in >60 sec:	☐	0 points
If chair stand time is 16.70 sec or more	☐	1 points
If chair stand time is 13.70 to 16.69 sec:	☐	2 points
If chair stand time is 11.20 to 13.69 sec:	☐	3 points
If chair stand time is 11.19 sec or less:	☐	4 points

Scoring for Complete Short Physical Performance Battery

Test Scores	____	**points**
Total Balance Test score	____	**points**
Gait Speed Test score	____	**points**
Chair Stand Test score	____	**points**
Total Score	____	**points** **(sum of points above)**

Interviewer: Where was this test performed?

Clinic

Other (specify)
_____
_____

Timing of Tests

The coordinator may split up the bedside tests onto 2 or more separate days. Irrespective of whether they are done on the same day or on different days, the order of the tests should be set:

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) MiniMental
3) Trailmaking
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

13. Trail Making B

13.1. The Trailmaking Test Part B

The Trailmaking Test part B (Trails B) is a timed test of working memory, visual processing, visuospatial skills, selective and divided attention, and psychomotor coordination.

The test results are reported on FHN Form 232 - Trailmaking B Score Sheet.

13.2. Equipment and Supplies

- #2 pencils with eraser
- Stop watch
- Trails B sample form
- Trails B test form

13.3. Safety Issues and Exclusions

None.

13.4. Participant and Exam Room Preparation

Prior to administration of the test, remind the participant to bring their glasses or hearing aid, if applicable. As with the 3MS, the Trails B should be administered in a quiet place, with minimal distractions, at a desk or table the participant can use as a writing table.

13.5 Detailed Measurement Procedures

The Trails B involves connecting, in alternating order, encircled numbers (1-12) and encircled letters (A-L) randomly arranged on a page. This test is scored by overall time required to complete the connections accurately. The examiner points out and corrects mistakes as they occur; the effect of mistakes, then, is to increase the time required to complete the test. This test usually takes 3-4 minutes to administer but up to 10 minutes is permitted, if needed.

The participant is first given a sample test.
Script:
"You will notice that this page has both numbers and letters. Begin at number one, and draw a line from number one to the letter A, A to two, two to B, B to three, three to C, and so on, until you reach the end. Draw the lines as fast as you can."

After completing the sample test, the participant is given the Trails B test form.

Script:
“Good. Now do this test the same way. Begin at number one, and draw a line from number one to the letter A, A to two, two to B, B to three, three to C, and so on, until you reach the end. Remember, first you have a number, then a letter, and so on. Draw the lines as fast as you can. Go.”

If an error is made during the test, it is pointed out by the test administrator, who instructs the examinee to continue with the test from the last correct connection. The clock does not stop during error correction.

The examiner records the time-to-complete the test ***(in seconds)*** for Question 5. If the participant is close to finishing but their ten minutes of time has almost expired, allow them to go over the allotted time so they can complete the task. Enter a maximum time of 600 seconds on the score sheet, and record the number of correct responses for Question 6.

If the task is not attempted due to a physical limitation such as vision or hearing impairment, severe arthritis, or illiteracy, that task is scored "Not Attempted/Disability". If a task is scored “Not Attempted/Disability", the reason the task was not completed must be specified in Item 104.

If the task is not successfully completed for any other reason, including errors due to cognitive dysfunction, refusals when no physical or functional disability is present, lack of response, enter a maximum time of 600 seconds on the score sheet.

13.6 Timing of Tests

The coordinator may split up the bedside tests onto 2 or more separate days. Irrespective of whether they are done on the same day or on different days, the order of the tests should be set:

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) MiniMental
3) Trailmaking
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

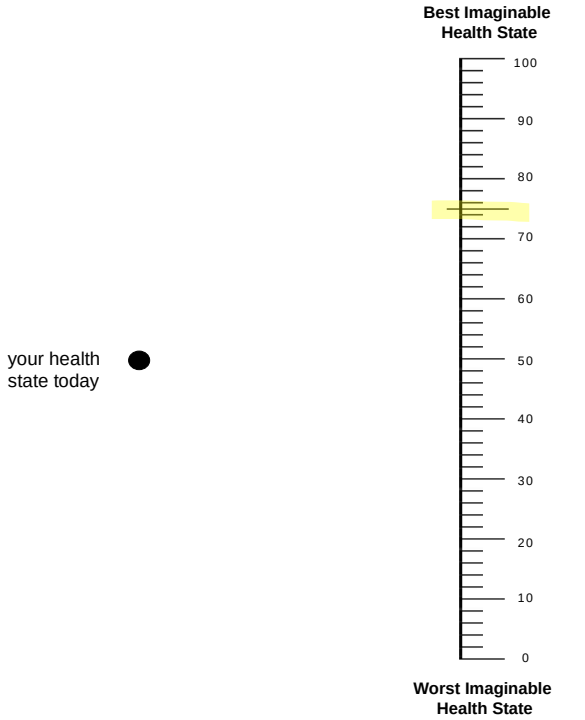
14. Feeling Thermometer Instructions

The Feeling Thermometer design is a visual scale where 100 represents the best imaginable health state and 0 being the worst imaginable health state or death. The Thermometer is self administered and must be filled in correctly to be valid. The participant should be instructed upon the design of the scale, 100 being their best imaginable health state and 0 being the worst. They should be instructed on the proper manner of completing the test. All assessments should be completed in the same manner. To complete the test the participant will need to draw a straight line from the provided black circle to the scale; intersecting the scale at a single point. To score the assessment, record the value where the straight line intersects the vertical portion of the scale.

The results are reported on FHN Form 230 - Feeling Thermometer.

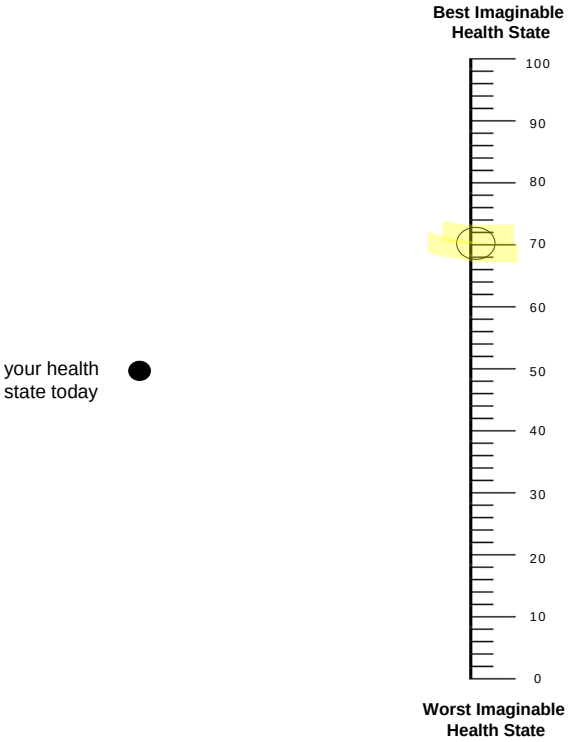
Examples have been provided for correct and incorrect completion of the Feeling Thermometer.

Example 1: Incorrect Completion of the Feeling Thermometer



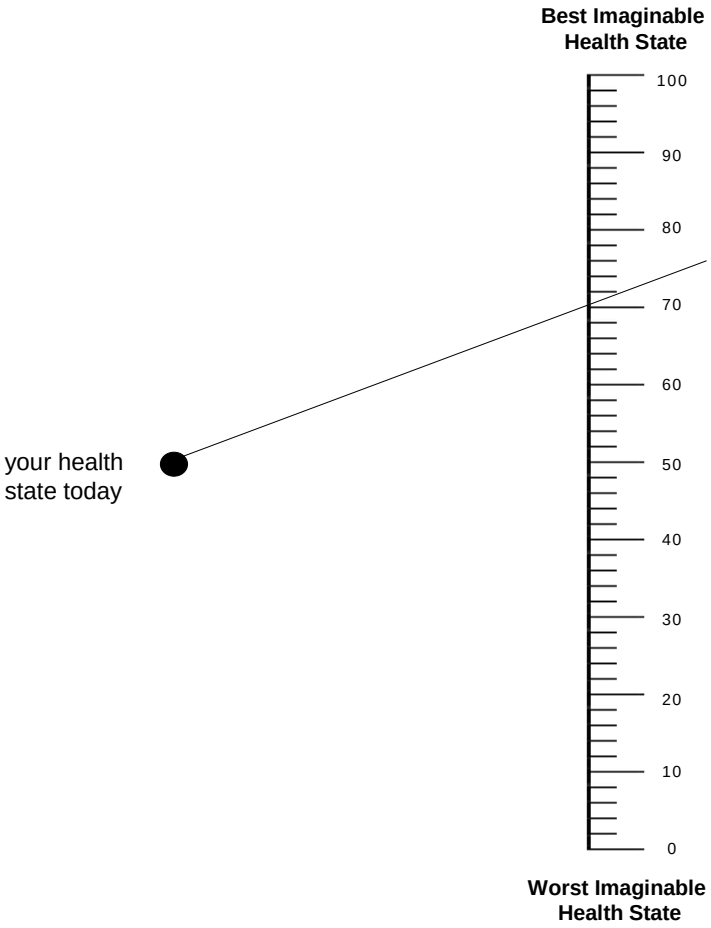
Placing a mark on the scale that did <u>not</u> originate from the black circle is not an acceptable method of completing the Feeling Thermometer.

Example 2: Incorrect Completion of the Feeling Thermometer



Circling a value on the scale is <u>not</u> an acceptable method of completing the Feeling Thermometer.

Example 3: Correct Completion of the Feeling Thermometer



A straight line originating from the black circle that intersects the scale at one point is the proper method of completing the Feeling Thermometer.

The intersect point in this example is at the 70 value.

Timing of Tests

The coordinator may split up the bedside tests onto 2 or more separate days. Irrespective of whether they are done on the same day or on different days, the order of the tests should be set:

1) Feeling Thermometer (this is done first to avoid mental and physical exhaustion from other tests affecting mood).
2) MiniMental
3) Trailmaking
4) Physical Function Tests (these are done last to avoid physical exhaustion affecting ability to do cognitive tests).

15. Bioelectrical Impedance Analysis (BIA) Procedure

15.1 Introduction

Accurate estimation of body composition and hydration plays an important role in the care of the end stage renal disease patient for a correct prescription of dialysis including ultrafiltration volume. There is interest in non-invasive, simple, and inexpensive techniques capable of estimating fluid content in different body compartments in order to determine the optimum hydration. Bioelectrical impedance analysis (BIA) which is used in nutritional analysis and intervention is considered such a technique.

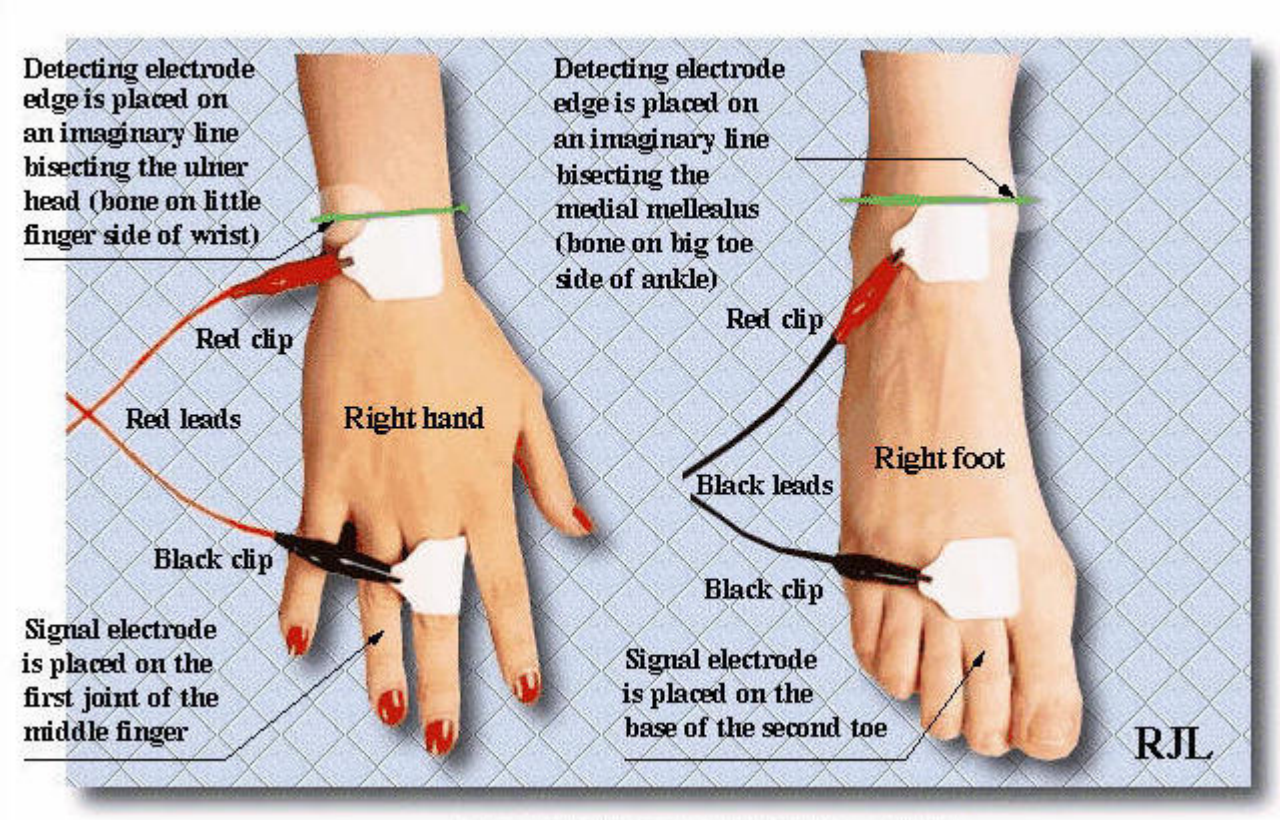
Single frequency bioelectric impedence assessments will be performed at baseline and at the F-1, F-4, and F-12 visits. All measurements will be conducted in the recumbent position, and will be performed immediately prior to a mid-week HD treatment (i.e., Wednesday or Thursday).

15.2 Subject Preparation

- The subject should not have exercised or taken a sauna within 8 hours of the study.
- The subject should refrain from alcohol intake for 12 hours prior to the study.
- The subject's height and weight should be accurately measured and recorded.
- The subject should lie quietly during the entire test.
- The subject should not be wet from sweat or urine.
- The subject should not have a fever or be in shock.
- The study and testing procedure should be explained to the subject.
- The exam area should be comfortable and free of drafts and portable electric heaters.
- The exam table surface must be non-conductive and large enough for the subject to lie supine with the arms 30 degrees from the body and legs not in contact with each other**.**
- The BIA – Quantum II analyzer should have a new 9 volt battery.
- The analyzer calibration and patient cables should be checked regularly.
- Record results on Form 242
- **The subject should be asked whether he or she has an implantable defibrillator or pacemaker. Patients with these devices at baseline will be excluded from FHN due to safety issues with the cardiac MRI. However, it is possible that an implantable defibrillator or pacemaker might have been placed AFTER baseline evaluation. Subjects with an implantable defibrillator or pacemaker should not undergo the BIA procedure.**

Electrodes Placement on the Hand and Foot

BIA TESTING PROCEDURE



15.3 Testing Procedure

- For subjects who have an arteriovenous fistula or graft in the upper extremity, the BIA procedure should be performed on the side opposite to the vascular access.
- For subjects with a catheter access, the BIA procedure should be performed on the right side.
- For subjects with a missing limb, the BIA procedure should be performed on the side opposite to the missing limb. If the subject is missing the designated digit (finger or toe), the lateral digit may be used to guide electrode placement.
- For subjects with missing limbs bilaterally, the BIA procedure should not be performed.
- The subject should remove his or her shoe and sock (generally the study is completed on the right side of the body). The same body side (left or right) should be used for follow-up testing.
- The subject should lie supine with the arms 30 degrees from the body and legs not touching (take care that upper thighs are not touching) **Remove any jewelry on the electrode side** and from around the neck.

- The electrode sites may be cleaned with alcohol, particularly if the skin is dry or covered with lotion. If electrodes do not stick despite use of alcohol, use NU prep as directed.
- Attach the electrodes and patient cables as shown in the illustration.
- Turn the analyzer on and make sure the subject refrains from moving. When the measurements have stabilized, record the displayed Resistance (R) and Reactance (Xc) with the subject's name, age, gender, height and weight.
- Remove and dispose of the electrodes. Be careful not injure the subject's skin or contaminate the operator.
- The entire testing time is less than 5 minutes - the BIA analyzer is on for less than one minute.

15.4 Operator Proficiency:

- Two consecutive measurements made on a single, stable subject should result in values within one percent.
- Please note: R does not lock onto an exact number because of muscle contractions in the heart and will fluctuate within 1-3 ohms). The recorded value for R should be the most representative number. If the number varies widely, check electrode placement, jewelry, make sure that no electrical equipment is on the chair and that the upper thighs are not touching.

Susan WIRTH
X 40124

Participant ID: _____ Participant Initials: _____

Clinical Center: _____ Site: _____ Visit Number: _____

CRF Date: ____ / ____ / ____ RC ID: _____

PHYSICAL ASSESSMENT

B. Ankle Brachial Index:

12. Right AB Index: ___ . ___ ___

13. Left AB Index: ___ . ___ ___

Calculation of Right Ankle Brachial (AB) Index (higher value of ankle systolic / higher value of brachial systolic):

Higher value in item # 7 or item #8 divided by value in item #6 or item 9.

Calculation of Left Ankle Brachial (AB) Index:

Higher value in item #10 or item #11 divided by value in item #6 or item 9.

BIOELECTRIC IMPEDANCE ASSESSMENT:

Assessment at Baseline Visit, 24 Month and 48 Month Visits.

14. Body position: ☐1 Supine *(preferred)* ☐2 Seated

Body position checked (in item #1) at Baseline Visit #3 must be used for subsequent testing.

15. Side measured: ☐1 Right ☐2 Left

Side measured (in item #2) at Baseline Visit #3 must be used for subsequent testing.

16. Measured Resistance (R): ___ ___ ___ (ohms)

17. Measured Reactance (Xc): ___ ___ ___ (ohms)

18. Technician ID: ☐1 ___ ___ ___ ___ *(Tech. ID for Anthropometry, ABI, BIA)*

OR ☐2 ___ ___ ___ ___ *(Tech. ID for Anthropometry)*

___ ___ ___ ___ *(Tech. ID for ABI)*

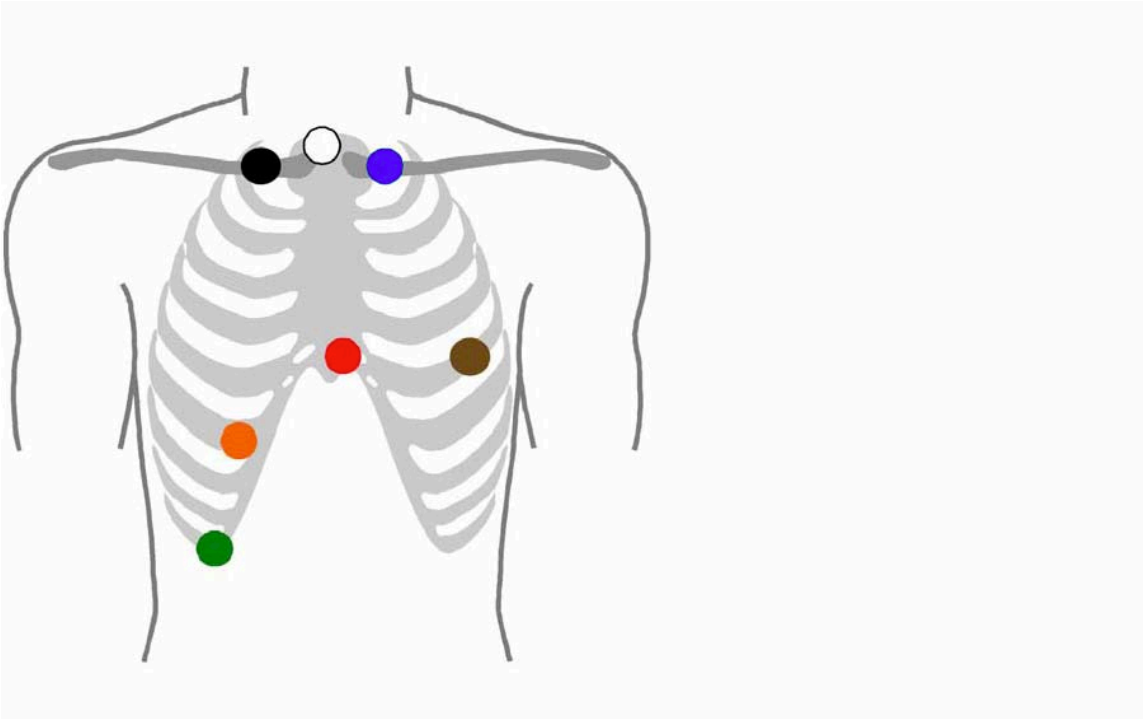
___ ___ ___ ___ *(Tech. ID for BIA)*

16. Holter Monitoring (Daily)

Technology & Services Info Sheet

KCI Holter System

3 Channel / 7 Lead Hookup



Brown Channel 2 (-) **White Channel 1 (-)** **Blue Channel 3 (-)**

Orange Channel 2 (+) **Red Channel 1 (+)** **Black Channel 3 (+)**

Green Ground

KCI - ELECTRODE APPLICATION INSTRUCTIONS

MATERIALS NEEDED:

Patient hook-up kit

1. **Cleartrace² LT disposable electrodes designed for long-term monitoring**
2. **Isopropyl alcohol pads (2)**
3. **Abrasive pad**
4. **Disposable razor**
5. **Tape for stress loops**
6. **2 AA Alkaline batteries**

Note: *Do not use 12-lead ECG or Stress Test Electrodes. Use electrodes designed for longer term 24 hour monitoring*

1. **Select an electrode placement from electrode placement chart.**
2. **Shave electrode area. Wipe the skin in the electrode area with an alcohol prep pad.**
3. **Wipe the skin in the electrode area with an alcohol prep pad again to insure the area is free of any oil.**
4. **Gently rub the electrode application area with the abrasive pad, rubbing the skin well. (Skin should be pink)**
5. **Repeat steps 1 through 4 for each of the 7 electrode sites.**
6. **Attach a colored leadwire to each of the 7 electrodes.**
7. **Remove the backing from a pre-gelled disposable electrode. Carefully place the electrode on a prepared skin surface site. Take care to place the gelled electrode firmly in contact with the skin surface.**
8. **Repeat step 7 for each of the 7 electrodes.**
9. **Tape the electrodes in place using a stress loop**

KCI - QUICK START HOLTER INSTRUCTIONS

1. Open battery compartment in back of Holter Monitor and with label facing up, slide flash card into slot in battery compartment.
2. Insert 2 new alkaline batteries.

Note: *All previous ECG patient data stored on the flashcard will be erased once the new battery is installed.*

3. Recorder should beep once and the LCD will start up.
4. After formatting the flash card, the recorder will display the patient's ECG waveform on all 3 channels.
5. Use the LCD display to verify a good patient hook up – Switch between the channels by pressing the event button once for each selection.
6. After a good patient hook up is confirmed, press and hold the event button for 4 seconds. This will start patient ECG data acquisition.

This is the start time for the Holter recording

7. Insert recorder in pouch and assist patient with strap
8. Instruct patient in use of Event Button
- **a. Press Event Button once at beginning of dialysis**
- **b. Press Event Button once at end of dialysis**

9. Instruct patient not to get recorder wet
10. Instruct patient when to return with the recorder

KCI - QUICK STOP HOLTER INSTRUCTIONS

1. Terminate recording by removing the batteries and flash card from Monitor (Press eject button to release the flash card).

2. Remove electrodes from patient and patient cable and discard electrodes.

3. Insert flash card into docking port on computer.

4. Double-click on the KCI Holter icon on the Windows screen.

5. Select the New Patient option.

6. Complete the Patient Information Screen per Renal Research Institute guidelines and click "OK".

7. After the data has been successfully downloaded and the automatic analysis is complete, exit out of the Holter software.

8. Remove flash card from docking port.

9. With a lint free cloth, wipe down the Holter Monitor and the attached patient cable using a disinfectant solution.

YOU ARE NOW READY TO HOOK UP YOUR NEXT PATIENT

KCI X5 Digital Holter Recorder System
RR Analysis Procedure

RR Analysis Guide

1. Introduction

This system has been enhanced to allow the user to specifically select the "RR" time interval to be analyzed

The RR analysis can be done on any portion of ECG in the recording. The user defines the start point and then the duration of the interval to be analyzed. The system can analyze a short interval of, for example, 20 or 30 minutes or a long interval of several days. The total analysis duration is broken up into segments with statistics reported for each segment. After the analysis is complete the RR analysis information is put into a tabular summary. From the tabular summary the RR data can be "cut and pasted" to any other spread sheet or database application (Excel, Access, etc.) for further computation and analysis. There is no limit on the number of times the user can conduct a RR interval investigation.

