3. Nocturnal Study Overview

3.1 Introduction

The mortality rate of patients receiving chronic hemodialysis therapy in the United States remains unacceptably high, in the range of 15 - 20% per year. [USRDS, 2001] The results from the recently concluded HEMO Study indicated that there was no benefit of either higher dialysis dose or higher flux on mortality or morbidity using standard three times per week hemodialysis therapy. [Eknoyan, 2002] It is therefore clear that major modifications to the dialysis procedure are needed in order to improve mortality and morbidity outcomes in chronic hemodialysis patients. The most physiologic method for providing replacement hemodialysis therapy is to provide dialysis on a more frequent basis. Six times per week nocturnal home dialysis provides the highest dose of dialysis and is more likely to decrease physiologic variations over time compared to any other type of hemodialysis. A randomized trial of standard three times per week dialysis versus nocturnal home hemodialysis will provide the least bias in comparing these two hemodialysis modalities.

In the FHN Nocturnal Trial, up to 250 consenting patients meeting eligibility criteria will be randomized in a 1:1 allocation to 1 of 2 hemodialysis regimens:

i) *Conventional hemodialysis* of 3 sessions per week. Patients may remain on their usual dialysis prescription subject to a minimum delivered eKt/V of 1.1 per session AND a minimum treatment time of 2.5 hours per session;
ii) *Long overnight home hemodialysis* of 6 sessions per week, with a minimum treatment time of six hours AND a minimum delivered standardized Kt/V (sKt/V) of 4.0

Once randomization occurs, the study patient will be followed for 14 months. It is anticipated that training for nocturnal home hemodialysis will require about 4 – 7 weeks; thus, the study design should ensure that patients in the nocturnal arm of the trial will be followed for a minimum of 12 months on home nocturnal hemodialysis therapy.

Patients assigned to the standard three times per week in-center hemodialysis arm will follow any dialysis prescription subject to two constraints to assure compliance with minimum national standards:

a) equilibrated Kt/V $\geq$ 1.1 and
b) treatment time $\geq$ 2.5 hours.

Patients assigned to the 6 times per week nocturnal home hemodialysis arm will follow any dialysis prescription provided their prescribed standardized Kt/V is at least 4.0 and treatment time is at least 6.0 hours, 6 times per week. These prescriptions should provide large differences in median levels of key parameters between the nocturnal and standard three times per week in-center hemodialysis groups

The objectives of this clinical trial are to determine:

1) The feasibility of recruiting and retaining subjects in a randomized trial of 6 times per week (“daily”) nocturnal home hemodialysis versus conventional three times per week in-center hemodialysis,
2) Patient adherence and acceptance of daily nocturnal home hemodialysis,
3) The safety of daily nocturnal home hemodialysis,

4) The effects of daily nocturnal home hemodialysis versus standard three times per week in-center hemodialysis on two co-primary outcomes:
    a) A composite of mortality with the change over 14 months in LV mass as measured by cardiac MRI
    b) A composite of mortality with the change over 14 months in the SF-36 RAND physical health composite (PHC)
5) The effects of the interventions on seven secondary outcome domains:
    a) Cardiovascular structure and function (change in LV mass),
    b) Health-related quality of life/physical function(change in the PHC),
    c) Depression/burden of illness (change in Beck Depression Inventory),
    d) Nutrition and inflammation (change in serum albumin),
    e) Cognitive function (change in the Trail Making Test B),
    f) Mineral metabolism (change in average predialysis serum phosphorus), and
    g) Survival and hospitalization (rate of non-access hospitalization or death).

    In addition, hypertensive status and anemia have been designated as main outcome domains, but without single first priority outcomes. While composites of mortality with LV mass and the PHC are co-primary endpoints, the changes in LV mass and the PHC, without the mortality component, will also be analyzed as the main secondary outcomes for evaluating the cardiovascular structure and function and the health-related quality of life/physical function domains, respectively.
6) The characteristics of the daily nocturnal home hemodialysis intervention compared to standard three times per week in-center hemodialysis, including measures of solute clearance, treatment time, volume removal, and non-dialytic components of the interventions
7) To determine the feasibility of implementing nocturnal hemodialysis in practice, including evaluation of barriers to implementation and an assessment of the cost of nocturnal HD. The incremental cost of delivery of daily HD compared to conventional HD will be estimated, and cost-effectiveness and cost-utility ratios of the two therapies will be compared.

Data to be obtained in the trial includes kinetic modeling visits held at baseline and monthly throughout the 14 month follow-up period including dialysis treatment and kinetic modeling parameters plus weight, blood pressure, protein catabolic rate, creatinine generation rate, monitoring of missed treatments over the previous month, serum albumin levels, local laboratory measurements and medication usage (including antihypertensives, erythropoietin dose, phosphate binders, iron dose, and vitamin D). Measures of quality of life, depression, physical function, and cost-effectiveness will be obtained at baseline and months 5 and 14. Bioelectric impedance will be performed at baseline and at months 3, 5, and 14. Cardiac MRI and comorbidity assessments will be obtained at baseline and month 14. Vital status, hospitalizations, and access procedures will be monitored throughout follow-up. Potential risks of daily nocturnal home hemodialysis to be monitored include vascular access complications (evaluated by primary unassisted patency), iron losses, malnutrition, patient burn out and electrolyte abnormalities.

3.2 Schedule of Procedures

The purposes of the baseline evaluation are to provide patients with further information regarding the study, further clarify eligibility criteria, determine suitability for the patient to receive nocturnal home hemodialysis and document baseline characteristics and clinical information which will allow assessment of the balance of important baseline prognostic variables between groups, as well as enable pre and post comparisons of specific outcomes. The length of the baseline evaluation is 4 to 12 weeks.

The baseline assessment will include one kinetic modeling session, (see Section 3.1), labeled as the B1 visit. Key laboratory measurements, including predialysis serum albumin and pre- and post-dialysis serum urea nitrogen, creatinine, and phosphorus will be obtained from local laboratory measurements for both baseline kinetic modeling sessions. Derived kinetic modeling parameters and the pre-dialysis albumin and phosphorus concentrations will be averaged to determine the actual assigned baseline value. A timed urine collection (minimum 24 hours) will be obtained for patients producing urine prior to the first kinetic modeling session for evaluation of the residual renal function exclusion criterion.

Comorbidities will be assessed at baseline using the modified Charlson comorbidity index [Hemmelgarn, 2003], supplemented by additional questions from the Index of Co-existing Disease Score [Miskulin, 2001]. The majority of baseline HRQL surveys will be administered by telephone through the Central HRQL Survey Center. Measures requiring visual and motor assessment will be administered by the Clinical Center's study coordinator. A baseline measurement of left ventricular mass index by MRI will be obtained at designated MRI facilities for the study and read by a Central reading center. Additional baseline measurements are described in Section 6.

In week one of baseline, the patient will be provided with literature on the clinical trial and be given the contact number for the Clinical Center.

In week two, the patient will visit the Clinical Center. The study will be presented to the patient in detail by a trained study coordinator and consent will be obtained. The home training staff will meet with the patient to help determine the suitability of the patient, from both a physical and psychosocial standpoint, for home hemodialysis. Each of the Clinical Centers performing nocturnal dialysis has a detailed, specific patient evaluation process that is used to assess if patients are appropriate candidates for home hemodialysis. This evaluation process includes a thorough physical assessment, including motor skills, vision, hearing, stamina, reading ability and motivation as well as a home inspection. [Ouwendyk, 2001] The details of this evaluation process will be provided in the manual of operations. If the patient is unable to medically and physically dialyze alone, then a hemodialysis partner will also be trained.

In week three, a visit to the patient's home will be performed to help determine the suitability of the patient's home environment for home dialysis and to determine any home modifications that may be needed prior to the start of home hemodialysis. This assessment will include the suitability of electrical supply, plumbing for water and for dialysate drainage, water supply and quality and storage capacity. Some or all of the costs for necessary modifications to the home may be borne by the patient. This issue will vary at individual clinical centers. These centers

will provide specific information to the patient regarding possible reimbursement for home modifications.

Based on the information obtained in weeks two and three, the Clinical Center will determine if the patient is a suitable home hemodialysis candidate. Once the baseline evaluation is completed, patients will be reevaluated by the study coordinator for eligibility to undergo randomization. If the patient is deemed eligible, the study coordinator will review the implications of randomization with the patient, and confirm the patient's desire to undergo randomization. All baseline data will be obtained prior to randomization of the patient. This data collection can begin anytime after the patient has signed the consent for the study. There will be an eight week window for completion of all baseline studies, including all laboratory data, questionnaires, functional assessments and cardiac MRI.