2. Functional Description

A. Setup

The following parameters must be set or verified by the user to begin the analysis:

- Analysis Duration – Total amount of time to be analyzed
  - o Lower Limit - 1 minute
  - o Upper Limit - End of the recording

- Segment Duration – Length of each segment to be analyzed
  - o Time
    - Lower Limit - 1 minute
    - Upper Limit - 60 minutes
  - o RR Intervals
    - Lower Limit - 100 RR Intervals
    - Upper Limit - 10,000 RR Intervals

(The user can select the Segment Duration to be Time or RR Interval but not both.)

Segments are calculated from the Start Time until the End Time (Duration = End Time - Start Time). If the final segment is incomplete, data will be taken from the ECG data beyond the Analysis Duration End Time, or, if at the end of the recording, will be "padded" with zeroes.

These system parameters are set by the user. The user need only set these parameters once unless changes are desired.

B. Start Point Selection

The user selects the start point using the system mouse.

C. Analysis

After Start Point Selection the user will select the "RR Interval Analysis Tool Bar Button".
The system will analyze the RR segments from the Start point until the End point.

The Following variables will be calculated:

- Time domain
  - o MeanRR -The mean RR interval during the segment
  - o pNN50 -The proportion of differences in successive RRintervals greater than 50 ms
  - o SDNN -The standard deviation of RR intervals (SDNN)

- Frequency domain
  - o VLF: 0 to 0.04Hz,
  - o LF: 0.04 to 0.15Hz,
  - o HF: 0.15 to 0.4Hz
  - o LF/HF Ratio

3. Editing (This is only noted here for explanation.)

The system provides a variety of editing possibilities. Because the RR interval analysis is dependent on the accuracy of the ECG record it is expected that the user will have edited the Time period to be analyzed.

4. Tabular Report

For each segment of the analysis period the following will be presented in tabular format:

- MeanRR
- pNN50
- SDNN
- VLF
- LF
- HF
- LF/HF Ratio

All the above values will be averaged and a "Total" row will be presented to the user.

This "Table" can be then exported to a variety of "Windows" applications including Access, Excel, etc. The user will NOT have to copy the data by hand and re-enter the data thus avoiding the problem of human error.

5. Operation

A. Setup

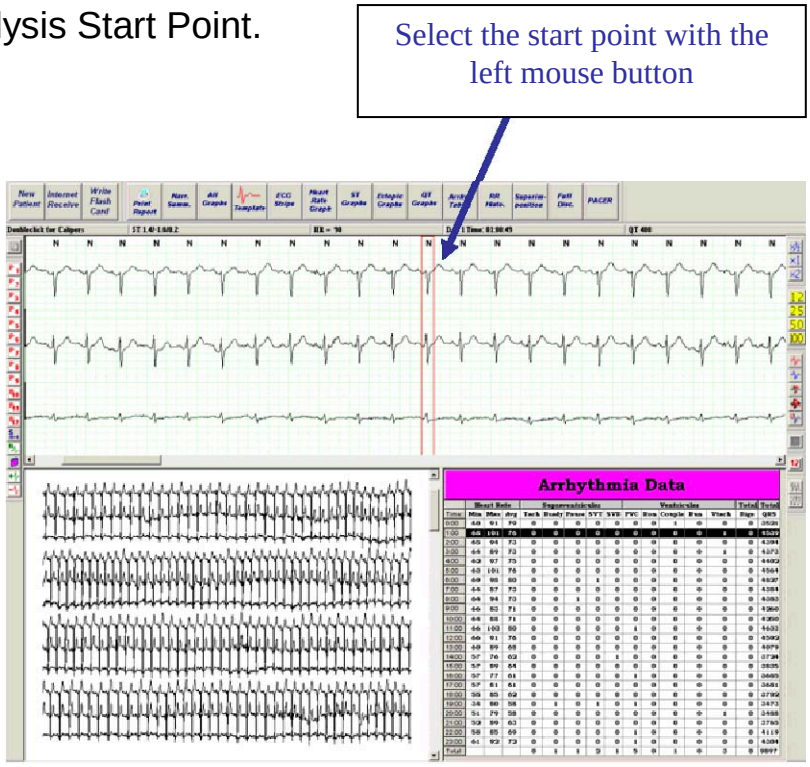
Analysis Duration and Segment Duration parameters are set within the analysis process. There is no separate Set Up dialog. Once set, they will be remembered by the system until changed by the user.

B. Analysis

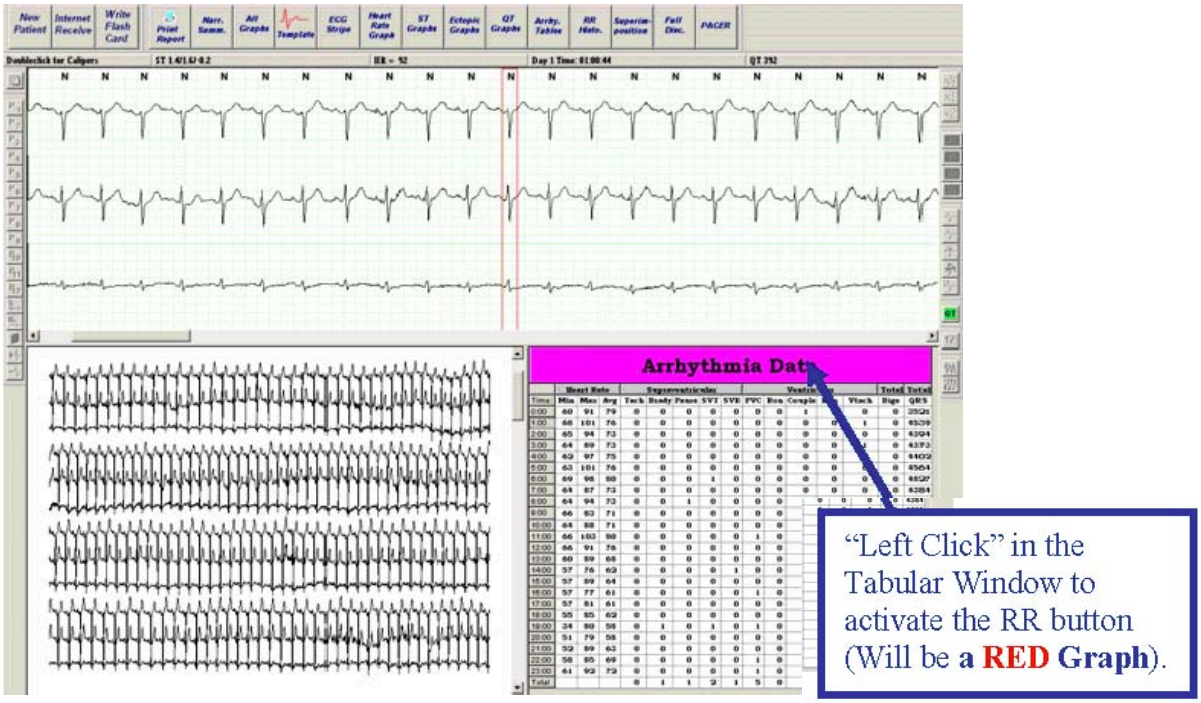
1. Open the patient ECG file.

2. Click on the Arrhy.Tables Button

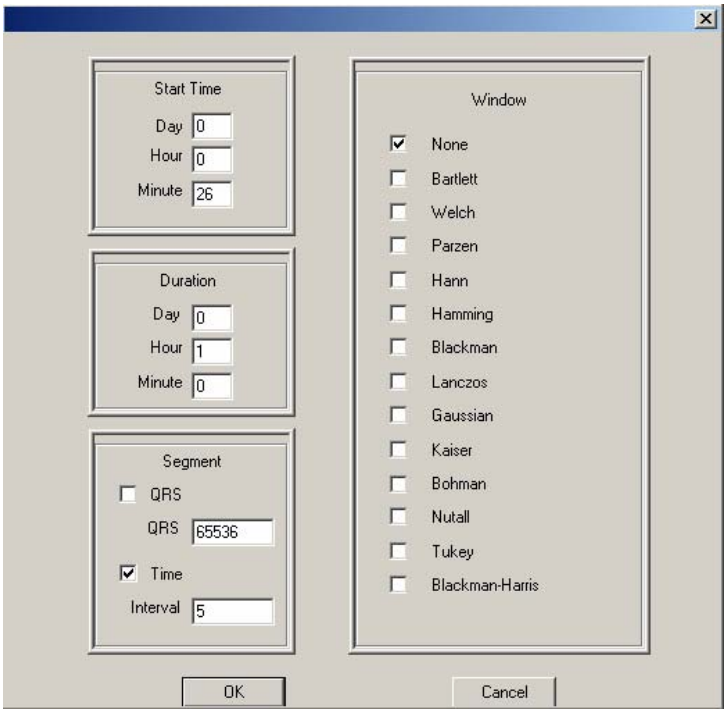
3. Set the Analysis Start Point.



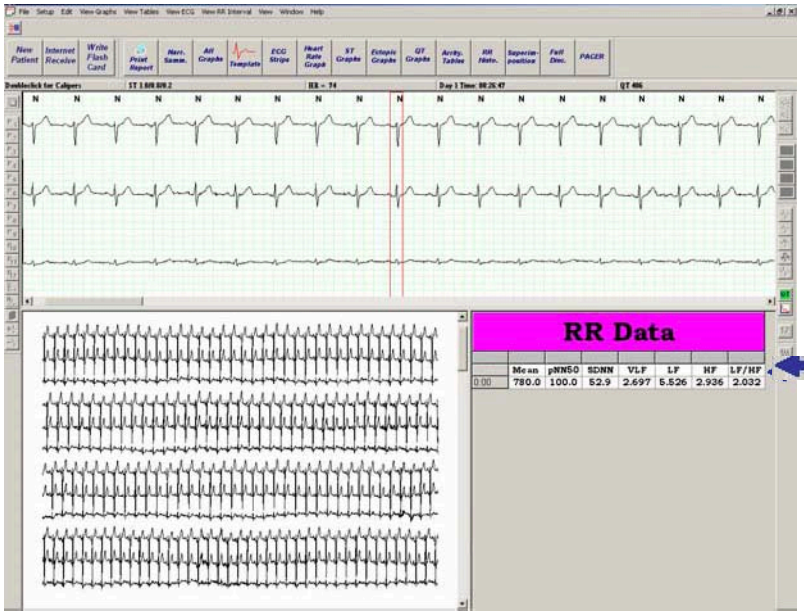
4. Open the RR Interval Analysis Tool by “Left Clicking” on the title bar of the Arrhythmia Data table.



5. Set or verify the Analysis Start time and Duration.
6. Set or verify the Segment Duration, either by specifying number of QRSs or by specifying a time interval (in minutes).
7. Set or verify the FFT Reference Window type. (See the published literature for explanations.)
8. Click OK.



9. Analysis results will be displayed in the table area. Results may be selected by holding down the mouse button while dragging across the table cells to be copied. Use normal Windows "Cut and Paste" methods to transfer the tabular data to another Windows application for further analysis.



RR calculation data can now be "cut and pasted"

10. To analyze another portion of the patient's ECG data, select another start time by following steps 1.

through 9. again. Data in the table will be replaced on each new analysis.

Technology & Services Info Sheet

KCI Customer Support Process

Thank you for your purchase of state-of-the-art diagnostic equipment from KCI Technology & Services. We have tested our equipment extensively and worked with all of our customers to refine the system so that it works properly and effectively.

We want to be sure that you get the support you need as quickly as possible to keep your patients safe and your office running smoothly and effectively.

Here are some simple steps you can do yourself if they apply to your situation:

- If the computer system stops completely, press and hold the power button until the system shuts down. Wait two minutes. Restart your computer. "Retrace your steps" and see if the system stops again at the same place.
- If your system has been moved recently, or if the office has been cleaned, check to see if any cables have come loose and reconnect them.
- Remove and re-insert the Flash Card into the recorder or the reader (the green light should come on).
- Unplug the USB cable from the Flash Card Reader to the computer, wait 30 seconds, then plug it back in.
- Remove and re-insert the batteries, checking for the correct polarity.
- Put in new batteries.

If you get an error message on the screen, write down EXACTLY what the error message says.

Call the KCI Technology & Services technical support group at
(908) 429-4300.
We will attempt to determine if it is a hardware or software problem, to help you through the problem over the phone, and decide if an office visit is required.

APPENDICES

Appendix A

Certification Procedure:

Each study site is required to be certified by the Holter core lab prior to enrolling patients into the protocol. For each study site, the following 6 essential steps must be performed according to the standards of the core lab to allow certification.

Step 1: setup of the Holter
Step 2: donning of the electrodes
Step 3: recording of data
Step 4: downloading the data from the flash card
Step 5: transferring the data to the FTP site
Step 6: setup the Holter for a new recording

It is expected that each study site is to have at least one coordinator to be certified. If a site has multiple coordinators, the certified coordinator will act as a local expert to assure data quality. In the event of poor quality data, the core lab will request for a re-test to be done.

Appendix B

Minimizing Movement Artifact on Holters:

Suggestions:

Personnel need to make sure they prepare the patients' sites correctly. The area to apply the electrode should be shaved and rubbed with the provided abrasive pad enough to be slightly pink. The snap of the electrode must be over the interstitial space, while the sticky part of the electrode must be over the boney portions.

Patients should wear a close-fitting undershirt. Loose clothing will be brushing against the electrodes & could potentially create more artifact. The undershirt would remain relatively still while their outer clothing moves.

Patients should also be instructed to minimize playing with the wires.

ANYTHING that will minimize movement of any part of the recording equipment will be helpful, within the constraints of normal life. Going to the gym or going out jogging ought to be discouraged.

18. Kinetic Modeling – Daily Trial

18.1 Introduction: Kinetic Modeling

The primary distinction between the treatment arms of the FHN Daily Hemodialysis Study is the frequency of the treatments: 6 times per week in the daily HD treatment group vs. 3 times per week in the conventional HD treatment group. Thus, in the conduct of the trial the main goal is to maintain the assigned treatment frequencies in both treatment groups, and precise targeting of dialysis dose within a narrow range based on intricate kinetic modeling algorithms is not required. Nonetheless, kinetic modeling will serve two important functions in this study: First, to provide guidelines for the conduct of the interventions, and second, to characterize the targeted and achieved separation between the daily HD and conventional HD interventions in treatment parameters related to solute clearance and to volume and blood pressure stability.

The guidelines for administration of the interventions are based on urea eKt/V are as follows:

Conventional HD arm: Subjects randomized to the conventional 3 times per week intervention may remain on their usual dialysis prescription subject to the following two constraints:

a) a minimum eKt/V of 1.1 per session,

and

b) a minimum treatment time of $\geq$ 2.5 hours per session.

It is important that both conditions (a) and (b) are stipulated as *minimum* conditions to assure that the dialysis prescriptions meet current standards for adequacy. It is expected that usual dialysis prescriptions for the large majority of patients will exceed both of these conditions, so that in most cases the study protocol will not require any modifications to the dialysis prescriptions of patients randomized to the 3 time per week arm. The details for how the dialysis prescriptions are monitored to assure that conditions (a) and (b) are satisfied are provided in Sections 18.4 and 18.5 below.

Daily HD arm: Subjects randomized to the *daily hemodialysis* arm will receive 6 dialysis sessions per week, where the target dialysis prescriptions are based on the following stipulations:

a) to maintain a target $eKt/(V_n)^*$ of approximately 0.90 per session,

and

b) a treatment time of 1.5 hours to 2.75 hours**.

*V_n = "normalized V" = $3.271 \times V^{(2/3)}$

**If a patient is unable to achieve the target $eKt/(V_n)$ of 0.90 within 2.75 hours, the patient's target $eKt/(V_n)$ will be reduced to that which can be achieved within a treatment time of 2.75 hours. If necessary, the maximum treatment time may be exceeded to maintain an ultrafiltration rate of <1.0 L per hour, or upon the discretion of the treating nephrologist for clinical reasons.

The use of the exponent of 2/3 for the definition of normalized V reduces the dependence of the dialysis prescriptions on the size of the patient, thus avoiding infeasible treatment times in larger patients and potentially underdialyzing smaller patients. Additional details on normalized V are given Section 18.3 below.

To facilitate the implementation of these targets for the daily HD group, at randomization the Data Coordinating Center sends an array of dialysis prescription options for a target $eKt/(V_n)$ of 0.90 in which the treatment times are between 1.5 and 2.75 hours. Subsequently, kinetic modeling data will be obtained monthly, and revised dialysis prescriptions provided if the running median V (over 4 dialysis sessions) increases by an amount that leads to a decrease in the updated prescribed $eKt/(V_n)$ to a value less than 0.75. This procedure is designed to assure that the running median achieved $eKt/(V_n)$ does not fall more than 0.15 $eKt/(V_n)$ units below that 0.90 target throughout follow-up. The window of 0.15 $eKt/(V_n)$ units was selected to be sufficiently wide to minimize the number of times prescriptions must be updated, but at the same time sufficiently narrow as to assure that an adequate weekly dialysis dose is achieved in the daily HD arm.

The Data Coordinating Center will also send revised prescriptions if the running median V changes by an amount that leads to an increase in the prescribed $eKt/(V_n)$ to a value greater than 1.05. In this case, reductions in dialysis dose in accordance with the revised prescription will be at the discretion of the treating nephrologist. Hence, in theory, the study protocol allows the dialysis prescriptions to drift arbitrarily above the 0.90 target in the 6 time per week arm. However, in practice it is expected that most treating nephrologists and their patients will elect to reduce the prescriptions to 0.90 in order to reduce total weekly treatment time.

The minimum and maximum session lengths of 1.5 and 2.75 hours represent a minimum and maximum total weekly treatment times of 9 and 18.5 hours, respectively, on a 6 times per week schedule. If divided by 3, these lower and upper bounds to treatment time would correspond to minimum and maximum times of 3 hours and 5.5 hours for a 3 times per week schedule.

If subjects in the daily HD arm develop an unwillingness or inability to follow the 6x/week treatment regimen specified by the protocol, efforts will be made to adopt a reduced treatment regimen which approximates the intended 6x/week regimen as closely as possible.

As described in Section 18.2, an important aspect of the design of the study is that although the dose target for the daily HD arm is expressed in terms of urea clearance, by varying both treatment frequency and total weekly treatment time the design is intended to achieve a large separation in the clearance of a wide range of solutes and in the stability of volume and blood pressure. The study design is not intended to determine the effects of each specific component of the daily HD treatment regimen, but rather is based on the pragmatic objective of determining whether the combination of factors associated with the daily HD regimen can improve outcomes.

18.1.2 Content of the Kinetic Modeling Chapter

Section 18.2 summarizes the targeted separation of selected treatment parameters between the daily HD and the conventional HD treatment groups. Section 18.3 provides the background and justification for the use of the exponent of 2/3 in the definition of the normalized V used to define

the targeted dialysis prescriptions in the daily HD arm. Section 18.4 describes the computation of kinetic modeling parameters. The kinetic modeling measurement schedule is summarized in Section 18.5, and kinetic modeling procedures and data collection are reviewed in Section 18.6. Section 18.7 provides the DOQI standards for blood draws to be used in kinetic modeling. Section 18.8 reviews the kinetic modeling reports to be provided by the Data Coordinating Center in the trial.

18.2 Targeted Separation in Dialysis Parameters Between Treatment Arms.

To understand the expected characteristics of the interventions in the two treatment arms, a simulation study was conducted to estimate the distributions of a number of key treatment parameters in the conventional HD and daily HD interventions. We used a sample of 3285 patients from the Renal Research Institute data base to obtain estimates of the distribution of urea generation rate, urea distribution volume (V), fluid intake per week, and dialyzer clearance (K) for potential patients in the trial. We then applied the dialysis prescriptions defined by the designs stated in Section 18.1 to simulate the targeted distributions of relevant parameters in the two treatment groups.

The results are presented in Table 18.1 below. The simulations assumed that all patients assigned to the 6 time per week intervention actually received their targeted dialysis prescription for 6 treatments per week, and that patients randomized to the 3 times per week intervention actually received exactly 3 treatments per week. Thus, the results indicate the targeted rather than the achieved separation in the listed treatment parameters between the two treatment groups. The projected total weekly treatment time (median 14.2 hours for the daily HD group vs. 10.5 hours for the conventional HD group) is approximately 35% greater in the daily HD group than in the conventional HD group. Largely due to the greater treatment time in the daily HD group, the target equivalent renal clearance of β_2-microglobulin (a marker for clearance of middle molecular weight solutes) is 38% larger in the daily HD group than in the conventional HD group, and the target standardized removal of phosphorus is 39% larger in the daily HD group. The targeted weekly standard Kt/V for urea, which is particularly sensitive to the frequency of dialysis treatments, is 55% higher in the daily HD group. The greater frequency of the treatments and the greater total treatment time in the daily HD arm compared to the conventional HD arm would provide a 50% reduction in the average amount of total ultrafiltration per dialysis treatment and a 100 x (1 - 1/1.35) = 26% reduction in the average ultrafiltration rate if patients fluid intake is the same in the two arms. Somewhat lower reductions in these ultrafiltration parameters would be projected if fluid intake is increased in the daily HD arm compared to the conventional HD arm.

Table 18.1: Summary of the Dose Treatment Regimens

Parameter	Conventional HD (CHD)	Daily HD (DHD)	% Difference in Medians (DHD vs. CHD)
Sessions per week	3	6	100%
Target prescription	Unspecified: eKt/V $\geq$ 1.10	eKt/(V_n) = 0.90	-
Hours per session	$\geq$ 2.5 (median = 3.50)	1.50 to 2.75 (median = 2.36)	-33%
Maximum interdialytic interval (median, hours)	68.5	45.6	-33%
Average interdialytic interval (median, hours)	52.5	25.6	-51%
Hours per week (median, 5^{th} – 95^{th} percentile)	10.5 (9.0 – 13.1)	14.2 (11.5 – 18.5)	+35%
eKt/V urea per treatment (median, 5^{th} – 95^{th} percentile)	1.39 (1.12 – 1.75)	0.92 (0.74 – 1.05)	-34%
Weekly stdKt/V urea (median, 5^{th} – 95^{th} percentile)	2.46 (2.18 – 2.80)	3.82 (3.32 – 4.17)	+55%
Weekly eKR β_2-microglobulin (ml/min per 35 L total urea volume) (median, 5^{th} – 95^{th} percentile)	12.8 (10.7 – 15.2)	17.6 (14.6 – 19.8)	+38%
Standardized phosphorus removal (mg/day) (median, 5^{th} – 95^{th} percentile)	299 (254-374)	415 (338 – 497)	+39%

eKt/V = equilibrated Kt/V, stdKt/V = standard weekly Kt/V, eKR = equilibrated equivalent renal clearance. Medians, 5^{th}, and 95^{th} percentiles based on simulations assuming distributions of patient characteristics and baseline dialysis prescriptions from the Renal Research Institute Database, n=3285.

18.3 Rationale for Dividing Kt by V_n

The rationale for factoring Kt by V_n rather than V involves pragmatic and physiological considerations. From a pragmatic perspective, factoring Kt by $3.271V^{(2/3)}$ rather than V reduces the effect of large V's on calculation of Kt/V, resulting in moderately higher eKt/V's for smaller patients and moderately lower eKt/V's for larger patients (Table 18.2). This reduces the dependence of the treatment time required to achieved a given eKt/V_n on the size of the patient, allowing more feasible treatment times in larger patients while avoiding unduly short times in smaller patients.

Table 18.2: **Achieved eKt/V for Different V's when eKt/(V_n) = 0.90**

Patient Weight (kg)	**Patient V (L)** (Assuming V = 0.6 × Weight)	**eKt/V**	**eKt/(V_n)**
42	25	1.01	0.90
50	30	0.95	0.90
58	35	0.90	0.90
67	40	0.86	0.90
75	45	0.83	0.90
83	50	0.80	0.90

In addition, empiric data from 3285 patients associated with the Renal Research Institute (RRI) suggests that this adjustment corresponds to current practice patterns at these dialysis units (Table 18.3). The final column of Table 5 indicates that mean eKt/(V_n) is approximately constant for different values of V, whereas mean eKt/V declines as V increases.

Table 18.3: Relationship of Treatment Time, eKt/V, and eKt/(V_n) to Patient Volume (V)*

Patient V (L)	Treatment Time (min)	eKt/V	eKt/(V_n)
< 27.5	189	1.51	1.35
27.5 – 32.5	202	1.43	1.36
32.5 – 37.5	212	1.35	1.34
37.5 – 42.5	224	1.29	1.35
> 42.5	240	1.21	1.34

*N=3285 from RRI database

From a physiologic perspective, factoring Kt by V raised to a power less than 1 is justified by the argument that toxin generation may be more directly related to body surface area rather than to volume. Native renal clearance is traditionally standardized to body surface area rather than volume of body water. The exponent of 2/3 is suggested by the physical relationship that the surface area of a 3-dimensional body is approximately proportional to its volume raised to the 2/3 power. At the same time, factoring V by an exponent greater than 0 retains some degree of volume dependence in the target dialysis interventions, consistent with current practice.