Once the baseline evaluation is completed, subjects will be re-evaluated by the study coordinator for eligibility to undergo randomization. All baseline case report forms, including valid results for each of the primary and main secondary endpoints must be entered into the database in order for a patient to be randomized. If the patient is deemed eligible, the study coordinator will review the implications of randomization with the patient, and confirm the subject's desire to undergo randomization.

For patients choosing not to be, or not able to be randomized, a baseline dropout form will ascertain the reason for dropout. Characteristics of randomized patients will be compared to those who are excluded between the screening visit and randomization (either due to ineligibility or unwillingness to participate). In addition, the reason for nonparticipation will be recorded.

The frequency of measurements is summarized in Table xxx below. Most questionnaires (including HRQL, depression, cognitive function, and treatment burden) and objective tests of physical function will be performed at baseline, and at 5 and 14 months post-randomization (B, F5, F14). The purpose of the 5-month (F5) assessment is to allow evaluation of short-term effects prior to significant attrition, while the 14-month (F14) assessment is intended to allow evaluation of longer-term effects. The cardiac cine-MRI will be performed at baseline and 14 months (B, F14) only. Biompedance will be performed at 3 month post-randomization (F3) in addition to baseline, 5, and 14 months (B, F5, F14). The purpose of the additional 3-month (F3) assessment is to elucidate early effects of the therapy on volume status.

Kinetic modeling sessions will be performed once in the baseline period and monthly after randomization through month 14. Kinetic modeling parameters, including information on the dialysis prescription and the pre- and post-dialysis concentrations of urea, creatinine, and phosphate, as well as pre-dialysis albumin will be obtained at each session, while other labs will be collected less frequently (see Table xxx B). The pre and post-dialysis blood pressures, post-dialysis weight, and the presence of intradialytic hypotensive episodes will also be obtained for the kinetic modeling session. Once during baseline and at months 1, 5, 9, and 14 of follow-up (B, F1, F5, F9, F14), start and end times, pre and post-dialysis blood pressures, and pre- and postdialysis weights will be retrospectively obtained for the one-week interval preceding the modeling session, generally including two additional dialyses (for a total of three dialyses, including the modeling session) for conventional patients, and five additional dialyses (for a total

of six dialyses, including the modeling session) in daily patients. In addition, information on the dialysis prescription (but not local laboratory measurements) will be recorded for quality control for one of the dialyses during the second week follow-up randomization.

The frequency of local laboratory measures other than those described above for basic kinetic modeling will depend on the frequency with which they are performed at the various Clinical Centers, and should follow DOQI clinical practice guidelines. Locally performed pre-dialysis hemoglobin, calcium, bicarbonate, potassium, and sodium should be recorded at baseline and at least once per month post-randomization, while ferritin, transferrin saturation, and parathyroid hormone should be recorded at baseline and at least once every 4 months. Only baseline values performed less than 3 months before randomization will be used for any analysis.

All prescribed medications will be recorded at baseline and at months 5, 9, and 14 during follow-up, (B, F5, F9, F14).

Adherence to therapy will be obtained at baseline and on a monthly basis. All events, such has hospitalizations, deaths, access procedures, and discontinuations will be monitored continuously throughout follow-up.

The two baseline kinetic modeling sessions are designated as the B-1-1 and B-1-2 visits. The follow-up visits are designated as F-05 (for the week 2 assessment), F-1 (month 1), F-2 (month 2), and so on through the F-14 visit. Visit windows of ± 1 week are designated for the F-05 visit, and of ± 2 weeks are designated for the remaining follow-up visits. However, if assessments that are designated for a specific visit window are missed during that window, attempts should be made to perform them during the following visit window.

Table 3.1 Nocturnal Trial - Summary of Data Collection Schedule

A. Health-related Quality of Life/Physical Function, Depression, Cognitive Function, and Treatment Burden Measures*

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	13 mo	14 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 should be done pre-dialysis, mid-week within 2 weeks of scheduled time.

B. Cardiovascular, Blood Pressure, and Nutritional/Inflammatory Measures (for labs and medications, see Part C below)

Measurement	Blinded Reading	Baseline	2 wks	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
Cardiovascular Measures																	
Cardiac cine-MRI	Yes	✓															✓
Predialysis and postdialysis systolic and diastolic blood pressures*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Predialysis and postdialysis weight*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interdialytic hypotensive episodes*	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Home blood pressure monitoring	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 3, 5, 9, and 14 of follow-up.

C. Laboratory Measurements and Medications, Anemia and Mineral Metabolism Measures

Measurement	Baseline	2 wks	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]	✓			✓			✓			✓			✓		✓	
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)

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

Measurement	Baseline	2 wks	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
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																
Patient interviews/questionnaires	✓						✓									✓

3.3 Patient Evaluation

The experience of most nocturnal home hemodialysis programs is that the only absolute requirement to be accepted is that the patient must be motivated and want to learn this new technique. There are also six other prerequisites that study participants for the trial must meet:
1) The patient must be willing to come to the home hemodialysis clinical center for a 4-6 week training program four days per week.
2) The patient must have reasonable memory.
3) The patient must have reasonable manual dexterity.
4) The patient must have reasonable vision.
5) The patient must have reasonable hearing.
6) The patient must be willing to come to the home hemodialysis clinical center once a month for a clinic visit.
In addition, the patient must understand that he or she will be responsible for the extra water and electricity costs associated with performing hemodialysis at home and that some clinical centers will ask the patient to pay for part or all of any modifications needed in the home in order to perform hemodialysis at home. Each clinical center will make a careful analysis of the patient home's needs and the patient will receive a detailed description of what he or she will be responsible for in regard to modifications of the home.

The initial patient evaluation will occur at the screening visit. During the initial patient evaluation, the patient will meet with a home training nurse (usually the clinical site study coordinator), the home training social worker and one of the home training technical support staff. Information that should be obtained prior to this visit include a recent history and physical from the patient's nephrologist, discharge summaries from recent hospitalizations, and information from the patient's dialysis unit regarding the patient's compliance from the dialysis unit charge nurse, dietitian and/or social worker and an assessment of psychosocial issues from the dialysis unit social worker.

The home training nurse and technical person will make an assessment of visual acuity and reading comprehension (ability to read and comprehend the patient instruction manual), hearing (ability to hear instructions given over the phone) and manual dexterity (ability to use the controls of the hemodialysis machine). In addition, the home training nurse will review the patient's medical history and perform a physical exam to determine if there may be any specific medical problems that could interfere with performing hemodialysis at home.

The social worker will make an assessment of patient insurance, mental health issues and acceptability of the patient and the patient's partner to performing the dialysis treatments at home. The social worker will determine if there is a history of mental illness, anxiety or confusion. The social worker will also determine the support from family and friends for the patient to perform hemodialysis at home. Information from several nocturnal hemodialysis centers indicate that dropouts from nocturnal hemodialysis are more likely to occur if the patient's spouse does not support the idea of performing hemodialysis at home. The social worker will also meet regularly with the patient and partner to get a better sense of who they are, of important psychological issues in their lives, and most importantly determine how they learn

best. This last point is important since it has been noted that the training goes best if the trainers mold their teaching to the patient's particular learning styles.

3.4 Home Evaluation

The assessment of the study participant's home or apartment should include an assessment of the following areas:

1) Water
2) Plumbing
3) Septic or sewer system
4) Electrical
5) Telephone
6) Storage

Detailed information on each of these areas is outlined below:

Well water check list:

1) AAMI water test
2) Water cultures and organisms identification
3) Pressure and flow test (20 PSI @ 3 GPM x 1 hr)
4) Well site evaluation (location on property and proximity to septic system if applicable)
5) Surrounding area evaluation (1 mile radius or up hill/mountain run off)
6) Past history of the well and depth (spring run off and summer dry season)
7) Water system in the home (pipe size and makeup, hot water tank)
8) Drain lines (PVC, copper, cast iron)

Municipal water check list:

1) AAMI water test
2) Water cultures and organisms identification
3) Pressure and flow test (20 PSI @ 3 GPM x 1 hr)
4) Water system in the home (pipe size and makeup, hot water tank)
5) Drain lines (PVC, copper, cast iron)

Septic system check list: (if applicable)

1) Age
2) Size, if available
3) Construction

Power check list:

1) Panel amperage
2) Circuit in the home and the room for water and treatments (20A GFI for machine and 20A GFI for the R/0) dedicated to each.
3) Lighting in the treatment room
4) Power history (frequent power outages)?
5) Correct wiring (correct polarity).