18.4 Calculation of Kinetic Modeling Treatment Parameters

Urea Kinetic Modeling Parameters

HD dosing is traditionally based on clearance of urea, expressed as Kt/V (K is the clearance of urea, t is the duration of the dialysis session, and V is the volume of distribution of urea in the patient). Traditionally, single-pool Kt/V (spKt/V), determined mostly from the pre- and postdialysis BUN values, has been used to define and measure the dose in conventional HD [Gotch, 1985]. However, because spKt/V overestimates the effective clearance due to the phenomenon of urea rebound, this trial will use equilibrated Kt/V (eKt/V) [Daugirdas, 1995;Pedrini, 1988]. Further, as described in Section 18.3, the target dialysis prescriptions in the daily HD arm will be based on a variant of eKt/V (denoted eKt/V_n) in which V is raised to the 2/3 power.

Step 0: Preliminary Estimate of Kru

The algorithm for calculating the urea kinetic modeling parameters first obtains preliminary estimates using a ballpark approximation of the patient's residual native kidney function (Kru), and then repeats the calculations using a more refined estimate of Kru.

Prior to formal kinetic modeling calculations, a preliminary estimate of Kru will be obtained using the results of the urine collection and an estimate of the BUN concentration at the midpoint of the collection period based on a linear interpolation between a "ballpark" estimate of the postdialysis BUN at the end of the preceding dialysis and the observed pre-dialysis BUN of the dialysis immediately following the urine collection. This ballpark estimate is necessary because while the study protocol requires measurement of the pre- and postdialysis BUNs from the dialysis immediately following the urine collection (denoted C0 and Ct, respectively), it does not require a postdialysis BUN from the prior dialysis.

The following procedure will be used to estimate the postdialysis BUN at the end of the preceding dialysis: Then, for patients following a three treatment per week schedule, estimate the postdialysis BUN of the preceding dialysis (denoted as Ct*) as:

$Ct^* = (0.86/1.08) \times Ct$	if day = 1 or 2
$Ct^* = (1.00/0.86) \times Ct$	if day = 3 or 4
$Ct^* = (1.08/1.00) \times Ct$	if day = 5 or 6.

An analogous set of equations will be developed for a six times per week treatment schedule. After estimating the mid-collection BUN from Ct* and C0 by linear interpolation, obtain a preliminary estimate of the residual renal clearance Kru as:

Kru = { [UUN × (Urine Volume)] / (Collection Time) } / {estimated mid-collection BUN},

where UUN represents the urine urea nitrogen concentration.

Step 1: Calculation of Predicted Dialyzer Clearance (Kd)

The first step is the calculation of single pool Kt/V and single pool V (Vsp) based on the data from a kinetic modeling session. To calculate these quantities for a single modeled dialysis session, the predicted extraction ratio (PER) and dialyzer clearance Kd will first be calculated using the formulas:

$$PER = \left[e^{\frac{K_0A}{Qb}\left(1-\frac{Q_b}{Q_d}\right)} - 1 \right] \Big/ \left[e^{\frac{K_0A}{Qb}\left(1-\frac{Q_b}{Q_d}\right)} - \frac{Q_b}{Q_d} \right]$$

and

$$Kd = 0.894(PER \times Qb) \times (1 - Qf/(0.894 \times Qb)) + Qf,$$

where Qb denotes the blood flow rate, Qd is the dialysate flow rate, KoA is the in-vivo dialyzer KoA, and Qf is the ultrafiltration rate. Based on results from the HEMO trial [Depner TA, Greene T, Daugirdas JT *et al.*: Dialyzer performance in the HEMO Study: in vivo K0A and true blood flow determined from a model of cross-dialyzer urea extraction. *ASAIO J* 50:85-93, 2004], the in-vivo KoA will be estimated from the manufacturer's supplied in-vitro KoA at a Qd of 500 ml/min, using the expression:

$$K_0A = 0.84 \times [\text{Manufacturer's in-vitro KoA at Qd = 500 ml/min}] \times [1 + \beta_{Qd} \times (Qd - 500)/300 + \beta_{reuse} \times (\text{reuse \#})]$$

where Qd denotes the dialysate flow using during the dialysis, (reuse #) denotes the number of reuses for the dialyzer used for the treatment, and β_{Qd} and β_{reuse} are constants which account for the effects of dialysate flow and reuse on the in-vivo KoA. Based on the HEMO Study results, β_{Qd} will be defined as 0.055, and β_{reuse} as -0.006. Due to reports of improvements in blood line pump segments since the HEMO trial, the actual blood flow Qb will be assumed to be equal to the nominal blood flow based on the blood pump speed, without the downward adjustments that were applied in the HEMO trial [Depner, 2004].

Step 2: Modeling single pool Kt/V and Vsp

Delivered spKt/V and Vsp will be determined from the above predicted Kd, the pre- and post-BUNs, the pre- and post weights, and the estimated Kru using an iterative modeling program that employs the 2-BUN algorithm of Depner and Cheer [Depner, 1989].

Step 3: Estimation of double-pool parameters using the Tattersall rate equation

After determining Vsp and delivered spKt/V, the modification to the Tattersall rate equation developed in the HEMO Study [Daugirdas, 2004] will be used to estimate eKt/V from spKt/V according to the formula

$$eKt/V = spKt/V \times (t/(t+Tp))$$

where t denotes treatment time, and Tp = 30.7 minutes for AV accesses and 18.5 minutes for venous catheters. The equilibrated postdialysis BUN under the modified Tattersall equation is:

$$Ceq = C0 \times (Ct/C0)^{(t/t + Tp)}$$

As described in Daugirdas [1996], The more accurate double pool modeled volume of urea distribution (Vdp) will be estimated as:

$$Vdp = Vsp \times \log(Fdp \times (C0/Ct))/(Fdp \times \log(C0/Ct)), \quad \text{(Eq 1)}$$

where C0 and Ct denote the pre and postdialysis BUNs, and Fdp is defined by

$$Fdp = Ct/Ceq.$$

Step 4: Computation of running medians for eKt/V and Vdp

In the fourth step of the kinetic modeling algorithm, running medians will be obtained for eKt/V and Vdp. Starting at the kinetic modeling session in Month 2 of follow-up, 4-session running median eKt/V and Vdp values (defined as meKt/V and mVdp) will be obtained as the medians of these quantities over the current session and the prior three modeling sessions. At baseline and the Month-1 follow-up sessions, the running medians will be calculated using the current session and all available prior modeling sessions. . Note that V is considered a physiologic constant whereas eKt/V may vary depending on conditions of the dialysis from session to session.

The calculation of the running medians is modified following access modifications to give increased emphasis to kinetic modeling sessions conducted after the latest access modification by making three copies of eKt/V and Vdp from sessions after the last access modification prior to calculating the running medians. Thus, for example, if the access was newly modified after the preceding dialysis but before the current dialysis, the 4-sesion running median is applied to three copies of eKt/V and Vdp from the current session and one copy from the three preceding modeling sessions.

Step 5: Calculation of equilibrated urea generation rate and whole body clearance

In the fifth step, calculate the whole body urea clearance as

$$Kwb = eKt/V \times mVdp/t.$$

Assuming a weekly steady state, the equilibrated urea generation rate (eG) is estimated by applying the 1-pool variable volume model with C0, mVdp, Kru, pre- and postdialysis weights, and Kwb as input parameters to calculate an estimated pre-dialysis BUN (C0) for a dialysis session beginning exactly 1 week after the current session.

Step 6: Obtain preliminary estimate of the BUN vs. time concentration curve for 1-week period

The BUN concentration curves will be generated using a 2-pool variable volume iterative model in which the postdialysis total volume of urea distribution is the running median V (mVdp) defined in Step 4, divided between the intracellular and extracellular compartments in a 2 to 1 ratio. Weekly steady state conditions will be assumed, including a constant urea generation rate [estimated as the equilibrated G (eG) from Step 5], a constant residual urea clearance (estimated in Step 2), and a constant weekly dialysis treatment schedule. The effective dialyzer clearance Kdeff and the intercompartment mass transfer coefficient (Kc) will be jointly estimated using the 2-pool model

and fitting the BUN vs. time concentration curve in the extracellular compartment to the measured pre- and postdialysis BUNs, and the equilibrated BUN (Ceq) defined by the Tattersall method as described above.

Note that in this approach patient-specific estimates of Kc are not estimated from the data since no delayed postdialysis BUNs are measured under the FHN protocol. Instead, Kc is imputed for each patient to be consistent with the modified Tattersall rate equation. Following estimation of Kc and Kdeff, the Runge-Kutta algorithm will be used to estimate the full BUN vs. time concentration curves for the intracellular and extracellular compartments.

Step 7: Recompute Kru

Kru = { [UUN × (Urine Volume)] / (Collection Time) } / {time averaged extracellular BUN}

where the time averaged extracellular BUN concentration is computed, using the 2-compartment model described above, over the collection period.

Step 8:

Repeat Steps 1 – 4 using the updated estimate of Kru.

Step 9:

Repeat the calculation of spKt/V by applying the 2-BUN weekly iterative algorithm with the updated mVdp, Kru, C0, Ct, pre- and postdialysis weights as input parameters. Then update the estimates of eKt/V, eG, and the weekly BUN vs. time concentration curves by repeating Steps 5 and 6.

Computation of eKt/Vn

Following the calculation of eKt/V, the normalized eKt/Vn will be calculated as:

$eKt/Vn = [eKt/V] \times 3.271^{-1} \times [Vant]^{(1/3)}$,

where Vant is the anthropometric volume estimated using the Watson formula. The above expression for eKt/Vn corresponds approximately to dividing the total treatment clearance (Kt) by $[3.271 \times V^{(2/3)}]$. The expression $[Vant]^{(1/3)}$ is used in place of the cube root of the modeled volume in the final term to avoid the risk that errors in dialysis delivery, which usually cause inflated estimates of modeled volume, would distort the calculation of eKt/Vn, and hence also distort the dialysis prescriptions. In particular, if the cube root of modeled volume were used, inflated estimates of modeled volume would lead to inflated estimates of eKt/Vn, and thus to dialysis prescriptions for lower than the intended dose levels. The factor 3.271 is equal to the cube root of 35, so that multiplication by 3.271^{-1} scales eKt/Vn to be equal to eKt/V when Vant = 35 L.

Computation of Standard Kt/V and Equivalent Renal Clearance

When patients are on conventional three times per week dialysis, urea Kt/V is generally accepted as a surrogate for dialysis dose. However, this trial requires consideration of a wider range of solutes and measures of clearance designed to generalize across different treatment schedules.

To compare different treatment schedules, clearance of urea have been expressed in terms of the quantity standard weekly Kt/V (stdKt/V), defined as:

stdKt/V = [eG/(mean predialysis peek)] × [total treatment time during 1 week] / V,

where eG denotes the equilibrated urea generation rate, the expression "mean predialysis peek" denotes the average of the predialysis BUN concentrations over all the dialysis in the 1 week period, and V denotes the volume of distribution for urea. The stdKt/V will be the primary measure of solute clearance in the study. An alternative measure is the so-called equivalent renal clearance (EKR), defined either as the ratio of the urea generation rate G to the time averaged concentration (EKR_{ave}) [Casino 96]. The concept of EKR_{ave} can be also applied to a spectrum of other solutes besides urea to more fully characterize the clearance of solutes by dialysis.

The mean pre-dialysis peak concentration and the time-averaged concentration of BUN will be obtained from the full weekly curves estimated in Step 9 of the above algorithm. The values of $EKR_{peak,}$ EKR_{ave}, and stdKt/V are then computed based on the ratios of eG (also obtained in Step 9) to these values.

Determination of Central Dialysis Prescriptions for the Daily HD Group.

At randomization, the Data Coordinating Center will transmit a collection of alternative dialysis prescriptions as close as possible to a target eKt/Vn of 0.9 subject to the constraint that the per session treatment time (t) is between 1.5 and 2.75 hours. The 0.9 eKt/Vn target implies that [eKt/V] $\times 3.271^{-1} \times [Vant]^{(1/3)} = 0.9$, or, equivalently, that the target eKt/V is

$$Target(eKt/V) = 0.9 \times 3.271 / [Vant]^{(1/3)} = 2.944 / [Vant]^{(1/3)}.$$

Based on the modified Tattersall formula, and the patients current running median volume, mVdp, a dialysis prescription with the target eKt/V should satisfy:

$$(K \times t) / f(mVdp) \times (t/(t + 30.7 \text{ min})) = 2.944 / [Vant]^{(1/3)}, \qquad \text{(Eq 2)}$$

where f(mVdp) the function of mVdp obtained by inverting Equation 1 in Step 3 of the above algorithm in order to produce an estimate of the mean single pool volume. In this calculation, the expected values of the C0/Ct and on Ct/Ceq used in Equation 1 will be first estimated from the dialysis prescription being considered.

When a patient is randomized to the Daily HD group the data coordinating center will provide tables that give the necessary prescribed treatment time (t) for a range of combinations of Dialyzer

KoA, Qb, and Qd in order that Equation 2 is satisfied as closely as possible with t between 1.5 and 2.75 hours. The dialysis prescriptions will depend on both Vant and mVdp. Updated prescription tables will be provided whenever the updated running median mVdp changes sufficiently that the resulting target eKt/Vn deviates by more than 0.15 units.

Tables 18.4a – 18.4h in the Appendix to this chapter provide example dialysis prescriptions for the Daily HD arm for mVdp and Vant ranging from 20 L to 50 L in increments of 5 L.

18.5 Kinetic Modeling Measurement Schedule

Table 18.5 describes the schedule for kinetic modeling visits, the determination of residual renal function, and the retrospective acquisition of other information from the dialysis session run sheets.

Table 18.5: Schedule of Kinetic Modeling and Dialysis-Session Related Data

Visit Number	Type of Data Collection			
	Complete Kinetic Modeling **(Form 273)**	1-Week Retrospective Data from Run Sheets **(Form 274)**	Monthly Dialysis Treatment Attendance **(Form 275)**	Residual Renal Function **(Form 206)**
B-01	✓	✓	✓	✓
B-02*	✓		✓	
F-1	✓	✓	✓	
F-2	✓		✓	
F-3	✓		✓	
F-4	✓	✓	✓	✓
F-5	✓		✓	
F-6	✓		✓	
F-7	✓		✓	
F-8	✓	✓	✓	
F-9	✓		✓	
F-10	✓		✓	
F-11	✓		✓	
F-12	✓	✓	✓	✓

* One additional baseline kinetic modeling session must be conducted if the deviation between the estimates of the estimated urea volume (Vdp) for the first two baseline kinetic modeling sessions exceeds 28% of their mean value (corresponding to a coefficient of variation > 20%).

Baseline Period.

As shown in Table 18.5, two kinetic modeling sessions, designated B-01 and B-02, will be conducted during the baseline evaluation phase of the trial. The two sessions should be spaced at

least one week but no more than six weeks apart. Form 273 must be completed for each kinetic modeling session.

If the deviation between the estimates of the estimated urea volume (Vdp) for the first two baseline kinetic modeling sessions (B-01 and B-02) exceeds 28% of their mean value, a third baseline kinetic modeling session (labeled B-03) will be required. The median of all baseline urea volume estimates will be used to determine the initial post-randomization dialysis prescription.
In order to prevent randomization of patients who are unable to achieve an eKt/V close to the minimum level of 1.10 in the conventional HD arm, subjects must achieve a mean eKt/V of at least 1.00 on the final two baseline kinetic modeling sessions in order to be randomized. If the mean eKt/V for the final two of the baseline kinetic modeling indicated above is less than 1.00, then an additional kinetic modeling session may be scheduled, and the mean eKt/V recomputed from the last two baseline sessions. This process may be repeated up to 4 times, and the minimum eKt/V requirement will be met if at any of these tries the average eKt/V for the final two assessments exceeds 1.00. The baseline minimum threshold of 1.00 is set 0.10 eKt/V units below the minimum of 1.10 in the conventional HD arm, to take into account the random variation that can be expected from the average eKt/V over two modeling sessions.

Tables 18.6a – 18.6h in the Appendix provide a sample grid of prescribed dialysis times for patients ranging in size from 20 to 55 liters in 5 liter increments. The target eKt/V is 1.10 per dialysis. Treatment times equal to or larger than the values indicated in the tables will lead to target eKt/Vs of at least 1.10. It is recommended that the selected treatment time be at least 5% larger than the minimum values listed in the tables in order to reduce the likelihood that the achieved eKt/V will fall below 1.0. We expect that the prestudy dialysis prescriptions for the large majority of patients will already substantially exceed 1.10, so that prescription adjustments will be necessary for only a minority of patients during baseline. Selectable dialysate flow rates are either 500 or 800 ml/min and selectable blood flow ranges from 200 to 500 ml/min in 50 ml/min increments.

A timed urine collection of at least 24 hours should be performed for all patients producing urine prior to one of the first two kinetic modeling sessions during baseline. The duration of the timed collection is optional as long as it is at least 18 hours and it extends to the start of the kinetic modeling session. Although the timed urine collection may be obtained in the interdialytic interval prior to either of the first two modeling sessions, it is recommended that the collection be obtained prior to the first baseline kinetic modeling session (B-01) when this is feasible. Performing the collection at this time has the advantage that patients who exceed the maximum residual urea clearance limit of 3.0 ml/min per 35 Liters can be identified early in baseline, allowing them to be dropped from the trial before additional efforts are expended needlessly. If logistical difficulties lead to a failed urine collection, the urine collection may be attempted again prior to the second baseline modeling session.

The dialysis run sheet should be reviewed for the 1-week period preceding the initial B-01 kinetic modeling session in order to record on Form 274 information pertain to treatment time, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during this period. The 1-week period for the retrospective data collection ends on the day prior to the kinetic modeling session, and will normally include the three preceding dialyses for patients on a 3 times per week treatment schedule.

Follow-up.

At randomization, the DCC will transmit alternative prescription reports for a target eKt/Vn of 0.90 (subject to a treatment time between 1.5 and 2.75 hrs) for all patients randomized to the Daily HD arm. The patients randomized to the Daily HD arm should initiate 6 times per week therapy on one of these prescriptions as soon as logistically feasible after randomization. The DCC will not transmit prescription reports for patients assigned to the conventional HD group, as these patients may continue on their usual prescriptions as long as their prescribed eKt/V exceeds 1.10. The minimum dialysis prescriptions needed to achieve an eKt/V of 1.10 are summarized for 5L increments of urea volume in Tables 18.6a – 18.6h in the Appendix.

The schedule for kinetic modeling during follow-up is based on calendar month. The calendar month following the month in which the patient is randomized is designated as F-1, with the subsequent month designated F-2, and so on. Thus, if a patient is randomized in the month of October, then F-1 corresponds to the month of November, F-2 to December, and so on for F-3 through F-12. Kinetic modeling sessions for the FHN Daily Study are conducted monthly (in calendar months F-1, F-2, ….., F-12). It is desirable, if arrangements can be made, that the modeling sessions be conducted during midweek dialyses (either Wednesday or Thursday), but for logistical purposes, it is recommended that the FHN Study kinetic modeling sessions be conducted to coincide with the dialysis clinic's usual monthly kinetic modeling sessions to avoid additional blood draws.

Kinetic modeling sessions do not need to be repeated in the event of interruptions or missing data on the dialysate concentrations (Question 19 on Form 273). Kinetic modeling session should be repeated, however, if any of the responses to Questions 8 through 18 can not be obtained, or if either the pre- and postdialysis BUNs are not measured. Kinetic modeling may also be optionally repeated at the discretion of the FHN Study team.

For patients who continue to produce urine, timed urine collections of at least 18 hours should be performed preceding the kinetic modeling sessions at months F-4 and F-12. As in baseline, the duration of the collection period is optional, as long as it is at least 18 hours and it extends to the start of the kinetic modeling session. For logistical purposes, we recommend that the collection be initiated after the patient completes the dialysis preceding the kinetic modeling session. If this recommendation is followed the duration of the collection period will be 21.25 to 22.5 hours for patients assigned to the Daily HD arm, and approximately 44 to 45 hours for patients assigned to the Conventional HD arm.

Similar to baseline, at months F-4, F-8, and F-12 the dialysis run sheet should be reviewed for the 1-week period prior to the kinetic modeling session to record on Form 274 information pertaining to treatment time, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during this period. As in baseline, the 1-week period for the retrospective data collection ends on the day prior to the kinetic modeling session, and will normally include the three preceding dialyses for patients on a 3 times per week treatment schedule, and six preceding dialyses for patients on a 6 times per week treatment schedule. If the kinetic modeling session is conducted during the first week of the calendar month, the period for retrospective data collection may extend

into the preceding calendar month.

18.6 Procedures and Data Collection

Kinetic Modeling Sessions (Form 273)

In general, it should not be necessary for the FHN Study coordinator to attend kinetic modeling sessions held during follow-up, since these sessions may coincide with the dialysis clinic's standard kinetic modeling. However, it is essential that arrangements be made to request measurement by the local laboratory of pre- and postdialysis creatinine and phosphorus in addition to the BUN. The pre and postdialysis blood samples should be drawn using DOQI standards (see Section 18.7). Because the baseline sessions will generally be held one to two weeks apart, it is likely that at least one of these will not coincide with dialysis clinic's regular monthly kinetic modeling.

Form 273 (the Kinetic Modeling Form) must be completed at each kinetic modeling session. The form should be completed for all available items even if certain items are missing. Question 5, which pertains to the type of kinetic modeling session, should be coded as "1 = Routine KM" unless the kinetic modeling sessions is being conducted as a repeat session due to missing data or is being repeated at the discretion of the FHN staff, in which case the question should be answered as "2=Redo". During follow-up, repeat kinetic modeling sessions are preferably conducted in the same calendar month as the original kinetic modeling session (which is being repeated), but if necessary the repeat session can be conducted in the subsequent calendar month, as long as it is conducted prior to the standard kinetic modeling for that month. Thus, during follow-up, exactly one Form 273 with Question 5 designating "1 = Routine KM" should be completed during each calendar month from F-1 through F-12. Additional kinetic modeling sessions would be designated as redos.

Items 6 through 19 on Form 273 should be completed using information from the dialysis run sheet.

Item 7 (Reuse number) should be designated as 0 for the first use of the dialyzer, 1 for the second use, 2 for the third use, and so on. This may at first seem counterintuitive, but note, for example, that at the second use the dialyzer is being reused for the first time, and in general the number of reuses is one less than the number of uses.

Question 9b addresses whether there has been a surgical or radiological intervention since the previous kinetic modeling session. This is intended as a quality control check to assure that no access revisions are missed in the database. In the event that a surgical or radiological intervention has been performed, this intervention should be documented on Form 272 if it has not already been done.

Question 10 deals with the needle type for the dialysis (single vs. double needle), and will almost always be double needle in this study (this question is included primarily for the Nocturnal Study).

Question 11 obtains the date of the dialysis preceding the modeling session, and is used to determine if the time-interval between the preceding and current dialysis was in accordance with the

patients assigned treatment schedule. In the event of deviations from the standard interdialytic interval, kinetic variables which are sensitive to predialysis solute concentrations will not be calculated.

Question 13 designates whether the total interruption time exceeded 15 minutes. Interruption time includes:

1) any lowering of the blood flow rate for greater than 15 minutes,
2) any time when dialysate was in bypass,
3) any time in the middle of dialysis when either blood or dialysate flow was interrupted due to problems with needle placement, clotting, water pressure, or other mechanical problems, etc.

Question 14 indicates the treatment time, in minutes. The treatment time should be based on the actual dialysis treatment time indicated on the machine readout for all delivery systems which provide this information. It is expected that almost all systems used for patients in the FHN Study include this information. In the event that the delivery system does not provide a machine readout of the treatment time, enter the difference between the start and end times of the treatment.

Question 15 asks for the average blood flow during dialysis if this is provided by the dialysis machine. Otherwise, the initial blood flow reading indicated in the dialysis run sheet at or after 30 minutes from the start of dialysis should be indicated.

Question 18 asks for the dialysate flow rate. If the dialysis flow rate was modified during the treatment, indicate the flow rate at 30 minutes following the start of the dialysis.

Question 17 regarding complications experienced during the dialysis treatment should be answered based on information in the dialysis run sheet.

Question 19 requests concentrations of selected substances in the dialysate. These fields may be skipped if the requested information is not present in the run sheet.

Question 20 is intended to documents the local laboratory measurements of the predialysis serum albumin and the pre- and postdialysis BUN, serum creatinine, and serum phosphate from the kinetic modeling session. Normally, the measurements will be transmitted by the dialysis clinic's local laboratory within two or three days following the dialysis treatment. The kinetic modeling session must be repeated if either the pre or postdialysis BUNs are missing. Every effort should be made to also collect the pre and postdialysis serum creatinines or serum phosphates, but the session need not be repeated in the event that these are missing.

Residual Renal Function (Form 206)

Timed urine collections of at least 18 hours are required once during baseline and at months 4 and 12 during follow-up. Urine is collected during the interdialytic interval preceding kinetic modeling sessions. Form 206 is required to document the information needed to compute residual renal clearance. *The timed urine collection should be performed for all patients who produce urine.* However, the urine sample needs to be analyzed only if the total urine output from the collection is

at least 100 ml/24 hours. If the volume is less than 100 ml, a sample need not be shipped for measurements at the dialysis facility's local laboratory.

Question 5 documents whether the urine output exceeded 100 ml/24 hours. If the urine output does not exceed 100 ml/24 hours, you may skip to the end of the form (Question Q200). If the urine output does exceed 100 ml/24 hours, continue with Question 6.

Questions 6 and 7 request the start and end times of the urine collection period.

Questions 8 – 11 request the start and end times of the dialysis treatments immediately prior to and immediately subsequent to the urine collection.

Question 12 obtains the volume of the collection.

Questions 13 – 15 are intended to document the local laboratory measurements of urine urea nitrogen, urine creatinine, and urine phosphorus.

Retrospective Review of Dialysis Run Sheets (Form 274).

For patients in the Daily HD Trial, Form 274 should be completed to document retrospective data from the dialysis run sheets over 1-week periods at baseline and at months 1, 4, 8, and 12 of follow-up. The periods for the retrospective review extend for one week prior to the initial kinetic modeling session during baseline, and for one week prior to the F-1, F-4, F-8, and F-12 kinetic modeling sessions during follow-up, excluding the kinetic modeling session itself. Thus, for patients undergoing 6 times per week dialysis, the 6 dialyses preceding (but not including) the kinetic modeling session should be documented on the form. For patients undergoing 3 times per week dialysis, the 3 dialyses preceding (but not including) the kinetic modeling session should be documented. The session immediately preceding the modeled dialysis is documented under Question 4, Session – 1. The prior session (2 dialyses before the modeling session) is documented under Question 5, Session – 2, and so on.

Attendance at In-Center Dialyses (Form 275)

Form 275 should be completed at the start of each calendar month in follow-up, beginning after month F-1, to document any missed dialyses during the preceding calendar month.

18.7 Procedures for Blood Draws.

Pre and postdialysis blood samples may be drawn using the dialysis clinic's usual procedures in the FHN Study. When possible, the FHN Steering Committee recommends that DOQI standard be used. The current DOQI standards for blood draws for kinetic modeling are described below.

DOQI Standards:

When dialysis adequacy is assessed by pre vs. postdialysis blood urea nitrogen concentration measurements, the blood samples must be drawn according to certain acceptable procedures.

1) Both samples (pre and post) must be drawn during the same session.
2) The risk of underestimating predialysis BUN due to saline dilution must be avoided by drawing blood before any saline has entered the patient during initiation of dialysis.
3) The risk of underestimating postdialysis BUN due to access recirculation must be avoided: Prior to sampling, one needs to either slow the blood flow through the dialyzer or to stop the dialysate flow to eliminate any re-entry of dialyzed blood back into the dialyzer.

Background

Summary of updated changes

The updated 2006 K/DOQI recommendations include the use of the dialysate stop flow method first recommended by Wu et al (Nephrol Dial Transplant. 1997 Oct;12(10):2124-7). The K/DOQI Committee was concerned about the risks of needlestick injury in trying to puncture a bloodline containing potentially hazardous infectious agents under time pressure, and for this reason, the time constraints of the slow blood flow method were relaxed, and a stop-blood flow method is preferred, as well as blood-drawing methods that don't involve needles at all (see CPR).

As was reviewed in the 2000 K/DOQI guidelines, there are 3 components of postdialysis urea nitrogen rebound. The first is due to access recirculation (AR), which resolved within seconds after stopping dialysis. The second is due to cardiopulmonary recirculation (CPR) which resolves within 1-2 minutes. The third is due to entry of urea from relatively undialyzed tissues and body compartments, which we will term remote-compartment (RC) rebound, which resolves within 30-60 min after stopping dialysis.

The focus of the blood drawing guideline is to limit the effect of AR on the postdialysis BUN sample because AR can cause both large overestimations of the delivered dose and large reductions in the true delivered Kt/V, often below 0.8 (at which level mortality risk is strongly increased) in patients with apparent Kt/V values of 1.4 or more (Daugirdas, AJKD) . Since the K/DOQI 2000 guidelines were published, it has become clear that rebound is relatively predictable based on the rate of dialysis (HEMO Pilot and HEMO2). For these reasons, the recommendation remains to draw the postdialysis blood urea sample within several minutes (15-18 sec) after the end of dialysis. Since the 2000 guidelines were published, some papers have shown that sampling blood about 30 min prior to the end of dialysis can predict the blood urea nitrogen level 30 min after the end of dialysis (Jean G et al, Kidney Int. 1999 Sep;56(3):1149-53.) This method is not recommended because of its relative complexity, because rebound is relatively predictable based on the rate of dialysis, and most importantly, because in the presence of AR, the dialysis dose can still be

markedly overestimated,

Predialysis BUN. The predialysis BUN must be drawn before dialysis is started to prevent this sample from reflecting any impact of dialysis. Dilution of the predialysis sample with saline or heparin must be avoided. Underestimating predialysis BUN will result in underestimation of delivered Kt/V or URR, and the protein catabolic rate (PCR) will be underestimated.

Recommended method when utilizing an arteriovenous fistula or graft:

1. Obtain the blood specimen from the arterial needle prior to connecting the arterial blood tubing or flushing the needle. Be sure that no saline and/or heparin is in the arterial needle and tubing prior to drawing the sample for BUN measurement.

Purpose: Prevents dilution of the blood sample.

2. Do not draw a sample for use as a predialysis measure of BUN if hemodialysis has been initiated, or if saline or heparin is present in the lines.

Purpose: Prevents sampling of dialyzed blood or dilution of sample, respectively.

Recommended method when utilizing a venous catheter:

1. Withdraw any heparin and saline from the arterial port of the catheter, following the dialysis clinic's protocol.

Purpose: Prevents dilution of the blood sample.

2. For adult patients, using sterile technique, withdraw 10 mL of blood from the arterial port of the catheter. For pediatric patients, withdraw 3 to 5 mL, according to the fill volume of the catheter. Do not discard this blood if the intent is to reinfuse it after the sampling is complete (see step 4).

Purpose: To ensure that the blood sample will not be diluted by heparin. Ideally, all the contaminating diluent is removed in step 1. Step 2 provides an additional margin of security. Because pediatric patients and their catheters are smaller, recommended volumes are reduced.

3. Connect a new syringe or collection device and draw the sample for BUN measurement.

Purpose: Prevents dilution of the sample, and preserves the blood from step 2 for reinfusion, if so desired.

4. Complete initiation of hemodialysis per dialysis clinic protocol. (Optional step: reinfuse the blood drawn from step 2.)

Purpose: Reinfusion minimizes blood loss and may be particularly desirable in pediatric patients who have significantly smaller blood volumes.

Postdialysis blood sampling procedure.

Proper timing for acquisition of the postdialysis BUN sample is critical. Immediately upon completion of hemodialysis, if vascular access recirculation was present, some of the blood

remaining in the angioaccess and extracorporeal circuit is actually recirculated blood. That is, some of the just-dialyzed blood has been routed through the angioaccess and the extracorporeal circuit for hemodialysis without that blood first having passed through waste product-rich tissues. If the blood sample is drawn immediately upon completion of dialysis, just-dialyzed blood that has recirculated into the angioaccess will dilute the sample. The consequence of sampling this admixture is a falsely reduced BUN value and artificially elevated Kt/V and URR. In this situation, the V will be falsely low and the K falsely elevated. Therefore, the amount of dialysis delivered will be overestimated.

Early urea rebound (≤3 minutes postdialysis) may be viewed as a two-component process.. The first component is secondary to blood recirculation within the angioaccess or catheter and is not present in patients without access recirculation. If access recirculation is present, urea rebound from recirculation begins immediately upon completion of hemodialysis and resolves in less than 1 minute, usually approximately 20 seconds. The second component of early urea rebound is cardiopulmonary recirculation that begins approximately 20 seconds after the completion of hemodialysis and is completed 2 to 3 minutes after slowing or stopping of the blood pump. Cardiopulmonary recirculation refers to the routing of just-dialyzed blood through the veins to the heart, through the pulmonary circuit, and back to the angioaccess without the passage of the just-dialyzed blood through any urea-rich tissues. The late phase of urea rebound (>3 minutes) is completed within 30 to 60 minutes after the cessation of dialysis. The late phase is a consequence of flow-volume disequilibrium (perfusion or parallel flow model) and/or of delayed transcellular movement of urea (diffusion model). Refer to K/DOQI Guideline 2: Method of Measurement of Delivered Dose of Hemodialysis, Single-Pool Versus Double-Pool Effects in Adult and Pediatric Patients. These components of urea rebound are schematically presented in Fig I-2.

Recommended methods for postdialysis blood sampling

a. Rationale: Reducing blood flow to 50-100 ml/min reduces the entry of cleared blood into the access and stops AR (unless there is needle reversal, in which case it still greatly reduces AR). The dead space of the bloodline attached to the access needle is usually 2-4 ml, and the dead space between the tip of the arterial bloodline and sampling area is usually about 7-12 ml, giving a total dead space of 10-15 mL. A flow rate of 50-100 ml/min is about 1 ml/sec. So waiting 15-20 sec will ensure that the column of blood at the blood sampling site has not been diluted with dialyzer outflow blood.

b. Method:

1) At the completion of hemodialysis, turn off the dialysate flow and decrease the ultrafiltration rate (UFR) to 50 mL/h, to the lowest transmembrane pressure (TMP)/UFR setting, or off. If the dialysis machine does not allow for turning off the dialysate flow, or if doing so violates the clinic's policy, decrease the dialysate flow to its minimum setting.

Purpose: Stop the hemodialysis treatment without stopping the blood flow completely. The risk of clotting the extracorporeal circuit is low.

2) Decrease the blood flow to 50 to 100 mL/min for 15-20 seconds (longer if the distance between the . To prevent pump shut-off as the blood flow rate is reduced, it may be necessary to manually adjust the venous pressure limits downward.

Purpose: Fills the arterial needle tubing and the arterial blood line with non-recirculated blood (in case there is any access recirculation) by clearing the dead space in the arterial needle tubing and the arterial blood line.

At this point, proceed with either the slow flow or stop pump technique:

2. Sampling

a. Continue slow flow while sampling

1) With the blood pump still running at 50 to 100 mL/min, draw the blood sample for postdialysis BUN measurement from the arterial sampling port closest to the patient.

Purpose: Drawing the blood from the arterial sampling port ensures the postdialysis BUN measurement is performed on undialyzed blood.

2) Stop the blood pump and complete the patient disconnection procedure as per dialysis clinic protocol.

2. Stop blood pump prior to sampling (initial slow flow period is STILL required!)

1) After the required slow flow period, stop the blood pump.

2) Clamp the arterial and venous blood lines. The arterial needle tubing distal to the blood sampling site.

3) Blood for postdialysis BUN measurement may be sampled by needle aspiration from the arterial sampling port closest to the patient (inlet bloodline). Alternatively, blood may be obtained from the inlet needle tubing after disconnection from the arterial blood line and attaching a vacutainer or syringe without a needle – method that may be preferred because it by definition limits the risk of needlestick injury.

4) Blood is returned to the patient and the patient disconnection procedure proceeds as per clinic protocol.

Stopping dialysate flow prior to sampling

Rationale: The method is based on data in the paper by Wu et al. The principle is the same – when dialysate flow is stopped, the dialysate outlet urea concentration starts to approach the inlet level, and AR, if present, has a progressively lower dilutional effect on inlet blood flow. With this method, blood flow rate should NOT be reduced, because one wants to equilibrate the remaining dialysate in the dialyzer with blood as quickly as possible. There is no data regarding the time course of this equilibration. The length of time for which dialysate was stopped in the Wu et al paper was 3 min., and the K/DOQI recommendation is to follow this validated method. It should be realized that, 3 min after stopping dialysis, the CPR component of rebound, as well as some early

components of the RC rebound will have resolved. Hence, the postdialysis BUN drawn using this method will be slightly higher than that obtained 15-20 sec after dialysis using the other methods.

Method:

1) Continue the blood flow rate at the prescribed rate, set the UF rate as close to zero as allowed, and put the dialysate into bypass.

2) Wait 3 min. At that point, sample the blood from either the sampling area in the inlet bloodline:

a) **Inlet bloodline sampling:** Take the sample from the inlet blood line – the blood can continue to flow during sampling or can be stopped.
b) **Inlet needle tubing sampling:** The blood pump is stopped, the inlet blood lines and needle tubing are clamped and disconnected from one another, and the blood is drawn using a Vacutainer screwed onto the luer lock connection on the inlet needle tubing.

3) After the sample is obtained, blood is returned in the usual fashion.

18.8 Kinetic Modeling Reports Generated by the Data Coordinating Center

Table 18.7 below provides a sample kinetic modeling report. Kinetic modeling reports will be generated by the Data Coordinating Center and emailed to the clinical site following the completion of Form 273 after each kinetic modeling session. The contents of the report are as follows:

1st Panel:

The first panel provides identifying information including the patient ID, alpha code, session date and number, and assigned treatment arm. The final item indicates the number of dialyses conducted in the 7-day period immediately preceding the kinetic modeling session as indicated on Form 274.

2nd Panel:

This panel provides demographic and weight and height information used to compute anthropometric volume, as well as pre- and post-dialysis BUNs and residual renal clearance. Residual renal clearance is taken to be 0 for patients producing under 100 ml/day of urine, and is estimated from the most recent timed urine collection otherwise.

3rd Panel:

This panel describes the dialysis prescription. The individual items are:

Dialyzer	Reported dialyzer.
Dialyzer K0A	In-vitro K0A of the reported dialyzer at the prescribed dialysate flow rate.
Prescribed Time	Prescribed duration of dialysis, in minutes.
Prescribed Blood Flow	Prescribed blood flow rate, in ml/min.
Actual Blood Flow	Actual blood flow reported on Form 273.
Actual Time	Actual dialysis duration reported on Form 273.
Prescribed eKt/V	The level of eKt/V that was reportedly prescribed by the Clinical Center based on the reported prescribed blood and dialysate flow rates, the dialyzer K0A, prescribed dialysis time, and the prior running median modeled volume.
Dialysis Flow	Reported dialysate flow rate in Form 273.
Interruptions > 15 min	Indicates whether reported interruption time exceeded 15 minutes.
Ultrafiltration Rate	Ultrafiltration rate (in ml/min) computed as the weight change divided by the duration of dialysis

4th Panel:

This panel contains the calculated kinetic modeling results. Note that all estimates of volume are expressed in liters, and again as a % of body weight. Individual items are:

Anthropometric volume	Anthropometric estimate of total urea volume calculated from age, gender, weight, and height according to Watson formula.
Adj modeled volume (run. median prior to current session)	In most cases, the running median volume is defined as the median of of the calculated kinetic volumes from four successive modeling sessions (see Step 4 of Section 18.4 for details).
Adj modeled volume (run. median including to current session)	Update of the running median volume including the current session.

Adj. modeled volume (current session only)	Estimate of the patient's kinetic volume based on the current session. If there are no errors in the delivery of dialysis, the kinetic volume is an estimate of the patient's total volume for the distribution of urea.
% deviation of cur. median vol vs. anth. vol	% difference between the first two volume estimates above. Positive % differences of over 30% suggest underdelivery of dialysis, possibly due to access recirculation.
% deviation of cur. session vol vs. prior median	% difference between the kinetic volume for the current session vs. the prior running median volume. Positive % differences above 20% suggest either underdelivery of therapy or measurement/sampling errors, while negative % differences greater than 20% suggest overdelivery of therapy or measurement/sampling errors.
Prescribed Dialyzer clearance	The prescribed dialyzer blood water clearance computed from the prescribed K0A, the reported blood flow rate, and the prescribed dialysate flow rate.
Effective Dialyzer clearance	The estimated dialyzer blood water clearance that was actually delivered. Smaller values for the effective than prescribed dialyzer clearance suggest an underdelivery of dialysis.

Estimates of PCR and Amount of Dialysis Actually Delivered

(Note: Single-pool and equilibrated values are provided for each of the following parameters)

PCR (single pool)	Protein catabolic rate computed from the single pool urea generation rate. The single pool PCR has been primarily used in previous studies, but may overestimate the true PCR since it does not take into account post-dialysis rebound.
PCR (equilibrated)	Protein catabolic rate computed from the equilibrated urea generation rate.
nPCR (single pool)	Normalized protein catabolic rate computed from the single pool urea generation rate.
nPCR (equilibrated)	Normalized protein catabolic rate computed from the equilibrated urea generation rate.
Urea removal [URR]	The urea reduction ratio. This is the fractional reduction in BUN concentration from the beginning to the end of dialysis. The URR takes on

values between 0 and 1, with 0 in principle representing no removal of urea, and 1 representing total removal of urea by dialysis.

Urea Removal [SRI]	The solute removal index (SRI) corresponding to the equilibrated Kt/V computed using the Daugirdas rate adjustment. The SRI is analogous to the urea reduction ratio, but accounts for estimated post-dialysis urea rebound, ultrafiltration, and urea generation. Like the URR, the SRI takes on values between 0 and 1, with 0 representing no removal of urea, and 1 representing total removal of urea by dialysis.
Total Kt/V (includes Kru) [single pool]	Total single pool Kt/V, including residual renal clearance. The total single pool Kt/V is calculated as $(Kd \cdot t + Kr \cdot 3360)/V$, where Kr represents residual renal clearance in ml/min. Kr is multiplied by 3360 since this represents the number of minutes in 1/3 of a week, so that $Kr \cdot 3360$ can be thought of total renal clearance corresponding to the time frame around one of three weekly dialysis sessions.
Total Kt/V (includes Kru) [equilibrated]	Total equilibrated Kt/V, including residual renal function.
Delivered Kt/V (excludes Kru) [single pool]	Single pool Kt/V according to variable-volume single pool model.
Delivered Kt/V (excludes Kru) [equilibrated]	Equilibrated Kt/V (eKt/V) estimated using the modified Tattersall adjustment.
Standard Kt/V	Standard Kt/V calculated as the ratio of the equilibrated urea generation rate to the average predialysis urea concentration over 1 week. The treatment schedule reported on Form 274 for the week prior to the kinetic modeling session is used in this calculation, which thus takes into account the number of dialysis treatments that were actually held.

Table 18.7

FHN Daily Study: Standard Kinetic Modeling Report

Patient ID:	60101	Visit Type:	F
Alpha Code:	DECO	Month Number:	6
Date of Session:	02/26/06	Treatment Arm:	3x/wk
		# Trtmnts Lst Wk:	3

Anthropometric and Biochemistry Inputs

Gender	Female	Pre-dialysis BUN	62.1 mg/dL
Age	52 yr	Post-dialysis BUN	18.3 mg/dL
Height (cm)	155 cm	Start Wt	58.8 kg
Height (in)	61 in	End Wt	55.7 kg
Res. Renal Clear. (Kru)	0.0 ml/min	Target Wt	54.7 kg

Dialysis Prescription

Dialyzer	F80A		
Prescribed eKt/V	1.49	Dialyzer KoA	868 ml/min
Target Time	158-174 min	Prescribed Blood Flow	350 ml/min
Prescribed Time	175 min	Blood Flow, 30 min	350 ml/min
Actual Time	160 min	Dialysate Flow	800 ml/min
Interruptions > 15 min?	No	Ultrafiltration Rate	19.4 ml/min

Calculated Outputs

Anthropometric volume	27.9 L (50% BW)
Adj Modeled volume (run. median prior to cur. session)	22.5 L (40% BW)
Adj Modeled volume (run. mean including cur. session)	23.1 L (41% BW)
Adj Modeled volume (current session only)	26.3 L (47% BW)
% Dev. of cur. mean 1-pool vol vs anth. vol	-17.4 %
% Dev. of cur. session's 1-pool vol vs prior mean	17.1 %
Prescribed dialyzer clearance	254 ml/min
Effective dialyzer clearance	212 ml/min

	SINGLE POOL		EQUILIBRATED	
	Cur. Sess	Run. Mean	Cur. Sess	Run. Median
PCR (g/day)	38.4	40.3	35.6	38.1
nPCR (g/kg/day)	0.97	0.97	0.89	0.92
Urea removal (URR or SRI)	0.71	0.79	0.66	0.74
Total Kt/V (includes Kru)	1.51	1.97	1.20	1.60
Delivered Kt/V (excludes Kru)	1.51	1.97	1.20	1.60
Standard Kt/V			X.XX	X.XX

18.9 Strategies for Patients Unwilling to Dialyze 6x/week.

If during follow-up subjects randomized to 6x/week therapy are unwilling or unable to continue to follow their 6x/week dialysis prescriptions stipulated by the protocol, efforts will be made to approximate the target 6x/week prescription as closely as possible with a revised prescription with either reduced total weekly treatment time or with a reduced frequency of dialysis sessions. The hierarchy of alternative options outlined in Table 7 below will be followed for patients unwilling or unable to adhere to the protocol 6x/week regimen.

In the event of a deviation from the 6x/week schedule specified by the protocol, the Clinical Center's personnel will consult with the study subject in an effort to adopt the highest option in the above table. If one of Options 1-4 is adopted, the Clinical Center's staff will periodically discuss the treatment options with the patient to determine if the patient is willing or able to return to a higher Option number, or ideally to return to the full 6x/week regimen specified by the protocol. Missed treatments will be monitored closely to ensure the safety of trial participants (Section 3.2).

Table 7: Stepped Options for Modifying 6x/Week Daily HD Regimen

Option Number	Description of Option
1	Maintain 6x/week treatment schedule, but reduce treatment time to the projected total weekly treatment time or an amount acceptable to the patient, subject to: a) minimum session length ≥ 1.5 hours, b) total weekly treatment time ≥ total weekly treatment time the patient would have had if assigned to the conventional HD group.
2	Adopt a 5x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the patient such that the projected weekly $stdKt/V_{urea}$ approximates the patient's target $stdKt/V_{urea}$ as closely as possible.
3	Adopt a 5x/week treatment schedule, without increasing the time per treatment, so long as a) minimum session length $\underline{\geq}$ 1.5 hours, and b) total weekly treatment time $\underline{\geq}$ total weekly treatment time the patient would have had if assigned to the conventional HD group.
4	Adopt a 4x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the patient such that the projected weekly stdKt/Vurea approximates the patient's target stdKt/Vurea as closely as possible.

18.10 Minimum Safety Guidelines

For the purpose of adhering to the study design and maintaining the desired separation between the two treatment arms, all efforts should be made to maintain patients on their assigned 3x/week or 6x/week treatment schedules. Further, the guidelines of MOP Section 18.9 should be followed for patients who are randomized to 6x/week dialysis but who become unwilling to maintain 6x/week therapy.

Distinct from the targets designed to maintain the study design, minimum eKt/V safety thresholds have also been set for both treatment arms to assure that all patients are dialyzed in accordance with KDOQI standards. Note that for 6x/week patients the safety thresholds fall substantially below minimum targets necessary to produce adequate separation between the treatment arms. Hence, all efforts should be made to maintain the stricter targets needed to achieve good separation between the treatment arms, and lower safety thresholds, which are used only to generate warning messages to assure patients safety, should not be substituted from the higher targets described in preceding sections.

For patients in either treatment arm who are dialyzing 3x/week, the minimum running median eKt/V for safety purposes is 1.10. The minimum eKt/V for a single dialysis is 0.90. (The lower limit for a single dialysis reflects the variability in an individual eKt/V measurement.) Warning messages will be sent by the DCC to the site Principal Investigator if either of these safety criteria are not met.

For patients in either treatment arm who are dialyzing 4x/week, the minimum running median eKt/V for safety purposes is 0.80. The minimum eKt/V for a single dialysis is 0.70.

For patients in either treatment arm who are dialyzing 5x/week, the minimum running median eKt/V for safety purposes is 0.60. The minimum eKt/V for a single dialysis is 0.50.

Appendix to Chapter 18

Tables 18.4a – 18.4h provide the minimum treatment times required to achieved a target eKt/Vn of 0.90 (with a treatment time between 1.5 and 2.75 hr) in the Daily HD arm for patients with modeled and anthropometric volume ranging from 20 L to 55 L. Patients on the six times per weak dialysis should receive treatment times at least as high as those indicated in the table to assure the targeted separation between the Daily HD and Conventional HD treatment arms.