Telephone checklist:

1) Telephone available in treatment room
2) If patient to have remote monitoring, second phone line with modem installed

Structure evaluation:

1) Floor joist and condition for room used for dialysis and for water treatment system
2) Adequate storage for dialysis supplies at home in an area close to the treatment room
3) If living quarters are rented, permission from landlord to make needed modifications

In addition, once all needed home modifications have been performed, a second home visit should be made to ascertain information on each of the following areas:

Water

1) Water treatment area clean, connections not leaking, pressure reading on R/O above 20 psi minimum pressure.
2) Water test supplies for hardness and chlorine available and patient testing both prior to treatments.
3) Water softener, if used, accessible and patient verbalizes duration and frequency of use.
4) R/O drain and machine drain lines placed in adequate drain for waste water.

Electrical

1) Dialysis machine and R/O on independent GFI outlet.

Telephone

1) Phone within reach of treatment area for contact with Rubin Center during treatment.
2) If remote monitoring to be used, phone line separate from house phone for computer monitoring during treatments working.
3) If remote monitoring, modem hooked up to dialysis machine and in stable position near machine to avoid dropping on floor.

Storage

1) Adequate storage for supplies in home.
2) Necessary supplies for each treatment kept near treatment for easy reach.

Sanitation

1) EPO kept in refrigerator. Arrangements made to keep it cold during treatment or to have companion bring it at the end of the treatment, discussed with patient.
2) Dialysis area clean and free of clutter. Top of machine open other than syringes for treatment.
3) No pets in Dialysis or water treatment areas.
4) Garbage double bagged and kept in covered garbage cans until the trash is removed.
5) Approved sharps container near treatment area for used needles and syringes

Safety

1) Smoke detector near treatment area with battery check performed while in the home.
2) Lighting adequate to assess drip chamber levels, monitor set up for possible contamination and visualize alarm screens during treatment.
3) Scale used gives same weight consistently to allow monitoring of weight removal.
4) Patient documenting treatment information on sheet each treatment.

Finally, the patient should be queried about any other problems that have or may occur by performing hemodialysis at home and these problems should be corrected.

3.5 Home Hemodialysis Training Progress

Each clinical center will develop a manual to be used for the training of home hemodialysis patients. Patients will need to be tested for proficiency in each of the following areas prior to being able to go home to perform home hemodialysis:

1) Emergency Procedures and when to call EMS
2) Set up for a hemodialysis treatment
3) Self cannulation of the fistula or accession of a permanent dialysis catheter and the securing of the access site to minimize the risk of disconnection
4) The operation of the hemodialysis machine
5) The use of supplies for the hemodialysis treatment, including the administration of approved medications (such as erythropoietin stimulating agents)
6) Safety monitoring during the hemodialysis treatment, including hemodialysis machine alarms and the use of leak detectors at the access site and on the floor under the HD machine
7) The use of appropriate infection control techniques
8) Adjustments during the hemodialysis procedure
9) Tear down after a hemodialysis treatment
10) Maintenance of the RO system and any related water treatment equipment

During the final week of training, the patient will perform the entire dialysis procedure, from set-up to tear down, without assistance but under supervision of the home training staff. Only when the home training staff is confident that the patient can perform hemodialysis safely at home will the patient be permitted to perform hemodialysis at home. There is no limit to the time that the patient may use for training as the paramount issue is that the patient is able to perform hemodialysis safely at home.

3.6 Principles of Recruitment And Retention

3.6.1 Publicity, recruitment and information brochures

The consortium will adopt a modification of the techniques used by at Lynchburg VA and Saratoga Springs NY for the recruitment of patients into the nocturnal dialysis program. The specific methods to be used at each Clinical Center will vary, as the referral patterns vary at each center. These recruitment techniques are designed to inform patients about the risks and benefits of home nocturnal hemodialysis therapy, and will include:

1) Addition of a nocturnal dialysis page on the web site of each of the Clinical Centers. A description of the nocturnal program will be provided. Linkage of each of these web sites to kidney-related web sites will also be pursued. The consortium has already obtained permission to provide information about the study on the Home Dialysis Central website (www.homedialysiscentral.com)
2) A generic recruitment brochure that summarizes the protocol of the randomized trial has been developed for the trial.
3) Development of print and radio advertisements to recruit patients into the study

4) Development of a video describing the protocol of the randomized trial that will be shown at the dialysis units at each of the Clinical Centers. The video used in Lynchburg VA will be used as a template to develop videos at each of the Clinical Centers.
5) Each Clinical Center will also have informational meetings describing this clinical trial. At these meetings, physicians with nocturnal patients, nurses training nocturnal patients and patients receiving nocturnal home hemodialysis will be present to speak to the audience and to answer questions.
6) Clinical Center PIs will also give talks at regional and national meetings for renal professionals and for dialysis patients

Each type of recruitment activity will need to be approved by the Clinical Center's Institutional Review Board prior to implementation. Recruitment efforts will begin towards the end of phase 1, when patients in the Clinical Centers will be informed about the clinical trial by these methods. These efforts will continue throughout the recruitment phase of the trial. All persons involved in the identification of potential study subjects will be required to complete training and maintain certification in human subjects protection and in adherence with the Health Insurance Portability and Accountability Act (HIPAA).

3.6.2 How to Select Patients and Patient Consent

The purposes of the screening evaluation are to identify patients for trial enrollment, provide potentially eligible patients with information regarding the study, obtain informed consent for participation and randomization, identify reasons for non-participation, and to gather estimates of rates of recruitment and randomization for relevant patient subgroups. The length of the screening evaluation is 1 - 2 weeks.

A trained study coordinator at each Clinical Center will review charts of patients on both hemodialysis and peritoneal dialysis to determine potential trial eligibility. In addition, it is anticipated that nephrologists from dialysis units that are not part of the Clinical Center will refer patients for possible inclusion into the FHN Nocturnal Study. The coordinator will approach potentially eligible participants and provide them with verbal and written information regarding the study. The study coordinator will also discuss the study with the patient's primary nephrologist to determine if the nephrologist believes that the patient is a suitable home hemodialysis candidate. The study coordinator will answer any questions the patient may have over the next week. If the patient is agreeable, informed consent to conduct a detailed baseline assessment and undergo randomization will be obtained and the patient will be asked to sign an Institutional Review Board - approved consent form. In addition, a consent will be obtained for the storage of blood.

Patients who decline participation will be invited to sign an Institutional Review Board approved "Screening Evaluation" consent. This consent will allow the collection and transmission to the study database of demographic information, comorbidities, and lab variables. This data will be used to assess differences between participants and eligible non-participants. In addition, the reason for non-participation will be recorded via a simple survey.

3.6.3 Retention plans

The nocturnal study requires a large commitment of time from study participants. Training will take, on average 4 -7 weeks and require visits to the home training center 3 – 5 times per week

during this time period. Patients desiring nocturnal dialysis but who are randomized to the standard arm of the trial will require frequent interactions with the study staff in order to maintain patient interest in completing the trial.

A number of techniques will be used to assist with patient retention:

1) Patients who live more than xxx miles from the home hemodialysis training unit will be reimbursed $75 for travel expenses at baseline and at F14 for the cardiac MRI test.
2) Study incentives will be provided to patients on a regular basis. In the HEMO study, incentives that were used included tote bags, umbrellas and tee shirts.
3) Study coordinators will be encouraged to maintain telephone contact will all patients at least on a monthly basis. For patients in the nocturnal arm of the study, more frequent contact will likely occur due to monitoring of the home therapy. For patients in the standard arm of the trial, this contact will ensure that hospitalizations or other changes in status will be obtained in a timely manner. This telephone contact will assist in maintaining patient interest in the study.
4) Study staff will strive to recognize patient milestones such as birthdays and anniversaries with cards and other items, as appropriate.

In addition, if during follow-up a patient randomized to the nocturnal arm is unwilling or unable to continue to follow their six times per week dialysis prescription as stipulated by the protocol, efforts should then be made identify a dialysis prescription which the patient is able to follow which approximates the target six times per week prescription as much as possible. If a patient remains unwilling or unable to maintain a six times per week hemodialysis schedule following consultation with the study team, the patient will be encouraged to dialyze five times per week with a treatment time sufficient to maintain the minimum dose of sKt/V. If the five times per week schedule is also untenable, the patient will then be permitted to dialyze four times per week. If a reduced treatment schedule 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 the full six times per week nocturnal regimen specified by the protocol. In accordance with the intent to treat nature of the protocol, these patients will continue to be followed for efficacy and intermediate outcomes and analyzed according to their original randomization assignment.

3.7 The Nocturnal Home Hemodialysis Prescription

3.7.1 Dialysis machines

All Clinical Centers will employ the use of machines that allow volumetric control of ultrafiltration.

3.7.2 Water quality

All Clinical Centers in the consortium will follow current AMMI standards for water, elemental and ionic purity. AAMI standards will be monitored in each home hemodialysis patient and each Clinical Center enrolling patients in the standard arm of the study monthly for bacterial and endotoxin counts and quarterly for electrolytes and heavy metals.