Tables 18.6a – 18.6h provide the minimum treatment times required to achieve a target eKt/V of 1.10 for alternative dialysis prescriptions for patients with modeled volume ranging from 20 L to 55 L. Patients on three times per week schedules should receive dialysis prescriptions at least as high as those indicated in these tables to assure adherence to DOQI standards for dialysis adequacy.

Table 18.4a

Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 20 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	162	159	156	154	153	151
250	500	159	150	144	140	137	134	132	131
300	500	148	139	133	128	125	122	120	118
350	500	141	132	126	121	117	114	112	110
400	500	136	127	121	116	112	109	106	104
450	500	133	123	117	112	108	105	102	100
500	500	130	120	114	109	105	102	99	97
200	800	165*	163	159	155	153	152	151	150
250	800	153	145	139	135	133	130	129	128
300	800	142	133	127	123	120	117	115	114
350	800	134	125	119	115	111	108	106	104
400	800	129	120	113	109	105	102	100	98
450	800	125	116	109	104	100	98	95	93
500	800	121	112	106	101	97	94	92	90

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4b
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 25 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	162	157	153	150	148	146
300	500	165*	156	149	144	140	136	134	132
350	500	159	148	141	135	131	127	125	122
400	500	153	142	135	129	125	121	118	116
450	500	149	138	130	125	120	117	114	111
500	500	145	135	127	121	117	113	110	108
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	162	156	152	148	146	144	143
300	800	159	149	142	137	134	131	128	127
350	800	150	140	133	128	124	121	118	116
400	800	144	134	126	121	117	113	111	108
450	800	139	129	121	116	111	108	105	103
500	800	136	125	118	112	108	104	101	99

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4c
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 30 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165	163	161
300	500	165*	165*	164	158	153	150	147	144
350	500	165*	163	155	148	144	140	136	134
400	500	165*	157	148	142	137	133	129	127
450	500	164	152	143	137	132	128	124	122
500	500	160	148	139	133	128	124	120	118
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	163	160	158	157
300	800	165*	164	156	151	147	143	141	139
350	800	165*	154	146	140	135	132	129	127
400	800	159	147	139	132	128	124	121	118
450	800	153	142	133	127	122	118	115	112
500	800	149	137	129	122	117	113	110	108

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4d
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 35 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165*	165*	165*
300	500	165*	165*	165*	165*	165*	162	159	157
350	500	165*	165*	165*	161	156	151	148	145
400	500	165*	165*	161	154	148	144	140	137
450	500	165*	165	155	148	143	138	134	131
500	500	165*	161	151	144	138	134	130	127
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	165*	165*	165*	165*
300	800	165*	165*	165*	164	159	155	153	150
350	800	165*	165*	158	152	147	143	140	137
400	800	165*	159	150	143	138	134	131	128
450	800	165*	154	144	137	132	127	124	121
500	800	162	149	139	132	127	122	119	116

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4e
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 40 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165*	165*	165*
300	500	165*	165*	165*	165*	165*	165*	165*	165*
350	500	165*	165*	165*	165*	165*	163	159	156
400	500	165*	165*	165*	165	159	154	150	147
450	500	165*	165*	165*	159	153	148	144	141
500	500	165*	165*	163	155	148	144	140	136
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	165*	165*	165*	165*
300	800	165*	165*	165*	165*	165*	165*	164	161
350	800	165*	165*	165*	163	158	153	150	147
400	800	165*	165*	161	154	148	144	140	137
450	800	165*	165	155	147	141	136	133	130
500	800	165*	160	150	142	136	131	127	124

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4f
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 45 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165*	165*	165*
300	500	165*	165*	165*	165*	165*	165*	165*	165*
350	500	165*	165*	165*	165*	165*	165*	165*	165*
400	500	165*	165*	165*	165*	165*	164	160	157
450	500	165*	165*	165*	165*	163	158	153	150
500	500	165*	165*	165*	165	158	153	149	145
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	165*	165*	165*	165*
300	800	165*	165*	165*	165*	165*	165*	165*	165*
350	800	165*	165*	165*	165*	165*	163	160	157
400	800	165*	165*	165*	164	158	153	149	146
450	800	165*	165*	165	157	150	145	141	138
500	800	165*	165*	159	151	145	139	135	132

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4g
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 50 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165*	165*	165*
300	500	165*	165*	165*	165*	165*	165*	165*	165*
350	500	165*	165*	165*	165*	165*	165*	165*	165*
400	500	165*	165*	165*	165*	165*	165*	165*	165*
450	500	165*	165*	165*	165*	165*	165*	163	159
500	500	165*	165*	165*	165*	165*	162	157	153
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	165*	165*	165*	165*
300	800	165*	165*	165*	165*	165*	165*	165*	165*
350	800	165*	165*	165*	165*	165*	165*	165*	165*
400	800	165*	165*	165*	165*	165*	162	158	154
450	800	165*	165*	165*	165*	159	154	149	146
500	800	165*	165*	165*	160	153	147	143	139

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.4h
Treatment Times Targeting an eKt/Vn of 0.90 Between 1.5 and 2.75 Hours
Volume = 55 L

Qb (ml/min)	Qd (ml/min)	500	600	700	800	900	165*	1100	1200
200	500	165*	165*	165*	165*	165*	165*	165*	165*
250	500	165*	165*	165*	165*	165*	165*	165*	165*
300	500	165*	165*	165*	165*	165*	165*	165*	165*
350	500	165*	165*	165*	165*	165*	165*	165*	165*
400	500	165*	165*	165*	165*	165*	165*	165*	165*
450	500	165*	165*	165*	165*	165*	165*	165*	165*
500	500	165*	165*	165*	165*	165*	165*	165*	162
200	800	165*	165*	165*	165*	165*	165*	165*	165*
250	800	165*	165*	165*	165*	165*	165*	165*	165*
300	800	165*	165*	165*	165*	165*	165*	165*	165*
350	800	165*	165*	165*	165*	165*	165*	165*	165*
400	800	165*	165*	165*	165*	165*	165*	165*	162
450	800	165*	165*	165*	165*	165*	162	157	153
500	800	165*	165*	165*	165*	161	155	150	146

*A prescribed eKt/Vn of 0.90 cannot be achieved in 2.75 hrs on this prescription
If possible, please employ higher Qb, Qd, or KoA.

Table 18.6a

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 20 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	174	166	161	158	155	153	152	151
250	500	156	148	143	139	135	133	131	130
300	500	146	137	131	127	123	121	119	117
350	500	138	130	124	119	115	113	110	108
400	500	133	125	118	114	110	107	105	103
450	500	129	121	114	110	106	103	101	98
500	500	126	118	111	106	103	100	97	95
200	800	169	162	158	155	153	151	150	150
250	800	151	143	138	134	132	130	128	127
300	800	139	131	126	122	118	116	114	113
350	800	132	123	117	113	110	107	105	103
400	800	126	117	111	107	103	101	98	97
450	800	122	113	107	102	99	96	94	92
500	800	118	110	103	99	95	92	90	88

Table 18.6b

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 25 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	213	203	197	192	189	187	185	184
250	500	191	181	174	168	165	162	159	157
300	500	178	167	160	154	150	146	144	141
350	500	169	158	150	144	140	136	133	131
400	500	163	152	144	138	133	129	126	124
450	500	158	147	139	133	128	124	121	119
500	500	154	143	135	129	124	120	117	115
200	800	207	198	192	189	186	184	183	182
250	800	184	174	168	163	160	157	155	154
300	800	170	160	152	147	143	140	138	136
350	800	160	150	142	137	132	129	127	124
400	800	153	143	135	129	125	121	118	116
450	800	148	137	129	124	119	115	112	110
500	800	144	133	125	119	115	111	108	105

Table 18.6c

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 30 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	251	240	232	226	223	220	218	216
250	500	226	213	204	198	193	190	187	184
300	500	210	197	188	181	176	171	168	165
350	500	199	186	176	169	164	160	156	153
400	500	192	178	169	161	156	151	148	145
450	500	186	172	163	156	150	145	142	139
500	500	182	168	158	151	145	141	137	134
200	800	244	233	227	222	219	217	215	214
250	800	217	205	197	191	187	184	182	180
300	800	200	188	179	173	168	164	161	159
350	800	189	176	167	160	155	151	148	145
400	800	180	167	158	151	146	142	138	135
450	800	174	161	151	144	139	135	131	128
500	800	169	156	146	139	134	129	126	123

Table 18.6d

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 35 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	289	276	267	260	256	252	250	248
250	500	260	245	235	227	222	217	214	211
300	500	242	226	215	207	201	196	192	189
350	500	229	214	202	194	188	183	178	175
400	500	220	205	193	185	178	173	169	165
450	500	214	198	187	178	171	166	162	158
500	500	209	193	181	173	166	161	157	153
200	800	281	269	261	255	251	249	247	245
250	800	250	236	226	220	215	211	208	206
300	800	230	215	205	198	192	188	185	182
350	800	217	202	191	183	177	172	169	166
400	800	207	192	181	173	166	162	158	154
450	800	200	184	173	165	159	153	149	146
500	800	195	179	167	159	153	147	143	140

Table 18.6e

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 40 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	328	312	302	294	289	285	282	280
250	500	294	277	265	257	250	245	241	238
300	500	273	256	243	234	227	221	217	213
350	500	259	241	228	219	211	205	201	197
400	500	249	231	218	208	201	195	190	186
450	500	242	223	210	201	193	187	182	178
500	500	236	218	204	195	187	181	176	172
200	800	318	304	294	288	284	281	279	277
250	800	282	266	255	248	242	238	235	232
300	800	260	243	231	223	216	211	208	205
350	800	245	227	215	206	199	194	190	186
400	800	234	216	204	194	187	181	177	173
450	800	226	208	195	185	178	172	167	164
500	800	220	201	188	179	171	165	160	156

Table 18.6f

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 45 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	366	348	336	328	322	318	314	312
250	500	328	309	295	286	278	273	268	265
300	500	305	285	271	260	252	246	241	237
350	500	289	269	254	243	235	228	223	218
400	500	278	257	243	232	223	216	211	206
450	500	269	249	234	223	214	207	202	197
500	500	263	242	227	216	208	201	195	190
200	800	355	339	328	321	316	313	310	308
250	800	315	297	284	276	269	265	261	258
300	800	290	271	257	248	240	235	231	227
350	800	273	253	239	229	221	215	210	206
400	800	261	241	226	216	208	201	196	192
450	800	252	231	217	206	198	191	186	181
500	800	244	224	209	198	190	183	178	173

Table 18.6g

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 50 L

Qb (ml/min)	Qd (ml/min)	KoA (ml/min) 500	600	700	800	900	1000	1100	1200
200	500	404	384	371	361	355	350	346	344
250	500	362	340	325	315	306	300	295	291
300	500	336	314	298	286	277	270	265	260
350	500	319	296	280	268	258	251	245	240
400	500	306	283	267	255	245	238	231	226
450	500	297	274	258	245	236	228	222	216
500	500	290	267	250	238	228	220	214	209
200	800	392	373	362	354	348	344	342	340
250	800	347	327	313	303	296	291	287	284
300	800	319	298	283	272	264	258	253	250
350	800	301	279	263	252	243	236	231	227
400	800	287	265	249	237	228	221	215	210
450	800	277	254	238	226	217	210	204	199
500	800	269	246	230	218	208	201	195	190

Table 18.6h

Treatment Times (min) Required to Achieve an eKt/V of 1.10

Modeled Volume = 55 L

Qb	Qd	KoA (ml/min)							
(ml/min)	(ml/min)	500	600	700	800	900	1000	1100	1200
200	500	442	420	405	395	388	382	378	375
250	500	396	372	356	344	335	328	322	318
300	500	367	343	325	312	303	295	289	284
350	500	348	323	305	292	282	274	267	261
400	500	335	309	291	278	267	259	252	246
450	500	325	299	281	267	257	248	241	235
500	500	317	291	273	259	249	240	233	227
200	800	428	408	395	386	380	376	373	371
250	800	379	357	342	331	323	318	313	310
300	800	349	325	309	297	288	281	276	272
350	800	329	304	287	274	265	257	252	247
400	800	314	289	271	258	248	240	234	229
450	800	303	278	260	246	236	228	221	216
500	800	294	269	251	237	227	219	212	206

20. Standards of Care

20.1 Dialysis Co-Interventions Not Related to Dose

a. *Dialysis Machines*:
All dialysis units should employ the use of machines that allow volumetric control of ultrafiltration.

b. Water Quality
Patients undergoing nocturnal dialysis are required to use ultrapure water. Centers are encouraged to use ultrapure. All dialysate water should at a minimum meet Association for the Advancement of Medical Instrumentation (AAMI) standards for endotoxin units of <2.0 E.U/ml and bacterial counts of <200 CFU/ml. The limits for elemental and ionic impurities will also be maintained within AAMI standards in all centers. Dialysis unit water standards will be captured on Form 603 at the start of the study for all participating units in both studies

All dialysis units are encouraged to monitor their water quality on a monthly basis

Patients on home dialysis are encouraged to have monthly water tests. In the Nocturnal Study, the results of the home water quality tests will be entered into database twice during follow up.

***c. Dialyzers*:**
Compared with conventional HD, patients on daily and nocturnal HD will have approximately twice the number of exposures to dialyzer membranes in a given time period. Because this could influence the interpretation of study results, standardized use of dialyzers is encouraged.

i) Flux: Subgroup analysis of the HEMO Study suggested a reduction in cardiac death with high-flux dialyzers (1). Only high-flux, high efficiency, biocompatible dialyzers should be used for all patients in both trials.

ii)Reuse: Reuse will not be permitted for any patients on home hemodialysis. For conventional HD patients in the Nocturnal trial, and for all patients in the daily study, non-reuse of dialyzers is encouraged.

If reuse is used, reuse techniques will follow manufacturers' recommendations and procedures approved by the medical directors of the Core Centers' dialysis units, with adherence to Association for the Advancement of Medical Instrumentation (AAMI) standards. Reuse number is collected monthly for each patient on the kinetic modeling Form 273.

d. *Dialysate Composition*:

i) *Acid Buffer*: Bicarbonate dialysate should be used in all patients in order to minimize intradialytic hypotension and cardiovascular instability (2). The dialysate bicarbonate concentration should be adjusted by the treating nephrologist in order to maintain a midweek predialysis serum bicarbonate of 20-27 mmmol/L (as determined by the local laboratory.

ii) *Sodium*: The dialysate sodium should be adjusted by the treating nephrologist. It is suggested that the dialysate sodium prescription should match the patient's predialysis serum sodium in order to maintain neutral sodium balance (6). In addition, to avoid increasing interdialytic thirst, weight gain,

and hypertension, the use of sodium ramping and high sodium dialysate is discouraged unless the center has biofeedback control or other mechanisms available to ensure patients maintain neutral sodium balance (7-10). Using dialysate sodium less than the patient's predialysis sodium is also be discouraged in order to avoid intradialytic hypotension and cardiovascular instability (11).

iii) *Potassium*: The dialysate potassium should be adjusted by the treating nephrologist. The suggested range is 1.5 – 4.0 mmol/L in order to maintain a predialysis serum potassium of 4.0 – 5.5 mmol/L. Dialysate potassium <1.5 should be avoided in order to decrease potential for intradialytic hypotension, cardiovascular instability, and arrhythmias (12;13).

iv) *Calcium*: The dialysate calcium should be adjusted by the treating nephrologist. The suggested range is suggested range is 1.25 to 1.5 mmol/L (2.5 to 3.0 mEq/L) in order to maintain a predialysis serum calcium (corrected for serum albumin) of 2.1 – 2.6 mmol/L (14). For subjects with intradialytic hypotension responsive to changes in dialysate calcium concentration, the dialysate calcium may be increased, provided that the adjusted pre-dialysis calcium concentration is maintained within target ranges (15-17) (see section 3.11.2 also).

v) Calcium-phosphate protocol for home nocturnal patients

Calcium- phosphate should be managed in home nocturnal patients according to the current standards of care.

vi) *Magnesium and Glucose*: The dialysate magnesium and glucose should be determined by the treating nephrologist according to clinical practice guidelines (18).

e. *Ultrafiltration and "Dry Weight" Targets*:

i) *Background*: Volume overload is the main cause of hypertension in ESRD patients, leading to left ventricular hypertrophy, pulmonary edema, and even sudden cardiac death (19). Volume depletion leads to symptomatic intradialytic hypotension, cramping, and fatigue, causing patient dissatisfaction with the dialysis procedure and poor quality of life (20). It is imperative that attempts be made to prescribe accurate ultrafiltration targets and attain dry weights equally in subjects from both groups. Using bioimpedance technology, it has been shown that the extracellular to intracellular fluid volume ratio is reduced toward normal physiologic values in daily HD patients, suggesting that improved blood pressure control may be at least partly due to closer attainment of true dry weight in these patients (London and RRI Studies, unpublished data). *It is difficult to determine if the daily HD procedure itself allows for easier fluid removal and thus closer attainment of dry weights, or if more effort was made to adjust dry weights in these patients.* Thus, for this study, it is critical to adopt a standardized approach for the determination and attainment of dry weight goals in both groups.

ii) *Setting the ultrafiltration prescription*: The ultrafiltration prescription will be determined by the treating nephrologist, and will be set to achieve the patient's goal "dry weight." (see below) It is suggested that the ultrafiltration rate during hemodialysis not exceed 2.0 L/hr in order to avoid intradialytic hypotension.

iii) *Determining the goal dry weight*:

Dry weight should be determined by the treating nephrologist by clinical examination, with emphasis on pre-dialysis blood pressure, jugular venous pressure, and pedal/sacral edema. It is suggested that the clinical examination be supplemented with a protocol to test the lowering of the patient's target weight. This involves to gradually lowering the target weight by 0.1L/session, until the patient cannot tolerate further lowering of the dry weight due to intradialytic hypotension or symptoms and the treating nephrologist deems that the true dry weight has been attained. The minimum tolerable

weight is then used as the patient's target weight for subsequent sessions, with reevaluation on a regular basis. Such an approach was utilized in the Renal Research Institute with success.

iv) *Approach to intradialytic hypotension*: Fluid overloaded patients often have intradialytic symptoms of hypotension and cramping due to slow plasma refilling (21). Patients with diastolic dysfunction may be particularly sensitive to filling pressures. Based on evidence, a standardized protocol is suggested for patients from both groups who experience intradialytic hypotension.

First, the subject should have a careful clinical examination by the attending nephrologist to assess volume status and to rule out non-volume causes of hypotension. If the patient is still deemed to be volume overloaded, he or she should be counseled to reduce sodium intake and interdialytic weight gains (22). The dialysate sodium should also be adjusted to the patient's predialysis sodium (23). In conjunction, the use of a blood volume monitor, such as continuous hematocrit monitor, may be used to guide ultrafiltration rate (24;25).

Where available, blood temperature monitoring may be used (26). If not available, constant cool temperature dialysate will be attempted, followed by ultrafiltration profiling or midodrine (27-30). Because of its adverse effects on interdialytic weight gain and hypertension (31;32), sodium profiling is discouraged, unless biofeedback or other mechanisms are available in order to ensure the patient remains in neutral sodium balance (10;33).

Failing these measures, under the discretion of the treating nephrologist, subjects may be advised to have additional dialysis treatments for ultrafiltration, until they are able to achieve their targeted dry weight. The treating nephrologist should adjust antihypertensive medications according to his or her discretion. Intradialytic hypotensive episodes and interventions will be recorded, along with the need for additional treatments. Regardless of the methods used to prevent, ameliorate, or correct intradialytic hypotension, the same methods should be applied uniformly to subjects randomized to both groups.

20.2 Non-Dialytic Co-Interventions

Recommendations regarding non-dialytic co-interventions are summarized in the table below.

Co-Interventions and Standards of Care Not Related to HD Prescription

Item	Recommendations*	Data Collection	Feedback
Tier 1			
Immunizations	Yearly Influenza Hepatitis B as per Appendix 2 Pneumovax as per Appendix 2	*None*	*None*
Diabetes Management	Target HbA1C <7.0%		
Lipid Management	Target LDL≤ 2.6 mmol/L		
Tier 2	*Targets (DOQI):*	*Regular local lab entry¥:*	*Automated feedback by DCC* to treating nephrologist and research coordinator for patients whose monthly labs fall outside of target for 3 consecutive months, or whose iron studies are out of target for 2 consecutive quarters
Anemia Management	hemoglobin 110 – 120 g/L ferritin 100 – 800 transferrin saturation ≥ 20%	hemoglobin ferritin transferrin saturation	
Calcium-Phosphate	phosphate <1.80 mmol/L calcium¶ 2.10 – 2.60 mmol/L	*phosphate* calcium	
Acid-Base Status	bicarbonate 20 – 27 mmol/L	bicarbonate	
Tier 3	*Routine monitoring frequency:*		
Ideal weight assessment	Weekly Monthly		
Formal vascular access monitoring	Weekly	*See "non-dialytic aspects of the intervention" in the protocol*	*None*
Visits by health-care professionals (other than nurses)			

*all lab values are pre-dialysis
¶corrected calcium (for albumin)
¥ all labs collected MONTHLY, except for transferrin saturation and ferritin which should be collected every 3 months (i.e. once per quarter)

The DCC will review the database monthly, and provide automated feedback for those items in Tier 2. These reports will be copied to designated members of the Standards of Care Committee. He/she will contact the local study coordinator for participants who generate 3 or more reports to determine the reason why the targets cannot be met. For those participants who are not able to meet targets despite adequate treatment, the further sending of automated reports may be discontinued. The Committee member will email the DCC to inform them of participants who should not have automated reports sent.

1) For those patients whose pre-dialysis Hgb is <110 g/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis hemoglobin has been less than the DQOI recommended target of 110g/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

2) For those patients who are on erythropoeitin AND whose pre-dialysis Hgb is >135 g/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis hemoglobin has been greater than the DQOI recommended target of 120g/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

3a) For those patients whose pre-dialysis phosphate is >1.80 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis phosphate has been greater than the recommended target of 1.8mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

3b) For those patients who have pre dialysis serum phosphorus less than the lower limit of normal (for the lab where serum phosphorus was measured) for three consecutive months, the DCC will send a message to the Clinical Center.

4) Albumin corrected calcium is defined as Serum calcium + (0.8 x [Normal serum albumin - Patient's albumin]), where Normal serum albumin is defined as XXXXX.

For those patients whose pre-dialysis albumin-corrected calcium is <1.90 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

"As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.

Re: Patient ID # _____

We wish to bring to your attention that this patient's pre-dialysis albumin corrected calcium has been less than the recommended target of 2.1mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

5) Albumin corrected calcium is defined as Serum calcium + (0.8 x [Normal serum albumin - Patient's albumin]), where Normal serum albumin is defined as XXXXX.

For those patients whose pre-dialysis albumin corrected calcium is >2.90 mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis albumin corrected calcium has been greater than the recommended target of 2.6mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

6) For those patients whose pre-dialysis bicarbonate is <20mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis bicarbonate has been less than the recommended target of 22mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

7) For those patients whose pre-dialysis bicarbonate is >27mmol/L for 3 consecutive months, the following message will be sent to the study coordinator and/or local principal investigator:

> "As part of the FHN trial standards of care, the DCC is monitoring participants' laboratory values.
>
> Re: Patient ID # _____
>
> We wish to bring to your attention that this patient's pre-dialysis bicarbonate has been greater than the recommended target of 25mmol/L for the last 3 months. If you are already aware of this and have instituted appropriate treatment, please disregard this message."

20.3 Kinetic Modelling Action Items

a) DCC will report and the Adherence Committee will review (in conjunction with Kinetic Modeling Committee) any patient who has persistent underdialysis.

b) The Adherence Committee will review those patients who falling below target KT/V for 3 consecutive months.

c) DCC will report and the Adherence Committee will review any patient who has persistent nonadherence to therapy.

20.4 Core Facility Action Items

The Central HRQL Survey Center or Holter Reading Center or MRI Reading Center will report within 24 hours to the research coordinator or treating Nephrologist any patient who has potentially life-threatening findings on tests done exclusively for the purpose of the study. For quality assurance, the DCC will also report these findings to the study center when received by the database. These findings may include, but are not limited to:

1. answers 2 or 3 on question #9 of the Beck Depression Inventory ("would you kill yourself")
2. ventricular tachycardia or other life-threatening arrhythmias on the heart rate variability test
3. lung, mediastinal, esophageal, cardiac mass or large pericardial effusion on cardiac MRI.

References

(1) Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347(25):2010-2019.

(2) Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN. Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. Kidney Int 1985; 28(3):535-540.

(3) Messa P, Mioni G, Maio GD, Ferrando C, Lamperi D, Famularo A et al. Derangement of acid-base balance in uremia and under hemodialysis. J Nephrol 2001; 14 Suppl 4:S12-S21.