Water quality may influence morbidity and mortality, due to the presence of endotoxins, bacteria, and elemental and ionic impurities [Ouseph, 2002]. Due to increased weekly dialytic time and possibly increased dialysate flows, daily home nocturnal hemodialysis patients may be exposed to up to 4 times the amount of dialysate as the conventional HD group. Thus, poor water quality may have greater negative impact on outcomes in the daily than the conventional HD group. Because of this issue and the potential concern of backfiltration in the nocturnal arm of the study, all patients in the nocturnal arm will provide ultrapure dialysate. The clinical centers will strive to provide ultrapure dialysate to all patients in the standard arm of the study. Patients who receive dialysis at one of the nocturnal Clinical Center's in-center hemodialysis units will receive ultrapure dialysate. Individual hemodialysis units that are not part of the nocturnal consortium will be encouraged to use ultrapure dialysate. Reimbursement to these dialysis units outside of the consortium is available for conversion of dialysis machines to accept ultrapure filters (up to $500 per machine) as well as for the ultrapure dialysate filters ($75 every three months). It is recognized, however, that individual hemodialysis units not part of the nocturnal consortium may not be able to achieve this goal due to other equipment or financial constraints.

Ultrapure dialysate will be obtained by the modification of existing dialysis machines to accept a filter such as the Diasafe © filter. This filter, or one similar to it, is an additional filter added to the water supply side of the dialysis machine in order to further improve the quality of the dialysate to that approaching ultrapure water. The filter will be changed on a regular basis as noted in the manufacturer's instructions.

3.7.3 Dialyzer membranes and reuse

The HEMO study results suggested an overall reduction in cardiac death in patients who received dialysis with high-flux dialyzers [Eknoyan, 2002]. In addition, the clearance of beta-2-microglobulin, one of the outcomes measures for this study, is cleared to a greater degree with the use of high flux compared to low flux dialyzers. Thus, all patients in the nocturnal arm of the study will receive hemodialysis using high flux dialyzers. A high flux dialyzer will be defined as one that achieves a beta-2 microglobulin clearance greater than 20 ml/min with first use. Patients on nocturnal dialysis will not reuse dialyzers. The clinical centers will strive to prescribe high flux dialyzers for all patients in the standard arm of the study. Patients who receive dialysis at one of the nocturnal Clinical Center's in-center hemodialysis units will be prescribed high flux dialysis and will not reuse. Individual centers that are not part of the nocturnal consortium will be encouraged to use high flux dialyzers and not to perform reuse of dialyzers. It is recognized, however, that individual centers not part of the nocturnal consortium may not be able to achieve these goals due to financial constraints and current contracting arrangements for dialysis supplies.

3.7.4 Dialysate composition

In the in-center hemodialysis group, standard dialysis baths will be used per local protocol and based on the patient's monthly laboratory values. In the nocturnal hemodialysis group, there will be a more frequent monitoring of electrolytes (potassium, calcium, phosphorus) during training and the first two months of nocturnal therapy. Nocturnal hemodialysis is known to decrease serum phosphate and even lead to hypophosphatemia. Persistently low serum phosphate may lead to weakness, osteomalacia and in extreme cases hemolysis. In addition, nocturnal

hemodialysis can lead to negative calcium balance due to calcium loss through ultrafiltration. This may lead to increase in PTH and alkaline phosphatase levels, as well as a decline in bone density as measured by DEXA. Conversely, overzealous supplementation of calcium through the dialysate can lead to low bone turnover. Anecdotal experience suggests that the desirable intact PTH levels for nocturnal hemodialysis should be at the lower range or below the DOQI guidelines currently at 150-300 pg/mL or 16.5-33 pmol/L. Therefore, a standard protocol will be used for monitoring the levels of phosphorus, calcium and PTH and for the adjustment of dialysate calcium and phosphorus levels.

Laboratory testing
The following testing will be performed in all nocturnal hemodialysis patients:

Baseline investigations
Pre-dialysis serum calcium, phosphorus, intact PTH, and alkaline phosphatase levels.

Ongoing treatment once patient starts hemodialysis at home
Pre and post hemodialysis serum calcium and phosphorus levels will be obtained weekly for one month, every two weeks for one month and then monthly. Alkaline phosphatase will be obtained monthly. Intact PTH levels will be obtained monthly for 3 months (unless within the desirable range) and then every 2 months with blood samples taken at the clinic, 3-4 hours after the end of a dialysis treatment.

In addition, it is recommended that patients have a DEXA test performed at baseline, then on a yearly basis. If the baseline DEXA test is not normal, then an additional test should be performed at 6 months. This test is not covered by the trial and needs to be ordered based on clinical indications.

Dialysate concentrations of calcium and phosphorus
Specific information regarding the composition of the dialysate bath for calcium and phosphorus are noted below. The NKF K/DOQI guidelines for management of bone disease should be followed unless specific guidance is given below.

Calcium
All patients should start with a 3.0 mEq/L (1.5 mmol/L) dialysate calcium. The concentration can be adjusted by adding powdered or liquid calcium chloride into the 'acid' concentrate. Seven mL of powder added into 4.5 L 'acid' concentrate increases the dialysate calcium by about 0.5 mEq/L (or 0.25 mmol/L). Adjustments are usually in the range of 2-3 ml of powder. Similarly, addition of 12 cc of an aqueous calcium chloride solution to the 1 gallon jug of acid concentrate increases calcium by 0.25 mEq/L (0.125 mmol/L). Ready made commercially available 'spikes' can be used.

Phosphate
Phosphate binder dosage will be tapered, as clinically indicated, during the first one to two months of nocturnal hemodialysis therapy. Increased phosphate intake should be strongly advised before dialysate phosphate addition is considered. The decision should be based on the

initially weekly and then monthly pre / post dialysis laboratory values. Patients should not add phosphate into the dialysate during the first dialysis after a night off.

Since no commercially available dialysate additive phosphate preparation is available, Fleet enema® or Fleet phosphosoda® (oral) containing sodium phosphate have been used. They can be added into the bicarbonate or the 'acid' concentrates if bicarbonate cartridges are used. The addition of 30 ml of Fleet® enema yields a dialysate phosphate concentration of about 1.2 mg/dL or 0.4 mmol/L. Changes in the amount of phosphate are usually in the range of 20-30 mL of Fleet® enema. A usual dose is 30 to 80 mL or more. The oral Fleet phosphosoda® solution is more concentrated and is added in volumes of 15 mL, 30 mL or 45 mL or more. Some patients have complained of itchiness at the higher dose but this is not uniform. As sodium phosphate results in increased dialysate sodium concentration, a dialysate sodium concentration of 137 mEq/L can be used if increased thirst or hypertension is observed.

Patient follow-up
The dialysate calcium level will be adjusted until the PTH level is in the target range. A modestly elevated post dialysis serum calcium level is acceptable to achieve this goal

In the absence of pre dialysis hypercalcemia, strive for a lower PTH target by increasing dialysate calcium if either the alkaline phosphatase of bone origin is still elevated and/or bone density by DEXA is significantly lower than in the previous study.

The dialysate phosphate level will be adjusted until both the pre- and post-hemodialysis phosphate levels are within normal limits.

In the absence of pre-dialysis hypercalcemia, and in the presence of high PTH and alkaline phosphatase levels, use a higher dialysate calcium is recommended before resorting to high dose vitamin D analogues. Otherwise use Vitamin D analogues in accordance with NKF K/DOQI guidelines.

3.7.5 Ultrafiltration
In the conventional hemodialysis group, both ultrafiltration profiling and sodium profiling will be permitted. In the home nocturnal hemodialysis group, it is unlikely that either ultrafiltration profiling or sodium profiling will be needed; however, they will be permitted on an individual patient basis. The use of both types of profiling will be collected on a monthly basis.

3.8 Monitoring for Potential Risks of Nocturnal Hemodialysis

Studies in nocturnal home hemodialysis patients thus far have not identified significant complications of the procedure. Surveys conducted for this study among the principal investigators for each Clinical Center in this consortium have not identified an increased risk of vascular access failure, or of complications from either hypokalemia or hypophosphatemia. We speculate that the low rate of access complications is due to self-cannulation of the dialysis access by the patient, a decreased incidence of dialysis hypotension and the daily use of heparin. Appropriate monitoring of serum electrolytes, with appropriate adjustments of the dialysate, has been successful in minimizing the risk of electrolyte abnormalities. Less is known about the effects of nocturnal home hemodialysis on secondary hyperparathyroidism and bone metabolism.

These and other potential adverse effects that have not yet been identified will need to be monitored during this study and details of this monitoring are provided below.

There is also a risk that there will be either a disconnection of the blood tubing at the vascular access site, or a leak from the dialysis machine. A number of monitoring systems will be in place to detect these problems. All patients on nocturnal dialysis will use enuresis sensors to detect blood leaks at the needle site. Interlink® devices will be used to secure catheter connections and mesh will be used to secure the needles and lines of patients using grafts or fistulas for dialysis access. Floor sensors will be used to detect fluid leaks from machines and lines. [Lockridge, Jr., 2001] Except where patients are monitored on a routine basis, all nocturnal patients will need to have a home partner who can assist with any alarms that may occur during the hemodialysis treatment.

In addition, patients will provide a copy of their "run sheets" to the home hemodialysis training center on a weekly basis. Patients will not need to provide a copy of the run sheets if they are being monitored centrally. The information on the paper copy run sheets will include start and stop times, blood and dialysate flow rates and blood pressure and pulse readings. This information will be reviewed by the principal investigator for each Clinical Center and will be used to both determine if the patient is compliant with therapy and also for safety evaluations. Similar information will be abstracted from the dialysis unit run sheets for the one week period preceding each kinetic modeling session for patients randomized to the conventional dialysis group.

Finally, a number of potential complications will be monitored by either the clinical site and/or the Data Coordinating Center on a routine basis. The clinical site will collect information on vascular access complications on Form 307 and forward these forms to the DCC on a xxx basis. The use of erthythropoetin stimulating agents (Form 204) and IV iron (Form 203) by study patients will be recorded and sent to the DCC on a xxx basis. Information on nutritional status will be collected on Form 207 (for serum albumin) and Form 273 (for patient weight) and forwarded to the DCC on a xxx basis. Serum electrolytes will be monitored on a routine basis as outlined in section xxx. All of these labs are obtained locally and the clinical center will be responsible for the timely ordering and interpretation of these lab results. Specific lab results will be sent to the DCC on Form 207 on a xxx basis. Finally, all adverse events will be recorded on Form 307 and sent to the DCC on a xxx basis. All deaths will be reported to the DCC within xxx days of the event using Form 306. All hospitalizations will be reported to the DCC within xxx days of admission. Form 303 will be completed when information is available on the hospitalization.

3.9 Deliberations and Recommendations of the FHN Nocturnal Site Investigators Subsequent to a Patient Death.

A patient death in the Nocturnal Study appeared to result from a mistake in this patient's technique to discontinue dialysis. We identified several possible ways to reduce the occurrence of similar incidents resulting in death or injury:

1. Interlink Catheter Caps or Tigo Connectors used with central IV catheter dialysis access devices can substantially reduce the risk of bleeding or air embolism when the lines are inadvertently left unclamped. An adverse effect of such caps or connectors is that they increase resistance to flow during dialysis, so may reduce dialysance for patients with limited blood flow. The use of such devices is therefore limited for standard thrice weekly dialysis where Qb must be high, but should be considered strongly for patients receiving home nocturnal hemodialysis.

2. Sleeping Aids may impair patient judgment, particularly if technical procedures are required earlier than the usual awakening time. Sleeping aids have been safely used by patients when they have a partner who actively participates in the put-on and take-off of home dialysis patients. On the other hand, there have been some recent concerns regarding zolpidem (Ambien) and other sedative-hypnotics. (http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html). It is recommended that sleeping aids not be used by patients who perform dialysis without a partner.

3. Central venous catheter access for dialysis may increase the risk for air embolism compared to peripheral AV fistulas or shunts. However, peripheral access is more vulnerable to needle dislodgment and bleeding than are central catheters. Several investigators felt that central catheters are indeed safer than peripheral access for home use. It is recommended that central venous catheters can continue to be used safely for home hemodialysis

4. Enuresis Monitors can detect unsuspected sources of bleeding and are used in home hemodialysis. The group considered whether an enuresis monitor at the catheter connection site may have detected the disconnection early enough to avoid air embolism. The investigators unanimously felt that this was unlikely. The patient probably sat up in bed, took a breath to call for her husband and suffered the air embolism. A moisture detector would not have likely prevented this event. Enuresis monitors are useful under the dialysis machine to detect blood leaks at the artificial kidney.

5. Is it ever safe for patients to perform put-on and take-off procedures alone, without a partner? The investigators universally agreed that selected patients have been trained to do this solo, as long as a partner is available in the home to assist in case of emergencies. In this case, the patient had been trained to perform these procedures with a partner, but the partner in the adjacent bedroom did not participate in the take-off procedure. The group recommends stressing the importance of adherence to protocol, periodic query of technique and re-training when necessary. In addition, it is recommended that the partner sign an agreement to adhere to the training requirements.

6. Most facilities provide procedure checklists for put-on and take-off procedures. Much as commercial airline pilots use checklists before every flight to assure compliance with established procedures - -even though they have done it thousands of times and know the procedure by heart, it is recommended that patients and their partners use checklists for each put-on and take-off procedure.

3.10 Template Nocturnal Study Consent Form

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

Patient Consent Form

TITLE: Frequent Hemodialysis Network: Nocturnal Hemodialysis Study

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

INSTITUTION: **Wake Forest University Health Sciences**

SPONSOR: National Institutes of Health (NIH)

IRB PROTOCOL NO.: **xxxx**

Principal Investigator: **Dr. John Burkart**

Co-Investigator: **Dr. Michael Rocco**

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. If you would like more detailed information 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 nightly home hemodialysis treatments (6 times a week, 6 to 8 hours per dialysis session) improves the health of patients on hemodialysis compared to conventional hemodialysis treatments (3 times a week, 3 to 5 hours per session). 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 Dr. John Burkart, 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 and experiences with nightly home hemodialysis treatments. However, these improvements have not been tested in a large trial conducted in many different centers that will allow scientists to determine if these possible benefits are due to the increased number of hemodialysis treatments and the increased length of hemodialysis treatments. 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 to 5 hours per session) or to have ***nightly home*** hemodialysis (6 days per week for 6 to 8 hours overnight per session, with dialysis performed at home). Half the patients will undergo nightly home hemodialysis. If you decide to participate and meet our study entry requirements, you will be enrolled in the study for 14 months.

The main goals of the research are to measure:

1) The change over 14 months in your Quality of Life and,
2) The change over 14 months in your heart size as 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 Insert dialysis units here and other dialysis units as necessary.

The study will begin inviting patients to participate during the second half of 2005 and will continue for 3 to 4 years. You will be asked to follow your assigned therapy for 14 months once you decide to participate. The study team may contact you every 6 months thereafter to inquire about your current health status and ask you some questions about your quality of life.

3. Study Procedure:

Once you agree to participate and sign the Informed Consent Form we will collect your demographic information (which includes age, gender, race, etc.), insurance data, medical records, treatment records, laboratory records and perform blood and urine tests, and record your monthly lab data. This information will be used to determine whether you fulfill all the requirements for you to continue with the study.

All these baseline tests will be performed within 3 weeks up to a maximum of 8 weeks after you agree to participate. We will also address specific concerns about any renovations that you may need to have done in your home in order to do your hemodialysis treatments at home.

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 we will ask you several questions about the reason(s) why you are not able to continue in the study.

During the 14 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 14 months. Some of them will be repeated more frequently as noted below.

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 and every month thereafter, just as they being done now. If you are randomized to the nocturnal arm of the study, additional bloodwork will be obtained in the first two months after you go home to allow your doctor to monitor you treatments at home.

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 5^{th} and 14^{th} month.

c) You will undergo a scan of your heart using the MRI machine at baseline and after 14 months. This scan will be done at The Wake Forest MRI center, which is located about 3 miles from the home hemodialysis training unit, 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 will require that a separate consent be signed for the MRI test.

d) You will be asked to answer questions over the telephone about your health and your quality of life at baseline and at the 5^{th} and 14^{th} months of the study. These questions will take about 30 minutes to answer.

e) If you are physically able, you will be asked to walk down a corridor, to rise 5 times from a chair and to stand to test your balance.

f) 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 at the 3rd 5^{th} and 14^{th} months of the study. There are no known risks associated with Bioelectrical Impedance Analysis.

g) You will be asked to measure your blood pressure at home using an automated blood pressure machine. You will be given this blood pressure machine as part of the study. You will be shown how to use this device. We will ask you to record your blood pressure at home at baseline and at the 5^{th} and 14^{th} months of the study. For each of these time periods, we will ask you to record 12 blood pressure readings during a 48 hour period in the

middle of the week and 12 blood pressure readings during a 48 hour period during the weekend.

h) You will be asked to provide a list of all the medications you take at baseline and at the 5^{th}, 9^{th} and 14^{th} months.

i) 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.

j) 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 about 35 mL (about 3 tablespoons).

Details of specific tests are available to you upon request.