(4) Williams AJ, Dittmer ID, McArley A, Clarke J. High bicarbonate dialysate in haemodialysis patients: effects on acidosis and nutritional status. Nephrol Dial Transplant 1997; 12(12):2633-2637.

(5) NKF-DOQI clinical practice guidelines for hemodialysis adequacy. National Kidney Foundation. Am J Kidney Dis 1997; 30(3 Suppl 2):S15-S66.

(6) de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. Kidney Int 2004; 66(3):1232-1238.

(7) Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. J Am Soc Nephrol 2001; 12(1):151-156.

(8) Song JH, Lee SW, Suh CK, Kim MJ. Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. Am J Kidney Dis 2002; 40(2):291-301.

(9) Ronco C, Brendolan A, Milan M, Rodeghiero MP, Zanella M, La Greca G. Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency. Kidney Int 2000; 58(2):800-808.

(10) Straver B, De Vries PM, Donker AJ, ter Wee PM. The effect of profiled hemodialysis on intradialytic hemodynamics when a proper sodium balance is applied. Blood Purif 2002; 20(4):364-369.

(11) Locatelli F, Covic A, Chazot C, Leunissen K, Luno J, Yaqoob M. Optimal composition of the dialysate, with emphasis on its influence on blood pressure. Nephrol Dial Transplant 2004; 19(4):785-796.

(12) Locatelli F, Covic A, Chazot C, Leunissen K, Luno J, Yaqoob M. Optimal composition of the dialysate, with emphasis on its influence on blood pressure. Nephrol Dial Transplant 2004; 19(4):785-796.

(13) Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lazarus JM et al. Cardiac arrest and sudden death in dialysis units. Kidney Int 2001; 60(1):350-357.

(14) NKF-DOQI clinical practice guidelines for hemodialysis adequacy. National Kidney Foundation. Am J Kidney Dis 1997; 30(3 Suppl 2):S15-S66.

(15) Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R, Perazella MA. Treatment of Severe Intradialytic Hypotension With the Addition of High Dialysate Calcium Concentration to Midodrine and/or Cool Dialysate. Am J Kidney Dis 2001; 37(2):294-299.

(16) NKF-DOQI clinical practice guidelines for hemodialysis adequacy. National Kidney Foundation. Am J Kidney Dis 1997; 30(3 Suppl 2):S15-S66.

(17) Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31(4):607-617.

(18) NKF-DOQI clinical practice guidelines for hemodialysis adequacy. National Kidney Foundation. Am J Kidney Dis 1997; 30(3 Suppl 2):S15-S66.

(19) Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int 1996; 49(5):1379-1385.

(20) Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: an overview. J Am Soc Nephrol 1999; 10(2):392-403.

(21) Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: an overview. J Am Soc Nephrol 1999; 10(2):392-403.

(22) Ahmad S. Dietary sodium restriction for hypertension in dialysis patients. Semin Dial 2004; 17(4):284-287.

(23) de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. Kidney Int 2004; 66(3):1232-1238.

(24) Leypoldt JK, Lindsay RM. Hemodynamic monitoring during hemodialysis. Adv Ren Replace Ther 1999; 6(3):233-242.

(25) Mitra S, Chamney P, Greenwood R, Farrington K. Linear decay of relative blood volume during ultrafiltration predicts hemodynamic instability. Am J Kidney Dis 2002; 40(3):556-565.

(26) Maggiore Q, Pizzarelli F, Santoro A, Panzetta G, Bonforte G, Hannedouche T et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. Am J Kidney Dis 2002; 40(2):280-290.

(27) Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. Am J Kidney Dis 1999; 33(5):920-926.

(28) Prakash S, Garg AX, Heidenheim AP, House AA. Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. Nephrol Dial Transplant 2004; 19(10):2553-2558.

(29) Donauer J, Kolblin D, Bek M, Krause A, Bohler J. Ultrafiltration profiling and measurement of relative blood volume as strategies to reduce hemodialysis-related side effects. Am J Kidney Dis 2000; 36(1):115-123.

(30) Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. J Am Soc Nephrol 2001; 12(1):151-156.

(31) Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. J Am Soc Nephrol 2001; 12(1):151-156.

(32) Song JH, Lee SW, Suh CK, Kim MJ. Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. Am J Kidney Dis 2002; 40(2):291-301.

(33) Ronco C, Brendolan A, Milan M, Rodeghiero MP, Zanella M, La Greca G. Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency. Kidney Int 2000; 58(2):800-808.

21. Specimens for Local Labs

21.1 Introduction

The FHN Studies do not use a central lab. All lab data are measured locally. The study requires no specific methods for drawing blood or centrifuging for any of these lab tests. Each site should follow the procedures normally used in that dialysis unit. The name of the local lab used by each dialysis unit is recorded in the study database on the dialysis unit form. The time interval during which each local lab is used will also be recorded. Thus, if we ever need to, we will be able to determine the local lab where any patient local lab value was measured.

Local lab data can be divided into local lab data related to kinetic modeling and local lab data not related to kinetic modeling. Details on local lab values related to kinetic modeling are in the two kinetic modeling chapters of this Manual of Operations. This chapter addresses only the local lab data not related to kinetic modeling.

The local laboratory measurements required for the FHN studies are summarized in Table 21.1 for the Daily Study and 21.2 for the Nocturnal Study. During baseline, requirements for the two studies are the same.

21.2 Ordering Local Lab Tests

The frequency that any lab measure is done can vary from dialysis unit to dialysis unit. In many cases, it is anticipated that the study measurements will coincide with tests that the dialysis unit would routinely be measuring them anyway. The study measurements must be done whether or not the dialysis unit would routinely be measuring then anyway. The FHN team members (Principal Investigator and Study Coordinator) associated with any dialysis unit face several tasks

1) The team members must look at the dialysis unit's usual schedule and determine if the study will require extra local lab measures that would not routinely be measured.

If there are,

2) The team members must set a method in place so that the extra lab tests are requested whenever they protocol requires them

3) The team members must set a method in place so that these extra tests are billed to the patient's Clinical Center's budget, not to the patient himself or his insurance company.

It is important that these methods be in place before the first patient is enrolled.

21.3 Baseline

Baseline requirements are identical for the Nocturnal and Daily Study. The following tests must be measured (and entered into the study database) twice on each patient in order for the patient to be eligible for randomization: Pre-dialysis serum albumin, Pre- and post-dialysis serum phosphate, Pre- and post-dialysis serum creatinine, and Pre- and post-dialysis serum urea.

The following tests must be measured (and entered into the study database) once on each patient in order for the patient to be eligible for randomization: Interdialytic urine for urea, creatinine, phosphate; Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium; Pre-dialysis transferrin and ferritin; and Pre-dialysis parathyroid hormone.

The patient eligibility checking program will look for each of these lab values and will not allow a patient to be randomized if the values have not been entered into the study database.

21.4 Follow Up

Follow up requirements are slightly different between the Nocturnal and Daily Study because the Nocturnal Study lasts two months longer. The detailed schedule of measurements is given in Tables 21.1 and 21.2. It is very important that in follow up, team members request extra lab tests whenever they protocol requires them and they would not usually be done or the unit missed doing them on a patient for any reason.

Note that pre-dialysis transferrin and ferritin and pre-dialysis parathyroid hormone must be entered into database at least once every 4 months, but that the center may optionally enter these labs at any additional time points.

21.5 Forms and Reports

Local Lab data is key entered onto Form 207, and, as noted, the name of the local lab used by each dialysis unit is recorded in the study database on the dialysis unit form.

Quality Control edit checks will be programmed into Form 207 so that any value that is too low or too high to be possible in a living human being, or would happen no more than once in, say, 100,000 measures, will be screened out of the form at the time of data entry. Also, the data will be cross tabulated and graphed for steering committee meeting reports, so steering committee members can scrutinize outliers.

During Baseline, as noted, the patient eligibility checking program will look for each of the required baseline lab values and will not allow a patient to be randomized if the values have not been entered into the study database.

During Follow Up, individual patient lab data reports, or flow-sheets, will include all data measured and will include normalized or calculated variables as needed.

The follow up missing forms reporting system will track cases in which a month passed and the required lab data form 207 was not entered by the middle of the next month. Special site-visit-like conference calls will be held as needed with any site that has significant numbers of missing forms.

The missing data report system will track cases in which a follow up Form 207 has been entered but not all required tests were run. These data will be summarized by Consortium Core, Clinical Center, and Dialysis Unit. Special site-visit-like conference calls will be held as needed with any site that has significant amounts of missing data.

Table 21.1 Daily Study Local Laboratory Measurements

Measurement	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Predialysis serum albumin	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre and post-dialysis serum phosphate, creatinine, urea	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interdialytic urine for urea, creatinine, phosphate	✓				✓								✓
Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre-dialysis transferrin and ferritin[1]	✓			✓				✓				✓	
Pre-dialysis parathyroid hormone[1]	✓			✓				✓				✓	

Table 21.2 Nocturnal Study Local Laboratory Measurements

Measurement	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo	13 mo	14 mo
Predialysis serum albumin	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre and post-dialysis serum phosphate, creatinine, urea	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interdialytic urine for urea, creatinine, phosphate	✓					✓									✓
Pre-dialysis hemoglobin, calcium, bicarbonate, sodium, and potassium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre-dialysis transferrin and ferritin[1]	✓		✓			✓			✓			✓		✓	
Pre-dialysis parathyroid hormone[1]	✓		✓			✓			✓			✓		✓	
1 These local labs to be entered into database <u>at least</u> once every 4 months (center may optionally enter these labs at additional time points)															

22. Specimens for NIDDK Repository

Archive Note: All FHN serum and plasma collected during FHN Trials and Extension Studies are stored at NIDDK's Central Biorepository at Information Management Services, Inc. (IMS) in Maryland. Permission to use biosamples must be requested through NIDDK at **https://www.niddkrepository.org**.

22.1 Background

Participants who are enrolled in the FHN Study will be invited to volunteer to provide biological samples to be stored for use in possible future studies. A separate repository informed consent will be required, although it may be part of the main consent form (Note: NIH approval is required for Repository Consents before specimens can be taken out of the Repository). A template repository consent form is provided in Appendix A. Among those participants who consent for storage of biological specimens, pre- and post-dialysis serum and plasma specimens will be collected at study months baseline, 4, and 12 for the Daily Trial and at study months baseline, 5, and 14 for the Nocturnal Trial. At each time point, the samples from U.S. centers will be shipped to the NIDDK Biosample Repository at Fisher BioServices, Germantown, Maryland.

See Section 22.6- 22.8 for when and how to ship samples from Canadian centers.

Contact information can be found in the FHN Address Directory. For general questions and biosample shipment notification, use 'bio-niddkrepository@fishersci.com."

22.2 Schedule, Type and Volume of Samples

Blood Samples Collected for NIDDK Repository

Specimen Type	Collection Time	Collection Periods*		
		Baseline	Month 4 (5)	Month 12 (14)
Serum	Pre-dialysis	3 x 7.5 ml	2 x 7.5 ml	3 x 7.5 ml
	Post-dialysis	1 x 7.5 ml	1 x 7.5 ml	1 x 7.5 ml
Plasma	Pre-dialysis	2 x 8 ml	2 x 8 ml	2 x 8 ml
	Post-dialysis	1 x 8 ml	2 x 8 ml	1 x 8 ml
Totals		54 ml	52.5 ml	54 ml

* Collection months in parentheses are specific to the Nocturnal Trial.

22.3 Training Requirements for Personnel Sending Samples

Each person shipping diagnostic specimens should be trained and certified according to DOT and IATA regulations. Someone at each institution will be responsible for training the appropriate personnel.

For U.S. Centers only: Before sending FHN patient specimens to Fisher BioServices, each U.S. center will participate in a trial labeling and mailing of sample vacutainer tubes. All study personnel who will potentially be shipping specimens to Fisher should participate in the preparation of this test package.
Dummy tubes will be supplied by Fisher BioServices and dummy labels will be supplied by the DCC for this exercise. The coordinators will label and ship water in a set of tubes with the aim of correctly recording the IDs on both the collection tubes and the mail-in form (# 255). Fisher personnel will evaluate the material upon receipt and notify the Center and DCC when problems are encountered. Coordinators may be required to repeat the exercise before sending actual patient samples. Approval of the test kit is required before a U.S. center can enroll patients.

For Canadian Centers only: Before sending FHN patient specimens to Fisher BioServices, each Canadian center will participate in a trial aliquoting, labeling and mailing of sample cryovials on dry ice. All study personnel who will potentially be shipping specimens to Fisher should participate in the preparation of this test package.

A dummy test kit containing vacutainers, cryovials, a specimen box, and mailing labels will be supplied by Fisher BioServices and dummy labels will be supplied by the DCC for this exercise. The coordinators will label and ship frozen water in a set of cryovials with the aim of correctly recording the IDs on both the cryovials and the mail-in form (# 256). Fisher personnel will evaluate the material upon receipt and notify the Center and DCC when problems are encountered. Coordinators may be required to repeat the exercise before sending actual patient samples. Approval of the test kit is not required before a Canadian center can enroll patients but needs to be completed prior to collecting and shipping actual patient samples.

22.4 Logistics for Biosample Repository for U.S. Centers

Overview: The BioRepository will provide sample collection kits including the necessary blood collection tubes, packing and shipping materials, and Federal Express labels for collection and shipping of the samples. The sample collection kits will be shipped to the clinical centers by Fisher. The tube labels to be used with all repository specimens will be supplied to the clinical centers by the DCC with detailed completion instructions provided. The tube labels include pre-printed 3-digit identification numbers, in which the first 3 digits designate the NIDDK BioRepository Site Identification code; the study team member will write in the FHN Participants' ID in the final 6 spaces on the label. The labels will also include two spaces in which the study staff should mark the participant's FHN alpha code, which will be used as an alternative ID by Fisher BioServices. Circle the appropriate type of specimen (plasma/serum) and the time of collection (pre-HD/post HD). Tubes should be labeled immediately prior to when blood is drawn from the patient.

The tubes should be centrifuged prior to shipment, at room temperature, within 2 hours after the draw, and then refrigerated. Follow the procedure identified in Section 22.5 for specific processing information.

For consenting participants, study staff will fill the number of pre- and post-dialysis serum shipping tubes (SST tubes) and pre- and post-dialysis plasma shipping tubes (PST tubes) and then store them in a refrigerator at +4 degrees Centigrade that is roughly equivalent to 39 degrees

Fahrenheit. When enough tubes are collected, they should be shipped refrigerated and in bulk to Fisher BioServices using the shipping kits and packing materials provided by Fisher.

A completed paper copy of the U.S. Biological Specimen Repository Mailing Form (Form # 255) should also be included in the kit shipped to Fisher. The information on the form must also be entered in the database.

On arrival at the BioRepository, a Fisher BioServices staff member will divide the serum and plasma into aliquots (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.

22.5 Fisher BioServices Repository Procedure Instructions for U.S. Centers

1. Be sure that 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. Complete and attach the participant I.D. labels provided by the DCC to the blood samples immediately prior to collection. Use the labels provided and place them lengthwise on the tubes. Circle whether the sample is serum or plasma and the timing of the collection either pre-HD or post HD. DO NOT write the participant's name or any other personal identification information (e.g., SS#, DOB) on the tubes.

Sample label:

5 x x - __ __ __ __ __ __ - __ __
Serum Plasma
Pre-HD Post-HD

The tube labels include pre-printed 3-digit identification numbers, in which the first 3 digits designate the NIDDK BioRepository Site Identification code; the study team member will write in the FHN Participants' ID in the final 6 spaces on the label. The labels will also include two spaces in which the study staff should mark the participant's FHN alpha code, which will be used as an alternative ID by the BioServices Repository.

3. Collect the specimen in the appropriate container; either SST/PST vacutainer tube.

4. After filling:
   Invert each SST tube gently at least 5 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 SST tubes for at least 15 minutes at 1300 g. Blood tubes containing anti-coagulants such as heparin or warfarin may take longer to clot in SSTs so it requires a longer centrifugation time.

   Invert each PST tube 8-10 times to mix the blood with the additives. PST tubes can be centrifuged immediately. Centrifuge the PST for at least 10 minutes at 1300 g.

Then move the tubes to the refrigerator until the shipment is ready to be sent. Be sure that the refrigerator is securely closed.

5. Double check the subject ID, and verify that ID information on the vacutainer tubes matches that on the U.S. Biological Specimen Repository Mailing Form # 255.

6. Date and identify the person completing the NIDDK Biological Specimen Shipment Form (#255). Make a copy of each form; keep the copy and send the original with the shipment.

7. Prepare shipments for FedEx pickup on Monday through Thursday. ***No Friday shipments, please.*** The facility is not fully operational on Saturday and Sunday when the package would be delivered. If there must be an exception, please coordinate with the Biosample Repository (see item 10 under Assembling the Shipper) before close of business on Thursday (5 pm, EST). Keep in mind major U.S. holidays when shipping.

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

9. 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.

10. Notify Fisher BioServices at 'bio-niddkrepository@fishersci.com' or by fax when you have scheduled the pickup and provide them the Federal Express tracking number(s). Use the contact information in the FHN Address Directory.

Assembling the FHN Refrigerated Laboratory Shipper

1. Insert each type of vacutainer tube into a separate bubble wrap pouch.
2. Place the pouches 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 vacutainer tubes on top of the bubble wrap. 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 #255) 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. Ship only on Mondays - Thursdays. **PLEASE DO NOT SEND** shipments on FRIDAYS for Saturday delivery. **The tubes can be refrigerated and stored through the weekend and then sent on Monday.**
11. In Section 6, check the "No" block indicating no dangerous goods are contained in the shipment. 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.
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.

US Fedex airbill needs to be added here

22.6 Logistics for Biosample Repository for Canadian Centers

The BioRepository will provide sample collection kits including the necessary blood collection tubes, cryovials, labels, freezer boxes, packing and shipping materials, and International Federal Express labels for collection and shipping of the samples. Additional documentation will be required to ship biological samples from Canada to the U.S. (see Sections 22.6-22.8 of the MOP.

The sample collection kits will be shipped to the Canadian centers by Fisher BioServices. The aliquot labels to be used with all repository specimens will be supplied to the Canadian centers by Fisher. The cryovial labels will include pre-printed 9-digit identification numbers, in which the first 3 digits designate the NIDDK BioRepository Site Identification code and the final 6 digits designate the participant's FHN Participant ID. The labels will also include two spaces in which the FHN Center should mark the participant's FHN alpha code, which will be used as an alternative ID by the Biosample Repository. After adding the participant's alpha code, serum or plasma and timing of the collection (pre-HD/post HD), the aliquot labels provided by Fisher should be placed on each cryovial prior to placing in a -70^{o}C (or greater) freezer.

For consenting participants, the FHN Center will collect the number of pre- and post-dialysis serum shipping tubes (SST tubes) and pre- and post-dialysis plasma vacutainers (PST tubes), aliquot the serum and plasma, place in a freezer box, and then store in -70^{o}C (or greater) freezer.

When enough samples are collected, they should be shipped on dry ice to Fisher BioRepository using the shipping kits and packing materials provided by Fisher. Regardless of the number of specimens stored, specimens should be shipped on a *quarterly* basis.

A completed paper copy of the International Biological Specimen Repository Mailing Form (Form # 256) for each participant should also be included in the kit shipped to Fisher. The information on the form must also be entered in the database.

On arrival at the BioRepository, a Fisher staff member will count the number of aliquots received for both serum and plasma and report any discrepancies to the shipping center and the DCC. Fisher will then place the aliquots in frozen storage.

22.7 Fisher Biosample Repository Procedure Instructions for Canadian Centers

1. Be sure that the SST and PST 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. Complete and attach the participant I.D. labels provided by the DCC to the blood samples immediately prior to collection. Use the labels provided and place them lengthwise on the cryovials. Circle whether the sample is serum or plasma and the timing of the collection either pre-HD or post HD. DO NOT write the participant's name or any other personal identification information (e.g., SS#, DOB) on the tubes.

Sample label:

5 x x - __ __ __ __ __ __ - __ __
Serum Plasma
Pre-HD Post-HD

The tube labels include pre-printed 3-digit identification numbers, in which the first 3 digits designate the NIDDK BioRepository Site Identification code; the study team member will write in the FHN Participants' ID in the final 6 spaces on the label. The labels will also include two spaces in which the study staff should mark the participant's FHN alpha code, which will be used as an alternative ID by the BioService Repository.

3. Collect the specimen in the appropriate container; either SST/PST vacutainer tube.

4. After filling:
   Invert each SST tube gently at least 5 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 SST tubes for at least 15 minutes at 1300 g. Blood tubes containing anti-coagulants such as heparin or warfarin may take longer to clot in SSTs so it requires a longer centrifugation time.

   Invert each PST tube 8-10 times to mix the blood with the additives. PST tubes can be centrifuged immediately. Centrifuge the PST for at least 10 minutes at 1300 g.

5. Divide the serum and plasma into aliquots: twenty 0.2 mL aliquots for the first 4 mL of both serum and plasma, and 0.5 mL aliquots for the remainder. Prepare the aliquots for storage by placing them in the freezer box and then placing the specimen box(es) in -70^{o}C (or greater) freezer.

   Note: If more than one patients' samples are drawn on the same day, more than one patients' aliquots can be placed in one freezer box as there are 81 slots available. Keep an empty row between each patients' samples to delineate the start of another patient's samples. However, do not separate one patient's samples into two boxes.

6. Double check the subject ID, and verify that ID information on the aliquots match that on the International NIDDK Specimen Shipment Form (# 256). Store the completed Form 256 until a sample shipment is ready to be sent to Fisher.

7. Date and identify the person completing the International NIDDK Specimen Shipment Form (# 256). Make a copy of each form; keep the copy and send the original with the shipment when it is time to do so.

8. Prepare shipments for FedEx pickup on a Monday or Tuesday in case there is a customs delay before the weekend.. Keep in mind the various major holidays for both Canada and U.S.

9. Assemble the package according to the instructions for dry ice shipping.

10. **Schedule a pickup with your local FedEx office**. Give them the repository account number, the time that pickup is required, the type of samples being sent, the number and type of boxes being shipped, and whether dry ice is required.

11. Notify Fisher BioServices at 'bio-niddkrepository@fishersci.com' or by fax when you have scheduled the pickup and provide them the Federal Express tracking number(s). Use the contact information in the FHN Address Directory.

22.8 Canadian Dry Ice Shipping Instructions - Instructions for Large Diagnostic Shipper, International (E-65)

1. Place the specimen box containing the frozen aliquots and the absorbent strip inside the inner leak-proof plastic bag. Seal the bag.
2. Place the plastic bag inside the Tyvek envelope by placing the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.

3. Put a layer of dry ice in the bottom of the box. (You can use dry ice rice pellets or blocks). Place up to 5 Tyvek envelopes containing boxes on the dry ice.

4. Fill the remainder of the space in the shipper with dry ice up to about four inches from the top.

5. Put the foam insert on top of the dry ice in the opening. Place the original Form 256s inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.

6. Close and tape the cardboard box.

7. Attach all labels to the same side of the box:
    a. Affix the dry ice label to the side of the box in the upper right corner. Enter the weight of dry ice in kilograms.
    b. Place the “UN3373 Diagnostic Specimens” label on the top, center, to the left of the dry ice label.
    c. Place the small repository address label below the “Up” arrows.
    d. Affix the document pouch below the dry ice label.

8. Use the pre-printed International air bill to ship the specimens to the NIDDK Biosample Repository at Fisher BioServices.
    a. Place the air bill along with the completed declaration statement and customs invoice inside the document pouch.
    b. If necessary, attach the documents to the lower right corner of the box below the dry ice label.

9. **Schedule a pickup with your local FedEx office**. Give them the repository account number, the time that pickup is required, the type of samples being sent, the number and type of boxes being shipped, and that dry ice is required.

10. Notify Fisher BioServices at 'bio-niddkrepository@fishersci.com' or by fax when you have scheduled the pickup and provide them the Federal Express tracking number(s). Use the contact information in the FHN Address Directory.

11. Notify the repository of the shipment and tracking number on the day the package is picked up by the courier.

International Fedex airbill here:

You will need the following documents needed for international shipments

DECLARATION STATEMENT
Importation of Diagnostic Specimens into the USA

The contents of this package are as follows:

- Frozen human serum and plasma in leak proof containers.
- These samples have not been exposed to any animal derived materials such as products derived from livestock or avian disease agents.
- This material is not of tissue culture origin.
- These samples are not known to be infectious or contagious.
- **Diagnostic specimens packed in compliance with Packing Instruction 650 (IATA).**

These samples are being shipped to the NIH/NIDDK Biosample Repository, Germantown, MD, USA, for investigational purposes funded under the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repositories - Biosample (Contract #N01-DK-3-2608). Samples are packed in the appropriate containers and are perishable. Specimens are being collected for laboratory analysis and are not known to be infectious. **Please do not delay.**

These samples are for investigational purposes only and have not been screened for HIV or Hepatitis B or C.

These specimens have been packaged, labeled, and shipped in accordance with International Air Transport Association (IATA) regulations.

These materials are being used for medical studies and have no commercial value.

Principal Investigator (Signature)	Date
Printed Name	Organization

22.9 Access to Data and Privacy

The Fisher Repository 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 FHN Trials all studies employing biosamples from FHN participants stored at the Fisher repositories must receive approval from the FHN Clinical Trial Ancillary Studies Committee and from the FHN Steering Committee. The process for submission of ancillary studies is described in Section 27 of the MOP. Section 26 also provides guidelines for conduct and publication, which must be adhered to by all ancillary studies making use of the FHN specimens.

The FHN Steering Committee will relinquish its authority over the FHN specimens residing in the biorepositories following the completion of the FHN Trials. 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

22.10 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 samples must be destroyed or returned to the repository after the approved period of use.

22.11 Withdrawal of Patient Consent for Usage of Repository Specimens

Patients who have consented and provided biospecimens (e.g., serum and plasma) to the NIDDK Repository can withdraw their consent for using their samples in research studies. During the study, the patient should make this request to the clinical center that enrolled them, who will then notify the DCC using the patient's ID and alpha code. The DCC will instruct the Repository to

destroy this patient's samples. After the study ends the patient should send a written request to: Mr. Shu-Cheng Chen, USRDS: 914 South 8th Street, Suite D-206, Minneapolis, Minnesota 55404, U.S.A. and provide their name and SSN. USRDS will use the matched patient ID and alpha code to notify the Repository to destroy this patient's samples.

Appendix A. Template Repository Consent for Provision of Biorepository Samples

This template consent can be downloaded from the FHN web page. Note: NIH approval is required for each IRB approved Repository consent before specimens from the FHN center's patients can be taken out of the Repository.

CONSENT TO PARTICIPATE IN FUTURE BIOCHEMICAL STUDIES (example pertaining to the Daily Trial)

Patient Name: _____
ID Number: _____
IRB Project Number: _____

Project Title: Frequent Hemodialysis Network: Daily Hemodialysis Trial
A multi- center randomized controlled study to demonstrate the efficacy, safety and feasibility of "Frequent Hemodialysis" in patients with End Stage Renal Disease**.**

You are being asked to take part in this process because you have chosen to participate in the "Daily Hemodialysis Trial". The purpose of this process is to keep samples of your blood and/or urine in a repository (like a bank for saving blood and other tissues) for future biochemical studies. Since new discoveries occur everyday, it is possible that there may be new tests in the future that can improve the search for more information about your illness and/or how to treat it more effectively.

If you choose not to take part in these future studies, it will not affect your participation in the main study in which you are participating.

Where the samples will be kept:

The National Institutes of Health (the NIH) is a government organization that is the sponsor for this study. They also pay for the storage of these blood samples. They have developed a special storage facility, called "Repository", to keep these blood samples. These samples are kept in special freezers so that they may be kept for long periods of time. We would like to send your blood samples to this Repository. 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 NIH-authorized Repository is Fisher BioServices Corporation at 20301 Century Blvd., Bldg. 6, Suite 400, Germantown, MD 20874. The Director of the project is Mr. Richard Frome at (240) 686-4702.

Protecting Your Privacy

The Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. 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.

Process for Collecting and Using Your Samples

Blood will be collected before and after three specified hemodialysis treatments (at the start of the study, after 4 month, and at the end of the study) throughout the 12-months of your participation in the main study. These samples would be stored in repository managed by National Institute of Health. Total amount of the blood for future biochemical studies approximately 150ml (about 10 tablespoons). Before the researchers in this study send samples to the Repository, each sample will be given a code number. Your name (or 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.

The NIH and the investigators' Institutional Review Board will need to approve future studies done on your stored samples. Results from future studies on your stored samples can be merged with data from other sources, such as your Medicare data. This requires that we retain sufficient personal identifiers to permit merging data from the two sources (data from this trial and other future sources of data about you). Protections will be established to assure that your identifying information will not be available to anyone other than specific investigators approved to do these studies, and that your personal data will not be directly viewed other than as aggregated with that of many other individuals.

Potential Risks

There are very few risks in having your blood used for research. The greatest risk is the release of information from your health records. The NIH will protect your records so that your name will be kept private. Even if your blood and tissue is used for this kind of research, the results will not be put in your health records. The results from this future research will not be sent to you or your doctor, will not be used in planning your care, and will not become part of your medical record. These tests are only for research purposes and have no effect on your medical care.

Potential Benefits

If you agree to take part in donating your biosamples, there will not be any direct medical benefit to you. However, we hope that information learned from this possible future analyses of these samples will benefit other people who receive hemodialysis or may need hemodialysis in the future. 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.

No Other Cost to You

Your blood will be used only for research and will not be sold. You will not be paid for allowing your leftover blood and tissue to be used in research even though the research done with your blood and tissue may help to develop new products in the future. Similarly there will be no cost to you for any blood and tissue collected and stored by the repository. You and/or your insurance company will not be charged for submission or testing of the samples. These tests are only for research purposes and have no effect on your medical care. No funds have been set aside to pay you for allowing your blood to be stored.

Your Rights as a Participant

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study, or choosing not to take part, will not result in any penalty or loss of benefits to which you are entitled. Your physician will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you agree to have your sample(s) stored in the Repository, you can change your mind up at any time, up until the end of the "Daily Hemodialysis Trial". You should contact your study doctor and let him or her know that you do not want us to use your blood and tissue. Then the blood will no longer be used for research. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the main study ends, you will not be able to withdraw your sample. Therefore, once the study ends, your blood samples will stay in the Repository indefinitely and can be used for research.

Contacts

For questions about the study or a research-related injury, contact the principal investigator _____ at _____

Signature

I consent to the future use of my blood samples in future medical studies.
(Check Y or N) Y N

You will be given a copy of this form.

Participant: _____ Date: _____

23. Billing

23.1 General Information

A. **Background**: The Centers for Medicare and Medicaid Services (CMS) is jointly sponsoring with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) two clinical trials to evaluate the effectiveness of more frequent hemodialysis sessions compared with conventional thrice-weekly hemodialysis. One of these trials compares daily in-center hemodialysis (6 times per week) with conventional in-center hemodialysis (3-times per week). The other compares nocturnal hemodialysis (6 times per week in the home) with convential in-center hemodialysis. CMS has agreed to pay for covered subject care-related expenses for Medicare beneficiaries enrolled in these trials. For subjects enrolled in the experimental arms of these trials (more frequent in-center or nocturnal hemodialysis), CMS also authorizes payment for one additional composite for the duration of the trial. The duration of the daily in-center hemodialysis trial will be 12 months after subject enrollment.

B. The duration of the **nocturnal hemodialysis** trial will be 14 months after subject enrolment. For subjects enrolled in the experimental arm of the nocturnal hemodialysis trial, CMS also authorizes additional home dialysis training payment at the composite payment rate plus $20 for each training session incurred not to exceed 30 training sessions payment per patient. The standard Medicare deductibles and co-payments will apply to both composite rate payments and training session payments.

1. The provider needs to complete the **Attestation Form** for all beneficiaries qualified and enrolled in the ESRD Daily Trial (Attachments 1 and 2) and forward to their respective fiscal intermediaries (FI).[1]

2. The provider will process claims following their normal billing procedures with the following exception: populate on the CMS billing **Form UB-92** (Attachment 3), Form Locator (FL) 63 or the 837I equivalent on the 72X Type of Bill (TOB) with "**Trial 49**" for dialysis services provided to the trial beneficiaries.

3. The FIs shall process claims for payment, with **Trial 49 populated in FL 63** in accordance with standard Medicare claims processing rules.

4. For **home hemodialysis** subjects enrolled in **Trial 49**, FIs shall follow the normal procedures in place to bill under **Temporary Method I**. This allows payment for home dialysis items and services on behalf of patients that have not filed a Form CMS-382 selection form.

Fiscal Intermediaries (FI)

The company that receives bills for Medicare, evaluates their appropriateness, and issues payment on behalf of Medicare

23. 2 FREQUENTLY ASKED QUESTIONS

Answers to many questions regarding the billing procedures can be found under the change request section in the following link:
http://www.cms.hhs.gov/manuals/pm_trans/R145OTN.pdf

1. What are the eligibility criteria for patients for whom the 4th treatment will be paid by Medicare?

   Medicare payments will be made for a 4th treatment for those subjects enrolled in either the nocturnal or in-center frequent hemodialysis trials in the experimental arm (6 times or more per week hemodialysis) and who otherwise would qualify for Medicare reimbursement for hemodialysis. A provider must fill out an attestation (see the link above) that the patient is enrolled in the trial and provide the Medicare identification number (HIC) for the patient. Only participating facilities listed in the addendum above who have their Medicare provider ID are eligible.

2. How many patients will have their 4th treatment paid by Medicare?

   Currently the instructions to the fiscal intermediaries do not limit on the number of patients who we will pay for. The protocol calls for 250 patients (altogether) in the experimental arms of the trials. For the time we can say no more than 250 patients, as this is the maximum called for under the protocol. The attestation must include an enrollment date and expected termination date. After the termination date for each patient, no additional payment for a 4th treatment will be made, unless they otherwise qualify through medical necessity.

3. Are Medicaid patients under 65 yrs of age in that group?

   Medicaid patients will not be paid by Medicare unless they are dual-eligibles and Medicare is the primary payer. Medicare patients under 65 who otherwise would qualify for Medicare reimbursement for hemodialysis are eligible.

4. Are private insurance patients under 65 and the first 33 months of their ESRD in that group? Are those patients who, within the study period, will become either 65 or exhaust their 33 month benefit within that group?

   Medicare cannot pay for any patients who would not otherwise qualify for Medicare reimbursement for their hemodialysis. This means private pay

patients in their first 33 months of ESRD would not qualify. The same applies to Canadian patients enrolled in the trial.

5. Medicare needs to assign a specific billing code for this study and the 4th treatment. What is that code?

   The attached link contains very detailed instructions concerning this issue. There is no special code, but trial 49 must be referenced.

6. What role will the intermediaries play?

   The intermediaries will receive the attestations and be responsible for checking a website (to be established) that will update the list of participating facilities as needed. The intermediaries will work with CMS information services to produce a regular report that will be sent to ORDI at CMS describing the patients who are receiving the 4th treatment. CMS will check this list against a list of patients to be sent to them that includes patient HIC, name, and participating facility to safeguard our system against fraud and abuse.

7. How will contact information be obtained for the intermediaries and within CMS for billing related questions? Will specific point persons be assigned by these entities?

   Each provider should know who their intermediary is. There is no specific contact for billing questions.

8. What about reimbursable medications? Any additional payments by Medicare/Medicaid?

   Medicare limits on reimbursable medications remain the same as under existing rules. No extra payments for those items will be made under this trial.

9. What about transportation? What is being proposed for the three additional days?

   Medicare will not pay for transportation for hemodialysis, except if an ambulance is warranted due to medical condition (not an ambulette) -- these rules are the same for all Medicare patients irrespective of participation in the trial.

23.3 POTENTIAL BILLING ERRORS

1. Ensure that **Attestation Forms** are completed and forwarded to the Fiscal Intermediaries for all patients that are part of the study.

2. Injectable medications will not be reimbursed for the fourth, fifth and sixth treatment of each week.

3. Nurses need to be well informed about the medication guidelines and not automatically administer medications.

4. Data Entry Clerks need to be aware of the patients and the drug administration policy as part of this study to ensure that information is entered correctly.

5. Billing Clerks must be aware of those patients that are part of the study to ensure that the billing is done correctly.

24. Economic and Cost-Effectiveness Evaluation

Archive Note: Data on Forms #266, #267, #268, 610 indicated below were not collected.

24.1 Possible Impacts on Costs and Effectiveness for Hemodialysis Patient Care

Although 6 hemodialysis sessions per week will cost more than 3 sessions per week, it is not clear how more frequent hemodialysis will affect the total costs of caring for a hemodialysis patient. One of the hopes is that patients dialyzed more frequently may have fewer hospitalizations and need fewer injectable medicines. This could save money for Medicare and patients, but may also adversely affect hemodialysis center finances. It is possible that patients dialyzed 6 times weekly may have more access problems than those whose access is entered only 3 times weekly. But the reverse could also happen. CMS needs to understand the impact of frequent hemodialysis on total Medicare costs, in order to make good policy decisions about how to pay for more frequent hemodialysis, if it proves to be more effective than conventional hemodialysis.

The initial time horizon will be the 5-year study period, but will also be extended to 10 years using Markov modeling approach to measure the long-term cost-effectiveness difference between the frequent and the standard hemodialysis. It is possible that frequent hemodialysis will be more effective, but also more expensive, than standard hemodialysis. In this case, we will have to estimate its cost-effectiveness in a standard way, by calculating incremental cost per quality adjusted life years (QALYs) saved. The quality of life data (utility), which is the effectiveness component of the cost-effectiveness analysis (economic evaluation), will be collected using Health Utility Index, Mark 3 (HUI3) (Form #223). The following description focuses mainly on the cost component of the evaluation.

24.2 Cost Analysis

In practice, we will be able to look only at the major costs from the payer (especially Medicare) and the provider perspectives. With respect to costs to the patient, we will be looking at the cost of home modifications for nocturnal hemodialysis, and also the out-of-pocket cost by the patients for CMS-covered services and prescription medications, which will be included in the claims data. Our ultimate goal will be to simulate the long-term costs to the Medicare program, if frequent hemodialysis were to be adopted by many centers, not those just participating in the trial. The major components of costs we will collect data on under the trial include:

Costs related directly to hemodialysis treatment by a facility:

- Hemodialysis costs – 40% of Medicare costs
- For home hemodialysis: Training vs. Maintenance
- Injectable medicines
- Costs of maintaining hemodialysis access

Other health care costs:

- Hospitalizations – 40% of Medicare costs
- Outpatient visits and procedures
- Oral medicines
- Home care by professionals or by family
- Travel to and from hemodialysis sessions

The last four parts of other health care costs (outpatient visits and procedures, oral medicines, home care by professionals or by family, and travel to and from hemodialysis sessions) will not be focused due to the expense of data collection itself. In the meantime, these costs will only comprise a very small fraction of the total costs. Wasting a large amount of resources to collect minute cost information is not worthwhile. Nonetheless, the estimate of these costs will be factored in for final analysis through imputation technique and sensitivity analysis. In particular, use of oral phosphate binder medications (Form #205) and the number of blood pressure medications will be collected. The drug claims data for a subset of Medicare beneficiaries in the trial will still be collected from CMS and the oral medication cost of these patients will be examined.

For most economic estimates, we need to understand the *payments* that will be made for medical care. Payments for specific services will be estimated in terms of standard Medicare payments for these services, irrespective of what insurance the study patients have (Medicare, private, HMO, Canadian). There is a specific need to understand the actual *costs* of performing standard and frequent hemodialysis. Therefore we need to estimate these costs, and not just the current Medicare payments for hemodialysis. For Canadian patients in particular, social insurance number, Ontario health insurance number, or British Columbia health insurance number is needed to link to the administrative data for hospitalizations.

24.3 Approach to Estimating Cost of Hemodialysis Itself

Equipment and supplies: A detailed list of equipment needed per station and an amortization schedule for capital equipment will be constructed and agreed to by hemodialysis administrators. A detailed list of supplies needed per hemodialysis session will be circulated to dialysis administrators for their comments. Use of the common GSA price list will permit us to estimate costs independent of local variations in costs and different contractual relationships among the providers. (Form #266, #267, #268)

Professional time: We will perform initial estimates of the range of professional time needed per standard hemodialysis from Medicare dialysis center cost reports as: professional FTEs (by type) / # dialysis sessions. Within the study, we will estimate the difference in professional time needed to do standard and frequent in-center hemodialysis by collecting facility-level data on a form very similar to the Medicare cost report (Form # 268). These data will be collected at two intervals during the study: early, when there will be few frequent hemodialysis sessions at any given center and during the height of the study when there are a peak number of patients on frequent hemodialysis. Professional time will be converted to cost using standard salary scales for the types of

personnel involved, again making estimates independent of geographical and other similar issues. An important issue will be to determine the variation in professional time per session, and number of patients served per hemodialysis station, from one type of dialysis center setting to another: large urban dialysis center, small rural dialysis center, numbers of standard and frequent hemodialysis patients. (Form #268, #610)

Overhead: Hemodialysis unit overhead as a proportion of a standard hemodialysis session costs will be estimated from current overhead rates from the Medicare dialysis center cost reports: Administrative salaries, space, heating, waste disposal, etc. Total estimated hemodialysis costs per session: (standard and frequent) will be reviewed iteratively with the dialysis unit administrators and CMS until there is agreement that the estimates accurately account for total costs, and no large "miscellaneous" category remains.

24.4 Home Hemodialysis

Medicare presently pays separately for the period of home hemodialysis training, and then for the maintenance hemodialysis once patients are home. The costs for personnel to train new home patients and support established home patients are not well understood. We also do not have a good understanding to the costs for home modifications needed to permit home hemodialysis. Therefore, we need to estimate these costs directly in the centers involved in the Nocturnal Hemodialysis Protocol.

Professional time: Dialysis center nurses and technicians involved in home hemodialysis training and support of patients at home will be asked to track time spent in each of two one week periods that they spend on (Form #610):

- Hands-on home hemodialysis training with patients;
- Support of established home hemodialysis patients;
- Management of other in-center patients;
- Other time not attributable to care of a specific patient (CME, administrative, etc.).

The study coordinators will be asked to complete a form listing costs of home modifications needed to permit home hemodialysis (Form #260). The entries on the form should be based on copies of actual invoices or bills if possible. The home modification costs should be listed irrespective of who pays for them (the center, the patient, assistance programs, voluntary agencies such as NKF, etc.)

24.5 Payments for Injectable Medicines

Medicare pays for injectable medicines administered in the course of hemodialysis (epoetin, iron, vitamin D analogues) based on:

- The specific medicine,
- Dose,
- Number of doses in monthly billing cycle.

One hypothesis is that frequent hemodialysis will reduce the need for these injectables, which will impact total costs. These data are needed both for the cost analysis and for the clinical analysis. (Form #203, #204, #205)

24.6 Payments for Access Procedures

Study coordinators are asked to report all access procedures and to classify them into one of a small number of procedure types (Form #271, #276, #277, #278). We will capture from Medicare billing records the actual Medicare payments for access procedures on Medicare primary coverage patients in the study. We will then determine the average payments for each of a small number of easily coded procedure types. These payments will then be imputed to all other access procedures on non-Medicare primary pay patients (private, HMO, Canadian).

24.7 Payments for Hospitalizations

Coordinators will be asked to report the dates of all hospitalizations (overnight stays) of any type for all study patients (Form #303) or date of admission and date of discharge (or date of in hospital death). The study PIs will be asked to identify the major indication for the hospitalization from a short list of major categories of events. Payments for hospitalizations of all study patients will be estimated in terms of the Medicare payment for the relevant Diagnosis-related Group (DRG) – which Medicare uses to determine payment for hospital admissions. DRGs are built on the basis of: primary diagnoses, secondary diagnoses (for complicating co-morbidities), whether a surgical procedure was performed, and the type of surgical procedure.

The assigned DRG will be available in the case of Medicare primary patients directly from Medicare claims data. We will obtain hospitalizations by DRG directly from HMOs. From Canadian centers, we will obtain the length of stay and primary reason from relevant ICD9/10 diagnostic codes and can derive from them the appropriate Medicare DRG codes. We will determine the average DRG payment for each major category of hospitalization type from the above patients, and impute an average DRG payment for hospitalizations of patients not in one of the above groups.

24.8 Summary

Assuming that frequent hemodialysis is shown to be medically effective, it will be essential to estimate the medical care costs of patients receiving frequent in comparison to standard hemodialysis. Most of the effort to make these estimates will not fall on the study coordinators. A major effort has been made to avoid burdening coordinators with collection of these data. But accurate reporting of certain data by the coordinators will be needed: occurrence of hospitalizations and access procedures, use of injectable medicines, and the special issues in home hemodialysis.

25. Outcomes Committee Review Work

Archive Note: Initially, a subset of hospitalizations was to be reviewed. However, early on in the Outcomes Committee (OC) review process, the OC decided to review all hospitalizations. Once the FHN Extension Study was completed and additional death data was obtained, the OC convened via conference call on 03/27/2013 to assign a final primary cause of death based on available information. The final classification documentation is included at the end of this chapter.

25.1 Introduction

This chapter describes Outcomes Committee and its formal review of hospitalizations and deaths.

25.2 Outcomes Committee Members

An Outcomes Classification Committee will be established. The Outcomes committee will be composed of Clinical Center Principal Investigators, Co-Investigators, and DCC members.

The Outcomes Committee will review all deaths and hospitalizations (for each study) to verify cause of death or hospitalization (see below). The members of the Outcomes Committee will be trained by the Data Coordinating Center in order to provide a standard classification system for patient deaths and hospitalizations. The Data Coordinating Center will remove any information that can identify the randomization status of the patient being reviewed so that members of the Outcomes Committee will be blinded to the patient's treatment allocation.

No member of the Outcomes committee may review a patient from within his or her own Clinical Center. The DCC will assign the reviews accordingly.

25.3 Getting permission to have hospitalization data released

After each hospitalization that does not lead to a death, a subject will sign a release to allow the hospital to provide the details of the hospitalization to the FHN Clinical Center team. (In addition, each subject will sign a blanket release form annually, to make it easier for the Clinical Centers to obtain details on hospitalizations that lead to death and to obtain details on deaths.)

The Study Coordinator or physician will present the release to the hospital where the patient was hospitalized to get hospital records.

25.4 Discharge Summary Submission Procedure

Enter Forms 302, 303 and 308 for a hospitalization

Enter Forms 305, 306 and 308 for a death

Hospitalization Discharge/Death summaries

- No more than 10 pages
- Include labs, x-rays, scans, blood cultures, labs as needed
- Black out all identifying and treatment information before faxing
- Write alpha code only at the top of each page
- Make sure pages are dark enough and legible before faxing

Fax these materials to the DCC, attn: Barb Weiss (DCC fax is 216-445-2781). The fax cover sheet should include patient ID, alpha code, hospital admission date or date of death, and the number of pages. The DCC will e-mail the center if there are any further questions or requests.

25.5 What data are on the Hospitalization Form 303 and SAE form 308

The hospitalization form 303 will be completed by the Site PI, Co-Investigator or Collaborator from the patient's Clinical Center and reviewed by the Core Consortium staff (i.e., the PIs (Chertow & Levin) and the lead study coordinators. The Clinical Center will contact the hospital involved. Data to be obtained and recorded on the hospitalization form include date of admission, date of discharge, whether a vascular access procedure was performed during the hospital stay, and the primary and secondary reason for hospitalization as coded by the categories on the form

All hospitalizations will be categorized by the Clinical Center (Site) PIs by

- access versus non-access hospitalization
- cardiovascular versus not cardiovascular
- primary and secondary reason for hospitalization

The answers to these questions will be based on either the discharge summary associated with that hospitalization or a narrative description of the hospitalization provided by a physician who was responsible for the care of the patient (a narrative description will be used when 6 months have elapsed and the discharge summary cannot be obtained). The FHN hospitalization form will also capture whether the Clinical Center PI's categorization was based on an actual discharge summary or some other form of documentation. The hospitalization form should be submitted to the Data Coordinating Center within 30 days of the patient's hospital discharge.

The standard adverse event questions about the expectedness and relatedness of the hospitalization are on the SAE form 308.

25.6 Hospitalization Report Folder for the Outcomes committee

For each patient, the DCC will prepare a Hospitalization Report Packet. The packet will include reports based on the detailed hospitalization form, serious adverse event forms dated before the hospitalization up to and including the date of the hospitalization, demographics, baseline co-morbidity, baseline MRI results and a blinded discharge summary for the particular hospitalization. An e-mail will be sent to the committee in advance of the call and will include the following attachments: a memo detailing the call including the cases to be discussed as well as a primary, secondary and third reviewer assigned to the case; pdf files of each hospitalization report packet blinded to patient identification and randomized assignment; and the Outcomes Committee Hospitalization Review Form 501.

25.7 Review of all Hospitalizations (for each study)

All hospitalizations will be adjudicated by the Outcomes Committee during the monthly conference call until resolution can be reached. The final categorization with respect to transplant status, access, cardiovascular, infection, trial relatedness, treatment arm and hospitalization codes will be recorded in the Form 501. The primary and secondary reviewers will be entered into the Outcomes Committee Hospitalization Review Documentation Form.

The DCC study coordinator on the conference call will complete Form 501 as adjudicated by the Outcomes Committee.

The clinical centers should check the weekly status reports and/or daily e-mail of critical F12/F14forms to view hospitalizations occurring more than 60 days ago where documentation has not yet been sent to the Outcomes Committee.

The order of hospitalization review will be determined by relatedness and date of hospitalization. Transplant hospitalizations will be reviewed last.