4. Potential Benefits of Nightly Home Hemodialysis:

Regardless of your treatment assignment, participating in the study will ensure that you will receive adequate dialysis treatment. The potential benefit to you is that the treatment you receive may prove to be more effective than your current treatment although this cannot be guaranteed. In the past, small studies have shown that more frequent hemodialysis at home may improve:

a) Blood Pressure: Most patients who have high blood pressure have been able to control blood pressure. Many patients will take less medication and some don't need to take any medication for blood pressure.
b) Heart Size: Many patients on hemodialysis have heart disease with mild to moderate heart enlargement. In some of these patients heart size may decrease or further heart enlargement prevented.
c) Nutrition: Many patients claim improvement in appetite and increased food and fluid intake. The therapy may allow more freedom in the choice of food as well. Many patients will no longer need to take phosphate binders.
d) Physical and Mental Function: Some patients claim increased energy and physical activity. This may go hand-in-hand with improved mental state, emotional state, and general quality of life.

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.

5. Potential Risks of Nightly Home Hemodialysis

The possible risks and discomforts of nocturnal dialysis and this research study include:

1. Disconnection of the dialysis needles or tubing from you dialysis access (fistula, arteriovenous graft or catheter): A gauze mesh is used to secure the dialysis tubing and needles to your fistula and arteriovenous graft. A locking device is used to secure the dialysis tubing to the catheter. Despite these precautions, it is still possible that there could be a loss of blood from disconnection of these devices, resulting in blood loss, air embolism (air in the bloodstream) and possibly death.

2. Infection from the dialysis catheter. If you choose to receive your nocturnal dialysis from a catheter instead of a fistula, you may be at increased risk of infection. In patients receiving hemodialysis at dialysis centers, patients with catheters for dialysis have a higher rate of infection of the blood than patients with fistulas that are used for dialysis. Whether this increased risk is also seen in patients on nightly home hemodialysis is not known.

3. Abnormal laboratory values: Some patients on nocturnal dialysis may develop a low potassium level or a low phosphorus level. We will be able to minimize any complications from these low levels by checking your blood work on a regular basis. A low potassium or phosphorus level can cause an irregular heartbeat, weakness and fatigue. If either your potassium level or phosphorus level becomes low, you will meet with the dietitian to receive instruction in a diet higher in these minerals. A low level of these minerals can also be corrected by either oral medications or by adjusting the amounts of these minerals in your dialysate. The decision on how to treat the low levels of these minerals will be made by your kidney doctor.

4. Hypotension, cramping, nausea and vomiting: These are symptoms that can be associated with any hemodialysis treatment. You may have fewer or less severe symptoms on nocturnal dialysis due to the lower blood flows and longer times on the hemodialysis machine.

5. Volume overload. Although you will be receiving dialysis six times per week, it will still be important for you in regulate your fluid intake.

Excessive fluid intake may result in fluid retention, swelling of the legs and shortness of breath.

6. Iron Losses: More time on dialysis could lead to more iron loss. Your iron stores, however, will be monitored regularly and iron supplements will be given as needed.
7. Loss of Nutrients: There may be increased loss of water-soluble vitamins and other nutrients. This loss may be compensated by an increase in appetite that has been seen in small studies. All patients will be prescribed daily multivitamins to help minimize these losses.
8. 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 been shown that some patients get energized with the therapy.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data for this research throughout the study.

6. Pregnancy

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, Norplant, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method involves the careful use of condoms and a spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. If you are a sexually active woman of childbearing potential and have not been using an accepted method of birth control, two negative pregnancy tests performed 15 days apart are required to check for possible early pregnancy prior to starting treatment

7. Alternative Therapies:

If you decide not to participate in this study, you can receive dialysis by either in-center hemodialysis three times per week or peritoneal dialysis daily. You will receive all standard therapy and medical care that is provided for patients with end-stage renal disease, whether or not you participate in this study.

8. Costs:
If you are randomized to standard hemodialysis, you will not incur any additional costs if you participate in this study. If you are randomized to nocturnal hemodialysis, you may incur additional costs:

1) Your living quarters may need some changes so that a hemodialysis machine can run in your bedroom. These renovations may include changes to your electrical and/or plumbing system. In prior studies, these costs have been, on average, between about $100 to $1000 in US dollars. Your home dialysis training center can give you more information about these costs for your particular living situation and whether you can be reimbursed for some of these costs.
2) You may have higher electricity and water costs due to running the hemodialysis machine at home.

You will not be charged for any extra doctor's visits, blood work, tests or procedures during this study. You will not be compensated for participation in this study. You will be reimbursed $75 for travel for your 5 month and 14 month visits if you live more than 25 miles from the home hemodialysis center.

9. Compensation for Injury:
Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. The Steadfast Insurance Company provides the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim. The Wake Forest University School of Medicine, and The North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. John Burkart at (336) 716-4650 (24 hour phone number).

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 Hospital name/ Dialysis Center Name, 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 Dr. John Burkart at 336-716-xxxx. For your own safety, we recommend that you should have all the studies scheduled to be done at month 14 of the study (the tests listed in section 3. above) performed at the time you withdraw from the study.

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.

If you are not interested in the trial or will not qualify during the screening, you will be invited to sign a "Screened Trial Non-Participant" form

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, as consistent with the Health Insurance Portability and Accountability Act of 1996.

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. John Burkart at 336-716-xxxx or your study coordinator Teresa Hoosier at 336-xxx-xxxx..

If you have any questions about the informed consent process or my rights as a research subject then I should contact the Chairman of the Institutional Review Board at (336) 716-4542.

.

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.

Patient Signature: _____

Print Name: _____Date: _____

Signature of person obtaining consent: _____

Print Name : _____Date: _____

Investigator Approval Signature: _____

Print Name : _____Date: _____

Once you have signed this consent form we will ask your additional consent for:

1) Permission for your personal health information by the study investigators with the sponsors.

2) Permission to sign 'Release of Information" form allowing us to obtain information from all the centers that have provided your care.

3) Permission to store blood and urine samples for future biochemical testing.

Your willingness to consent (or deny consent) to numbers 3,4, and 5 will not affect your general participation in the study.

Appendix 1

PROTOCOL SIGNATURE PAGE

Protocol Title:	Frequent Hemodialysis Network – Nocturnal Trial
IDE:	G050161
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
Cleveland, OH 44195

Nocturnal Study

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.

Study Visit: Baseline Visit

Detailed description of what is expected from the Baseline Visit

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.

   If applicable, explain in detail the ancillary studies and the storage of repository blood for future research.

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 explain the Bill of Rights.

   A separate consent may be signed for HIPPA, storage of blood and ancillary studies.

c) Once the subject has signed the FHN consent form, make sure that the participant's primary care
   nephrologist is notified by email or fax.

TIP: In order to access the participant's chart as quickly as possible after an SAE occurrence, it may be wise to have the participant sign a medical release of information at this visit.

IF PARTICIPANT CONSENTS:

Assign the participant with an ID number from the list of IDs set up by the DCC for each participating site. The ID number is 6 digits and the first 4 represent the participating site number. The last 2 digits are sequentially assigned numbered, starting from 01 to 99. For example, for LHSC-WC participating site 4001, the numbers 400101 through 400199 will be set up (i.e. PATIENT 1 = ID# 400101). Once an ID number has been assigned to a specific participant, this participant CANNOT be assigned a different number throughout the study and this number CANNOT be reused for another participant in the study. Once the screening form (Form 100) 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. Please refer to the MOP, section 5, for further instructions.

Form 100 - Review inclusion/exclusion criteria
This form establishes the patient as a participant in the study. Once Form 100 is entered into the database, the participant is assigned a 2-digit alpha-code. Each participant's assigned alpha code will need to be documented, along with the participant ID number on all forms.

The participant's emergency contact information is captured on this form. Emergency contacts must be available 24hrs, have access to the participant at his location and aware of emergency mental health resources.

Form 107 – Direct Patient Contact Form
This form is electronically submitted to the Quality of Life (QOL) Interviewing Center.

To let the QOL Interviewing Center know that you have a patient ready for interview, access the following website and enter the requested information.
https://surveyweb2.ucsur.pitt.edu/DialysisQOL/

Your Center ID is:
Your Password is: <password>

If you have any questions regarding this website, please send an email to survey@pitt.edu.

Form 108 – Patient Future Linkage – US Sites
If participant refuses to provide a social number, they may still participate in the study. If participant discloses social security number, complete form and ship by traceable courier to the USRDS.

Form 109 – Coming Soon! – Canadian Sites

CHART REVIEW

Form 104 – Co-Morbidity Assessment and Medical History
To be completed by the participant's physician. The physician may provide the study coordinator with a compiled list of the participant's medical history. Once the study coordinator has transferred the med history information onto the data collection sheet, an MD associated with FHN should review and sign off. In the case that the participant's physician does not contribute in any way to this form, the corresponding FHN physician, associated with that clinical center, needs to review the participant's medical chart(s).

Form 203 – IV Iron Therapy

IV iron (dose, frequency, cumulative monthly dose)

Form 204 - Injectable Medications Form

Erythropoeitin/Darbopoeitin (route, frequency, weekly dose, cumulative monthly dose) and IV vitamin D metabolites (frequency, weekly dose)

Form 205 - Medications and Supplements Form
Phosphate binders (daily dose) and other OTC medications. Exclude IV iron, synthetic IV and SC erythropoietin, and vit D analogues.

Form 207 – Local Biochemistry Form
Collect the following information: Pre dialysis hemoglobin, calcium, bicarbonate, sodium, potassium, ferritin, transferrin saturation and parathyroid hormone.

Form 271 – Patient's Access at Start of Study
If the participant has more than one access, ensure that the access captured on this form is presently being used.

This form must be must be completed at baseline as well as whenever the participant's access changes.

PATIENT SUITABILITY – To be completed by the home assessment team

Form 101 – Nocturnal Trial Evaluation of Home Environment
This will include an assessment of the participant's water, plumbing and electrical suitability.

Form 102 – Nocturnal Trial Evaluation of Patient and Caregiver
This will include an assessment of the participant's level of literacy and motivation, and also his motor skills, vision, hearing and stamina.

BLOOD PRESSURE
For further detail, please refer to the email sent out by Brett Larive January 20, 2006.

Ask the participant which days and what times he/she currently dialyzes. This data is entered into Form 213. A collection worksheet will be generated with a schedule of times when the participant should record blood pressure readings (Form 214).

Form 213 – Nocturnal Study Generating Patient Home BP Worksheet

Enter data on this form to generate a participant worksheet.

Form 214 – Patient Home BP Collection Worksheet
Explain to participant in detail how you want him/her to check blood pressures.
Demonstrate use of the Omron Blood pressure machine. Give participant generated worksheet.

Form 215 – Nocturnal Study 2-Day Home BP
Enter BP information into the computer

KINETIC MODELING

Form 206 – Residual Renal Function

Obtain a urine specimen to evaluate GFR. This will be an interdialytic specimen sent for urea, creatinine and phosphorus. The timed urine should be collected for every participant producing at least 80ml/24 hrs. If less than 80 ml, the sample does not need to be measured by the local lab.

GFR must be greater than 10ml/min/1.73m² as measured by the average of urea and creatinine clearances.

The duration of the timed urine collection is optional as long as it is at least 24 hours.

Ensure participant is given proper instructions and a 3000cc container prior to urine collection.

Form 273 – Kinetic Modeling

Perform kinetic modeling**.** If the delivered eKt/V of at least 1.10 in the baseline kinetic modeling is less than 1.1, then an additional kinetic modeling session may be scheduled and the mean delivered eKt/V recomputed from these two baseline sessions. This process may be repeated up to 4 times and the minimum eKt/V requirement is met if at any of these tries the average eKt/V for the final two assessments exceeds 1.10.

Obtain lab work to determine Kt/V
Pre dialysis serum albumin, BUN creatinine and phosphorus
Post dialysis BUN, creatinine and phosphorus

The minimum dialysis dose in the standard arm will be an eKt/V of 1.1 for at least 2 of 3 consecutive sessions, and a minimum time of 2.5 hours. In the nocturnal arm there will be a minimum prescription of 6 hours per session for 6 days a week and a minimum standardized Kt/V of 4.0.

Form 274 – Retrospective Dialysis Run Sheet Data

The dialysis run sheet should be reviewed for the 1-week period preceding theB-01 kinetic modeling session in order to record information concerning treatment times, blood pressure, weight, and hypotensive symptoms for each dialysis treatment performed during this period. The 1-week period for retrospective data collection ends on the day prior to the kinetic modeling session.

A “hypotensive episode” is defines 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 participant’s dialysis session lasting 15 min. or greater.

TESTS AND QUESTIONNAIRES

Form 105 - Baseline Demographics, Employment, and Income

Record the participant’s response

Form 406 – Consent for Repositories
To be completed for every participant consented to the trial, even if he/she refused to participate in sample repository.

Form 255(USA) 256 (Canada) – Biological Specimen Repository Mailing Form
For participants who have consented to collection of biological specimens for the repository, obtain extra blood samples, spin the blood tubes, aliquot and store in –80 freezer (Canadian sites), and fill out this form.

Ship samples to the repository as stipulated. Please ensure that the sample is sent early in the week in order to avoid a weekend arrival. Once a shipment has been sent, notify the repository by email or facsimile. Include the expected arrival date and waybill number.

QOL FORMS – READ MOP PRIOR TO ADMINISTERING ANY TEST
Administered pre-dialysis or six hours post
If you wish, these forms may be divided into 2 sessions.

Form 230 - Feeling Thermometer results – 1ST QOL test administered
Participant must draw a line from the dot to the number, which represents his/her imaginable health state at this particular moment.

Form 231 - Modified Mini Mental Status
To be completed in a quiet place, with minimal distractions. Follow all scripts provided for the examiner.
Ensure to bring an extra pen, stop watch, at least 2 blank sheets of paper, and the flash cards (close your eyes and the pentagons).

Form 232 - Trail Making B Form

To be completed in a quiet place, with minimal distractions. Follow all scripts provided for the examiner.
Ensure to bring pencils with eraser and stop watch.

Form 233 - Clinical Center Miscellaneous Questions
This form allows the database to identify participants that did and did not consent to provide linkage information to the USRDS. The database cannot assume a participant did not consent because there is no form 108 or 109 in the system.

Employment Status change is to be completed at the end of the trial. Record participant employment status, whether or not it has changed since baseline, and if the participant's employment status has changed, if so provide explanation.

Form 234 - FHN Combination Physical Function Tests

To be completed in a space which will allow you and the participant to walk side by side in a straight line for 4 meters. Follow all scripts provided for the examiner. Ensure to bring stop watch, pen, measuring tape and chair.

If you wish, these forms may be divided into 2 sessions.

BIOIMPEDANCE TEST

Performed pre -dialysis, mid-week

Form 242 – Single Frequency Bioelectric Impedance (BIA) Assessment
Ensure that an examining table is available for the participant.

CARDIAC MRI

Form 250 – Dialysis Session Before MRI

Completed after the MRI is performed. Data is obtained from the last dialysis treatment before MRI.

Form 251 – Cardiac Mailing Form
Items 1-6 completed by Study Coordinator
Items 7-35 completed by MRI technician

When this form is complete, it should be photocopied. Send the copy of the form along with the MRI images to CICL. Maintain the original form with the participant's other completed study forms.

The coordinator should have 2 CDs of the MRI. One CD is shipped to the CICL (as mentioned above) and the other is kept with the participant's records.

Form 252 – MRI Central Data Entry Form

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

DROP OUT FORM

Form 103 – Nocturnal Trial Pre-Randomization Dropout

Fill out form if a participant has proven to be ineligible for the trial after signing the consent.

FORMS COMPLETED BY THE QOL INTERVIEWING CENTER

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

The DCC computes scores based on HRQOL interview data and determines if the participant is eligible to participate in the trial. If eligible, participant is randomized.

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.

During the baseline and follow-up periods, additional forms may need to be completed in the event of serious adverse events (SAE), AE, access problems, protocol deviations etc. (See appendix A)

2. Month 1: Follow-upVisit 1 (F-01)

Detailed description of what is expected from F-01 – Month 1

NOCTURNAL PARTICIPANTS

Form 201 – Nocturnal Study Results of Training
This form is administered after the participant has successfully completed their first nocturnal dialysis session.

Form 207 – Local Biochemistry Form
Collect the following information: Pre dialysis hemoglobin, calcium, bicarbonate, sodium, potassium, ferritin and transferrin saturation.

Kinetic Modeling

The schedule for the kinetic modeling during follow-up is based on calendar month. The calendar month following the month in which the participant is randomized is designated as F-01, with the subsequent month designated as F-02, and so on.

Form 273 – Kinetic Modeling Form
Kinetic Modeling described above.

Form 274 – Retrospective Dialysis Run Sheet
The periods for the retrospective review extend for one week prior to the kinetic modeling session (i.e.
Participants undergoing 6 times per week nocturnal dialysis, the 6-dialysis treatments preceding (but not
including) the kinetic modeling session should be captured on this form).

*******Unless the participant is being monitored centrally, he/she will have to provide a weekly copy of their run sheets to the home hemodialysis training center. This information should also be reviewed by the PI for each clinical center to determine if participant is compliant with assigned therapy and also for safety evaluations.

CONVENTIONAL PARTICIPANTS

Form 207 – Local Biochemistry Form
Collect the following information: Pre dialysis hemoglobin, calcium, bicarbonate, sodium, potassium, ferritin, transferrin saturation and parathyroid hormone.