25.8 Deaths

The death Form 306 along with the SAE Form 308 will be completed by the Co-investigator from the involved Clinical Center, who will classify the death using a modification of the HEMO Study coding system. This system will allow for the classification of deaths by organ system, such as cardiac and infection-related.

A death discharge summary or other information will be sent by the Clinical Center to the Data Coordinating Center, who in turn will forward this data (as previously detailed in Section 25.6 of the MOP) to members of the Outcomes Committee. For hospitalizations resulting in death, the same information as described above for hospitalizations will be obtained. If the death did not occur in the hospital, then the principal investigator will

provide a narrative describing the circumstances of the patient's death and the presumed cause of death based on the patient's history and events leading up to the patient death. Assignments to reviewers will be done as detailed above for hospitalizations. The primary death code as confirmed or agreed upon by the Outcomes Committee will be entered into the Detailed Death Form 306 by the DCC. The DCC study coordinator on the conference call will complete Form 503 as adjudicated by the Outcomes Committee. The primary and secondary reviewers will be entered into the DCC Death Review Documentation Form. The death code chosen by the committee will be used for subsequent analysis.

FINAL FHN Cause of Death Classifications per Outcomes Committee*
Used for F305 and F305B Datasets – Field = OC_CAT

Post Study OC categories defined	Database code (FHN_Death_Notification, OC_CAT)	Confirmed by M. Rocco	Original F306 categories	F306 Category Description
CVD1	54DA	Atherosclerosis/ ischemic	01	01=Ischemic Heart Disease (includes atherosclerosis)
CVD2	54DB	CHF/Cardiomyopathy	02 and 04DK	02=Congestive Heart Disease (CHF) 04DK=Cardiomyopathy (without IHD or CHF)
CVD3	54DC	Arrhythmias	03	03=Arrhythmias and conduction problems (includes sudden death (due to arrhythmia, not due to IHD))
CVD4	54DD	Cardiac, sudden death; specific heart-related cause unknown; other heart conditions	04	04=Other Heart Diseases and Conditions (includes sudden death due to heart conditions other than IHD/arrhythmia)
Access-related infection	54DE		20DE	Other access infection
Non-access infection deaths	54DF		18DB	Other infection (not recorded in previous category)*
Other dialysis related deaths	54DG		21	Other hemodialysis complications
Other access deaths	54DH		20	Hemodialysis vascular access complications
GI Bleed	54DI		13DC	GI bleeding, site unknown
Cancer	54DJ		10	Malignancy
Accidental	54DK		23DF	Accident unrelated to treatment

deaths				
Other death	54DL	Other death (not recorded in previous categories)	--	--
Sudden death, unknown	54DM	Sudden death, unknown cause	24DA	Sudden death, unknown cause
Unknown death, unknown cause	54DN	Other death, unknown cause	24DB	Other death, unknown cause

26. FHN Study Publication Policy

26.1 Introduction

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

1. To assure timely publication of the results of the Study to the appropriate professional audiences,
2. To avoid premature publication of results that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically convincing) or that might compromise the ability to publish the results in high quality peer reviewed journals (as by premature release to the lay press),
3. To maintain high standards of quality of all material published by the Study,
4. To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees, and
5. To assure equitable attribution of credit to all of the professionals participating in the Study.

To accomplish these ends, it is the policy of the Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Study Chairman after consultation with Chairman of the Publications and Ancillary Studies (PAS) Committee to specifically appoint writing committees, and that all such materials must be reviewed and approved by the PAS Committee and/or the Steering Committee before publication.

26.2 Scope of policy, and exception for local publicity materials

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

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

26.3 Source of suggestions for publications of the study

Suggestions for topics appropriate for preparation of abstracts, peer reviewed papers, or chapters and reviews are made by the PAS Committee. In addition, all participants in the Study are invited to suggest topics appropriate for preparation as abstracts, peer reviewed papers, or chapters and reviews from the Study. Such suggestions should be made to the DCC and the Chair of the PAS Committee, who shall review the request to be certain that there is no overlap with materials previously assigned to other writing committees. Where such overlap exists, the Chair of the PAS Committee may make recommendations to the Study Chair that the suggestion be referred to an existing writing committee, that additional study participants be added to existing writing committees, or make other suggestions

to resolve the overlap. However, final decision in this matter will be made by the Study Chair after consultation with the Chair of the PAS Committee.

It is the policy of the Study to encourage non-physician professionals to prepare scientific presentations to their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may well overlap with material being prepared by writing committees for medical journals, it is the policy of the Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in section 4.6.

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

26.4 Assignment of writing committees

Topics suggested for presentation or publication that do not overlap with an existing committee will be circulated to the Principal Investigators of all clinical centers, DCC, and the NIH. These groups are requested to suggest and justify names for lead authors (Chair of writing committees) and co-authors. These names will be collated and reviewed by the PAS Committee. A recommendation for a writing committee will then be made to the Chair of the PAS Committee who will decide on the final composition of the writing committee. If a topic is suggested by a participant of the Study, the writing committee will be formed as just described except that the person making the suggestion will be considered as the potential lead author. The Principal Investigator of an ancillary study should be considered for lead author of material derived from this study. If only a subset of clinical centers participate in an ancillary study, only investigators from these centers should be considered to be on writing committees relating to this study. Appointments of writing committee chairmanships will be made in an equitable fashion to all professionals -- physicians, study coordinators, nurses, statisticians, and others -- in a fashion that recognizes the special contributions of each member of the Study to its performance. Any dispute about lead author or co-author will be settled by the Chair of the PAS Committee. In all cases, writing committees dealing with an issue that requires analysis of data by the Data Coordinating Center will have a member of the DCC assigned to it.

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

26.5 Classes of reports of the study

There are four classes of reports of the Study:

A. Reports of the major outcomes of the Study. It is assumed that there will generally be only one or two such reports derived from each Phase of the Study.

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

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

D. Reports of investigations initiated outside the Study, but using data or samples collected by the Study. The investigators may be FHN or other investigators, but the source of the ideas and the funding for the study will have been derived outside the Study itself. Writing committees for this type are formed and presentations and publications made in accordance with the general policy rules for FHN publications. However, the Principal Investigator of an ancillary study should take primary responsibility in publishing the results of the study.

26.6 Authorship policy

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

Type A publications:
abstracts: the Frequent Hemodialysis Network (FHN) Study Group[1], presented by XXXX.
papers: the Frequent Hemodialysis Network (FHN) Study Group[1], prepared by XXXX.
[1]The FHN participant box, detailed below, must be included in these papers. If a journal's publication policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:
abstracts and papers: Authors' names, and the Frequent Hemodialysis Network (FHN) Study Group[1]
[1]The FHN participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

Type C and Type D publications:
abstracts and papers: authors' names and the FHN Study
[1]The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. In Type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

26.7 Listing of professional participants in the participant box

The FHN participant box will list all professionals who have participated in the Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center staff listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not

by the specific position that he/she held in the study. The centers will be listed in the following order:

NIH
Study Chair
Clinical Centers (in alphabetical order)
DCC

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

26.8 Acknowledgement of support and reprint addresses

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

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

The following information regarding reprint requests should be included in all papers prepared for the Study. The DCC will maintain an inventory of all Study publications and will mail out the reprints.

Requests for reprints should be addressed to:

FHN Data Coordinating Center
Department of Quantitative Health Sciences, Wb4
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

26.9 Schedule for completion of writing assignments and resolution of overlaps between writing committees

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

26.10 Review of abstracts and presentations by the PAS committee

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

1. The writing committee wanting to submit an abstract, give a talk, or submit other material for which there is an explicit submission deadline shall contact the Chair of the PAS

Committee. In the event that the Chair is unavailable, the Vice Chair may be contacted. The Chair (or Vice Chair) will name a subcommittee of two members of the PAS Committee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be sent by the submitter directly to these two reviewers so as to reach them no fewer than seven (7) days prior to the deadline for submission.

2. The members of the subcommittee shall review the material and notify the Chair solely of their approval or disapproval. If there is unanimous approval, the PAS Committee Chair (or Vice Chair) shall inform (through the DCC) the submitter that he/she has Study approval for the submission.
3. All materials submitted for approval in this fashion will be distributed, together with notice of the disposition, to all members of the PAS Committee and to the Chair of the Steering Committee. All approved materials will also be forwarded to the NIH Project Officer, and for record purposes to the Principal Investigator of the Data Coordinating Center, and will be distributed to the entire membership of the Steering Committee at the next meeting of that Committee.

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

1. In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.
2. In case of a poster presentation, the content of the poster material must be submitted for review.

26.11 Review of papers by the PAS committee

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

1. The Chair, PAS Committee, shall appoint a panel of two primary reviewers, one of which must be a PAS Committee member, and one of whom may be any professional member of the Study Group with appropriate expertise. The Chair (through the DCC) shall distribute the material to all members of the PAS Committee and to the Principal Investigator of each center participating in the Study. The two members of the review panel shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PAS Committee. The P.I.s of the various clinical centers will be given a deadline by which any comments or critiques that study personnel at their center may wish to make must be received by the Chair, PAS Committee. This mechanism will assure that each professional participating in the Study will have an opportunity to review any materials that will be submitted for publication bearing his/ her name as a participant and co-author.

2. The Chair, PAS Committee shall schedule a meeting of the Committee (generally by conference call), including review of papers and other non-time critical materials as Agenda items. The reviews of the panel members and any comments received from the center P.I.s will be distributed to the committee with the agenda.
3. While discussion of the submitted papers and other materials will be led by the two appointed reviewers, all members of the Committee will be invited to participate and all shall vote on final disposition.
4. In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.
5. The Chair of the PAS Committee shall be responsible for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non-acceptance of the material as submitted but with suggestions for revision and resubmission, he and the writing committee may agree not to proceed with a report to the Executive or Steering Committees at that time, pending revision and resubmission.
6. If there is a recommendation for approval or final approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the Chair, PAS Committee shall report this outcome in writing to the Executive Committee for final action. In the case of a dispute between the PAS Committee and the author(s), the Chair, PAS Committee shall provide a copy of the submitted material and a summary critique to the Executive Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.
7. The authority to grant final approval for a formal scientific paper of the Study rests with the Steering Committee, or the Executive Committee in the interim between meetings of the Steering Committee.
8. All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the Steering Committee. All materials receiving final approval by the Executive or Steering Committee will also be forwarded to the NIH Project Coordinator, and for record purposes to the Principal Investigator of the DCC.
9. In the event that editors of a scientific journal to which an approved FHN scientific manuscript is submitted suggest or require revisions of the manuscript, the revised manuscript must be reviewed again by the PAS Committee prior to resubmission in the same manner as described above. Generally, the Chair will appoint the same reviewers who first read the paper to review the revision, and every effort will be made to expedite such repeat reviews.

26.12 Criteria for review of materials by the PAS committee

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

1. Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved FHN materials reflect well on the Study.
2. Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the Study or compromise the eventual publication

of FHN findings in high quality peer reviewed journals. In this later regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer reviewed journal.

26.13 Maintenance of records of publications and presentations

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

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

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

26.14 Acknowledgement and acceptance of FHN Study policies on publications and presentations by the professional participants in the study

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

FHN STUDY

Statement of Understanding of Policy
Concerning Publications and Presentations

To assure that all professionals involved with the FHN Study know and understand the policies of the FHN Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the Manual of Operations Section 26 detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized below.

I. Material Covered by These Policies

All material to be presented orally or submitted for publication or dissemination by individuals associated with the FHN Study and dealing with any aspect of the FHN Study must receive prior review and approval by the Publications and Ancillary Studies (PAS) Committee with the following exception:

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

II. Assignment of Writing Committees for Publications

The PAS Committee will solicit volunteers for each writing committee for abstracts and publications and make a recommendation on the writing committee and topic to the FHN Steering Committee Chair. The FHN Steering Committee Chair will decide on the final composition and topic of the committee after consultation with the Chair of the PAS Committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be by the Chair of the Steering Committee.

III. Authorship

The FHN policies specify the authorship for each of the four different classes of publication or abstract (See Section 26.5 of the Manual of Operations). These policies are binding and must be followed in all publications derived from the FHN Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by members of the PAS Committee before being submitted (See Section 26.10 of the Manual of Operations). These abstracts must be delivered to the

reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the FHN Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PAS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Committee for formal review by the entire Committee (see Section 26.11 in the Manual of Operations). If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair of the PAS Committee at least 30 days prior to the deadline, to permit such review.

VII. Certification by FHN Study Participant

This is to certify that I have read the above statement of policies of the FHN Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the FHN Study.

_____ _____

(Signature) (Date)

_____

(Print or Type Name and Institution)

27. FHN Study Ancillary Studies

27.1 Definition

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

27.2 Funding of ancillary studies

Ancillary studies will not be funded by the main study, but will require an independent source of funding.

27.3 Approval procedures

1. Proposals may be generated by a participating clinical center or by other interested investigators providing at least one center is included as a co-investigator. These applications are submitted to the Data Coordinating Center for review by the Publications and Ancillary Studies Committee.

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

a. Hypothesis to be tested.
Specific outcome variables that will be assessed.
Need for data from the DCC.

b. Significance of the proposed ancillary study.
c. How will performance of this ancillary study affect the main Study? Specifically:

i. Will there be any deviations from the main Study protocol? If so, what will they be?
ii. How much additional participant, staff and DCC time will be required to complete this ancillary study?
iii. Will additional funds be requested for the study and what will their source be?

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

a. Hypothesis to be tested.
b. Significance of the study.
c. Conduct and performance of the study including specifying the study population and the data to be collected.
d. Sample size justification.
e. Quality control of the data.
f. Data analysis methods.

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

27.4 Publication of ancillary study results

The policies regarding publications and presentations of the result of ancillary studies are the same as those governing the publications and presentations of results of the main study (see Section 26). These policies are designed to:

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

FHN Daily and Nocturnal Trials

Talking Points - Core PI's to review these talking points with Site PIs
Version 1.2, February 2, 2006

1. Review Necessary Requirements for Site PI
    a. HIPAA certification. Have you taken a course? When were you last certified?
    b. IRB certification. Have you taken a course? When were you last certified?
    c. Basic GCP. Have you taken a course? When were you last certified?

2. General Principles of RCTs – Threats to a Study
    a. Equipoise - Before and after randomization, you and your staff must speak to a patient as if you are not certain which of the study arms is best. Otherwise, this could bias his performance on the physical function tests, for example, making him feel he has to do especially well if he is on the "good" treatment and making him sluggish if he knows he is in the "other" arm.'
    b. Bias. For example, in recruited population, ascertainment of endpoints (especially unblinded Quality of Life)
    c. Power. The power of the study is determined by recruitment of patients, completeness of follow-up, and maintenance of the targeted separation between groups (# treatments/week).

3. Protocol Design
    a. Review Study hypothesis - including endpoints
    b. Data analysis plan:
    There are two primary outcomes that are considered to be equally important. These are 1. 12-month change in the SF 36 physical health composite score or death, and 2. 12-month change in LV mass by a centrally-read cardiac MRI or death. The primary analysis will be conducted keeping each patient in the exact group the patient was randomized to, whether the patient ever received the protocol treatment assigned to that group or not. That is, the primary analysis plan is being done using Intent-To-Treat. For this reason, it is essential that all planned data be collected even for patients who are no longer following the planned treatment schedule.
    c. Review what happens to patients at the end of the study. (Nocturnal: may ask for NIH/CMS for extended follow-up).
    d. Do you have any issues with the study that preclude your involvement? Or preclude the involvement of your site?

4. Screening, Informed Consent and Randomization
    a. Sites must be absolutely sure that the patient fulfills all the inclusion criteria and does not fulfill any of the exclusion criteria. <u>For Nocturnal Study:</u> must have adequate home site, be able to pass the training, and does not need 4x a week dialysis on a regular basis. Evaluation of the likely suitability of the patient for nocturnal home dialysis during the baseline phase is essential, because if a substantial number of patients do not succeed in the training phase after randomization, the power of the study will be severely compromised. <u>For Daily Study:</u> must have adequate transportation.
    b. All baseline data must be collected before a patient can be randomized. If the patient is missing "just one thing" that is listed in the manual of operations as being required for

randomization, the patient is not eligible to be randomized until that piece of data is received. There are no special waivers

c. Once a patient is randomized, that patient is in the study throughout the scheduled follow-up period. All follow up data should be collected. This applies even if the patient is randomized to the experimental arm and stays on 3 times a week in center dialysis and never once receives the experimental (more frequent) therapy.

5. Good Clinical Practice (GCP) Record Keeping

a. Documentation & record keeping:

Essential Document file

Protocol and any amendments (& re-review)
Operations Manual & other written instructions
IRB-Approved consent forms
IRB correspondence
Information provided to patients
Recruitment advertising
Subject compensation/reimbursement
Serious Adverse Events / Safety Reports
Notes-To-File

Tracking logs for IRB submissions, SAEs, Safety Reports received from Sponsor, IRB-Approved Consent Form Versions, patient consent and re-consent, Signatures /Delegated Responsibilities, Researchers Training, Subject, Telephone, Notes-to-file

b. Recruitment procedure and consenting.

Allow sufficient time to consider all options
Provide opportunity for questions
Assess & reinforce comprehension as necessary
Sign & date form
Provide copy of signed form to patient

c. Baseline investigations
d. Treatment documentation
e. Discharge summary; important lab data for cause of hospitalization.
f. Adverse events reporting. What is an Adverse Event? What is a serious Adverse Event? Need to fill out forms

6. Clinical Care During the Trial

a. Dialysis Management. The need for strict adherence to the protocol for management of renal replacement therapy should be emphasized. Patient safety must, however, be the foremost concern. Investigator judgment must be used to ensure that rigid adherence to the protocol does not at any time result in compromise of patient safety.

b. Adherence and Planned reductions in therapy. The success of the study will be determined in large part by the extent to which patients randomized to 6 x/week dialysis maintain their 6x/week schedule. If a patient who is randomized to the frequent dialysis arm is unable or unwilling to maintain the 6x/week schedule, then guidelines in the protocol and MOP should be followed to maintain a treatment schedule which approximates the 6x/week schedule as closely as possible. These patients are retained in the statistical analysis under the intent-to-treat analysis plan.

Form 309 must be completed prior to known reductions in dialysis treatments (4 or more planned missed treatments within the next month) or in treatment time (planned average

time per session 30 minutes or more lower than minimum time under the study protocol for a period of at least 1 week). Treatment deviations due to hospitalizations are not counted. This form should be filed advance when you plan to deviate from the study plan for dialysis, including cases in which the deviation was requested by the patient.
c. Catheter malfunction. The most common cause of under-delivery of dialysis dose is likely to be catheter malfunction. Catheter malfunction should be suspected if the achieved blood flow rate is less than 90% of the prescribed rate or if catheter recirculation is > 15%, or high venous pressures (use your standard protocol). If the patient can't meet the targeted blood flow, you must prolong treatment to achieve the targeted Kt/V. Catheter replacement prior to the next planned dialysis treatment should be considered if catheter malfunction is present.

d. Monitoring Adequacy of Hemodialysis Treatments. The detailed algorithms for ensuring that the target dose of hemodialysis is achieved should be discussed. The use of calculation worksheets for the initial prescription of hemodialysis and modification of dose based on measurement of Kt/V should be described. Daily Study: Use Kt/V(2/3). Nocturnal Study: Patients must stay on dialysis 6 hrs a session for 6 days a week; with a std Kt/V of 4.0 or greater in experimental arm, and 3x wk meeting K/DOKI Kt/V goal in standard arm.
e. Isolated Ultrafiltration. The specific indications for isolated ultrafiltration will be left to the discretion of the primary physicians, however it is expected that the use of isolated ultrafiltration will be limited to patients with respiratory compromise or cardiac dysfunction manifested by objective criteria such as impaired oxygenation.
f. Associated therapy: monitoring so within K/DOQI for blood pressure, lipids, glucose

7. Vanguard Phase and DCC Status Reports

a. The performance of each center in recruiting patients, maintaining adherence to the targeted treatment schedules, completing the required case report forms, and obtaining the required measurements under the protocol will be summarized on a weekly basis in reports provided by the Data Coordinating Center.

b. The first year of the trial has been designated as a Vanguard phase. The DSMB will advise the NIH on whether the trial should be completed based on our performance during the Vanguard phase. Review the specific benchmark criteria which have been designated for the Vanguard.

8. Oversight Structure
   a. PI Steering Committee
   b. Executive Committee
   c. External DSMB

28.1 Introduction to Certification for Quality Control

FHN Personnel must be trained and certified in order to perform the tasks specified in the FHN protocol. The central database will track the certification status of personnel, and no one will be allowed to perform specified study tasks unless they have been appropriately trained and certified. This will help to ensure the quality of the tests and measurements done.

Those trained by a master instructor are considered to be trained as trainers and can train and certify other people. The people the trainers certify will not be considered to be trained as trainers.

Note that although the initial study training session in Cleveland (September 2005) also included training in billing, non-dialytic aspects of treatment, standards of care, and data entry, there are no specific training or certification requirements for these tasks.

28.2 Nocturnal Study Only

Home Blood Pressure Measurements

Home blood pressure training, using the Omron Blood Pressure device, was conducted by master instructor Ruth Bullas, RN, at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 17.

Those individuals who attended this training session are considered to be fully certified.

Those trained by a master instructor are considered to be trained as trainers and can train and certify other people. The people the trainers certify will not be considered to be trained as trainers.

28.3 Daily Study Only

Holter Monitor Placement

Holter training was conducted by master instructor, Christopher Chan, M.D. at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 16.

In order to be considered fully certified, personnel must submit test cases to Chris Chan for his approval. This must be done before the first procedure is done on an actual study patient.

Details of holter certification are provided in the Holter chapter of the Manual of Operations Chapter 16.

28.4 Both Daily and Nocturnal Studies

Modified Mini Mental Status Exam (Form 231)

Modified Mini Mental Status Exam training was conducted by master instructor, Manjula Kurella, M.D. at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 11.

Those who attended this session are considered to be fully certified as 'trainers'.

Those individuals trained by a master instructor are considered to be 'trainers'. These trainers can instruct and certify other study staff members on how to correctly perform a specific test. The additional study staff are not certified to train others.

Physical Function Testing (Form 234)

Physical Function Testing training was conducted by master instructor, Patricia Painter, M.D., at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 12.

Those who attended this training session are considered to be fully certified as 'trainers'.

Those individuals trained by a master instructor are considered to be 'trainers'. These trainers can instruct and certify other study staff members on how to correctly perform a specific test. The additional study staff are not certified to train others.

Trail Making B (Form 232)

Trail Making B training was conducted by master instructor, Manjula Kurella, M.D., at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 13.

Those who attended this session are considered to be fully certified as 'trainers'.

Those individuals trained by a master instructor are considered to be 'trainers'. These trainers can instruct and certify other study staff members on how to correctly perform a specific test. The additional study staff are not certified to train others.

Feeling Thermometer (Form 230)

Feeling Thermometer training was conducted by master instructor, Josee Champagne, at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 14.

Those who attended this session are considered to be fully certified as 'trainers'.

Those individuals trained by a master instructor are considered to be 'trainers'. These trainers can instruct and certify other study staff members on how to correctly perform a specific test. The additional study staff are not certified to train others.

Single Frequency Bio-Electrical Impedance Analysis (Form 242)

Bio-electrical Impedance Analysis training was conducted by master instructor, Glenn Chertow, MD, at the September 2005 training session in Cleveland. For details on this procedure, see Manual of Operations Chapter 15.

Those who attended this session are considered to be fully certified as 'trainers'.

Those individuals trained by a master instructor are considered to be 'trainers'. These trainers can instruct and certify other study staff members on how to correctly perform a specific test. The additional study staff are not certified to train others.

Cardiac MRI

Cardiac MRI training was described by Sanjay Ragajopalan, MD., at the September 2005 training session in Cleveland. MRI technicians were trained on conference calls by Sanjay Ragajopalan, MD, Javier Sanz, MD, and Mbabazi Kariisa, MPH. For details on this procedure, see Manual of Operations Chapter 7.

In order for an MRI lab to be considered fully certified, MRI technicians must submit test cases to Sanjay Rajagopalan for his review and approval. Details of Cardiac MRI certification are provided in the MRI chapter of the Manual of Operations, Chapter 7.

This certification must be done before the first procedure is done on an actual study patient except in highly unusual instances in which test cases cannot be done due to local restrictions. In this case, review Chapter 7 of the MOP for details.

28.5 Data Quality Control

Edit checks are applied upon data entry and discrepant data will not be accepted into the study database. If data already in the study database appear to be discrepant, a data discrepancy inquiry will be sent to the clinical center. The DCC will track when the inquiry was sent, what item was questioned, who responded to the inquiry, what was the response, whether the database was changed, and if so, when.

28.6 Database Back-Ups and Disaster Recovery

Data are backed up nightly, with a full back up done weekly. Data tapes are stored off site monthly.