Kinetic Modeling

For participants randomized to the conventional in-center HD group, it is desirable, if arrangements can be made, that the modeling sessions be conducted during mid-week dialysis sessions (either Wednesday or Thursday), but
for logical purposes, it is recommended that the FHN kinetic modeling sessions coincide with the dialysis clinic's usual monthly kinetic modeling sessions to avoid additional blood draws.

Form 273 – Kinetic Modeling Form
Kinetic Modeling described above.

Form 274 – Retrospective Dialysis Run Sheet
The periods for the retrospective review extend for one week prior to the kinetic modeling session (i.e.
Participants undergoing 3 times per week conventional dialysis, the 3-dialysis treatments preceeding (but
not including) the kinetic modeling session should be captured on this form.

In-center Attendance

Form 275 – Attendance at In-Center Dialysis Sessions
This form is completed by the coordinator at the start of each calendar month following randomization in
order to document missed dialysis treatments during the prior calendar month.

3. Follow-upVisits for F-02, F-03 F-04, F-06, F-07 F-08 F-10, F-11, F-12, F-13

Complete the following forms as described above.

Nocturnal Participants:
Form 207
Form 273,

Form 274

Conventional Participants:
Form 207
Form 273
Form 274
Form 275

Pre-dialysis transferritin, ferritin and PTH may be captured any time during the following time intervals:
F1-F3, F4-F6, F7-F9, F10-F12, F13-F14

4. Month 5: Follow-up Visit 5 (F-05) and Visit 14 (F14)

FOR ALL PARTICIPANTS (Nocturnal and Conventional)

Medications:

Form 203 – IV Iron Therapy

IV iron (dose, frequency, cumulative monthly dose)

Form 204 - Injectable Medications Form

Erythropoeitin/Darbopoeitin (route, frequency, weekly dose, cumulative monthly dose) and IV vitamin D metabolites (frequency, weekly dose)

Form 205 - Medications and Supplements Form

Phosphate binders (daily dose) and other OTC medications. Exclude IV iron, synthetic IV and SC erythropoietin, and vit D analogues

Blood Pressure Measurements:

Form 213 – Nocturnal Study Generating Patient Home BP Worksheet

Enter data on this form to generate a patient worksheet.

Form 214 – Patient Home BP Collection Worksheet

Explain to patient in detail how you want him/her to check blood pressures. Demonstrate use of the Omron Blood pressure machine. Give patient worksheet.

Form 215 – Nocturnal Study 2-Day Home BP

Enter BP information into the computer.

Laboratory Measurements:

Form 207 – Local Biochemistry Form

Collect the following information: Pre dialysis hemoglobin, calcium, bicarbonate, sodium, potassium, ferritin, transferrin saturation and parathyroid hormone.

Form 255(USA) 256 (Canada) – Biological Specimen Repository Mailing Form

For participants who have consented to collection of biological specimens for the repository, obtain extra blood samples, spin the blood tubes, aliquot and store in –80 freezer (Canadian sites), and fill out this form.

Ship samples to the repository as stipulated. Please ensure that the sample is sent early in the week in order to avoid a weekend arrival. Once a shipment has been sent, notify the repository by email or facsimile. Include the expected arrival date and waybill number.

Form 273 – Kinetic Modeling Form

Kinetic Modeling described above

Kinetic Modeling

The schedule for the kinetic modeling during follow-up is based on calendar month. The calendar month following the month in which the participant is randomized is designated as F-01, with the subsequent month designated as F-02, and so on.

Form 206 – Residual Renal Function

Obtain a urine specimen to evaluate GFR. This will be an interdialytic specimen sent for urea, creatinine and phosphorus. The timed urine should be collected for every participant producing at least 80ml/24 hrs. If less than 80 ml, the sample does not need to be measured by the local lab.

GFR must be greater than 10ml/min/1.73m² as measured by the average of urea and creatinine clearances.

The duration of the timed urine collection is optional as long as it is at least 24 hours and extends to the start of the kinetic modeling session.

Form 274 – Retrospective Dialysis Run Sheet

The periods for the retrospective review extend for one week prior to the kinetic modeling session (i.e.

Participants undergoing 6 times per week nocturnal dialysis, the 6-dialysis treatments preceeding (but not

including) the kinetic modeling session should be captured on this form).

*******Unless the participant is being monitored centrally, he/she will have to provide a weekly copy of their run sheets to the home hemodialysis training center. This information should also be reviewed by the PI for each clinical center to determine if participant is compliant with assigned therapy and also for safety evaluations.

QOL FORMS

Administered by the study coordinator

Should be administered pre-dialysis or 6 hours post

Form 230 - Feeling Thermometer results
Form 231 - Modified Mini Mental Status

Form 232 - Trail Making B Form

Form 233 - Clinical Center Miscellaneous Questions
Form 223 - Clinical Center Miscellaneous Questions
Form 234 - FHN Combination Physical Function Tests

Administered by the HRQOL Interviewing Center

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

***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

BIOIMPEDANCE TEST

Performed pre -dialysis, mid-week

Form 242 – Single Frequency Bioelectric Impedance (BIA) Assessment

CARDIAC MRI (F-14)

Form 250 – Dialysis Session Before MRI

Completed after the MRI is performed. Data is obtained from the last dialysis treatment before MRI.

Form 251 – Cardiac Mailing Form
Items 1-6 completed by Study Coordinator
Items 7-35 completed by MRI technician

When this form is complete, it should be photocopied. Send the copy of the form along with the MRI images to CICL. Maintain the original form with the participant's other completed study forms.

The coordinator should have 2 CDs of the MRI. One CD is shipped to the CICL (as mentioned above) and the other is kept with the participant's records.

Form 252 – MRI Central Data Entry Form

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

NOCTURNAL PARTICIPANTS

Form 209 – Participant Dialyzing at Home Log Sheet
This form is given to the participant along with a self-addressed stamped envelope at the participant's scheduled clinic visit. At the end of the week, the participant should mail completed form to the study coordinator.

Form 212- Nocturnal Trial Patient's Water Quality Monitoring
This form is to be completed by the home assessment team. Arrange date and time for this to occur.

***Note that Day 1 of data collection coincides with the participant's scheduled clinic visit irrespective of whether the participant dialyzes or not that evening.

CONVENTIONAL PARTICIPANTS

Form 208 – Participant In-Center Log Sheet
For conventional participants, dialysis sessions 1, 2, and 3 will need to be captured on this form. The study coordinator may either pick up completed form at the dialysis center or provide a self-addressed stamped envelope.

Form 275 – Attendance at In-Center Dialysis Sessions
This form is completed by the coordinator at the start of each calendar month following randomization in
order to document missed dialysis treatments during the prior calendar month.

5. <u>Month 9: Follow-up Visit 9 (F-09)</u>

FOR ALL PARTICIPANTS (Nocturnal and Conventional)

Medications:

Form 203 – IV Iron Therapy

IV iron (dose, frequency, cumulative monthly dose)

Form 204 - Injectable Medications Form

Erythropoeitin/Darbopoeitin (route, frequency, weekly dose, cumulative monthly dose) and IV vitamin D metabolites (frequency, weekly dose)

Form 205 - Medications and Supplements Form

Phosphate binders (daily dose) and other OTC medications. Exclude IV iron, synthetic IV and SC erythropoietin, and vit D analogues

Laboratory Measurements:

Form 207 – Local Biochemistry Form

Collect the following information: Pre dialysis hemoglobin, calcium, bicarbonate, sodium, potassium, ferritin, transferrin saturation and parathyroid hormone.

Form 273 – Kinetic Modeling Form

Kinetic Modeling described above

Form 274 – Retrospective Dialysis Run Sheet

The periods for the retrospective review extend for one week prior to the kinetic modeling session (i.e. Participants undergoing 3 times per week conventional dialysis, the 3-dialysis treatments preceding (but not including) the kinetic modeling session should be captured on this form).

CONVENTIONAL PARTICIPANTS

In-center Attendance

Form 275 – Attendance at In-Center Dialysis Sessions

This form is completed by the coordinator at the start of each calendar month following randomization in order to document missed dialysis treatments during the prior calendar month.

Appendix A

PARTICIPANT IS UNWILLING OR UNABLE TO CONTINUE FOLLOWING THE 6X/WEEK DIALYSIS PRESCRIPTIONS STIPULATED BY THE PROTOCOL

All participants will be strongly advised throughout the study to adhere to the randomized therapy. If deviations from the protocol occur during the course of the trial, protocols will be developed to treat such deviations in a standardized manner. Efforts to develop a dialysis prescription which approximates 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 (Table 1) will be implemented. If the participant remains unwilling or unable to maintain a 6x/week dialysis schedule following consultations with the study team, the participant will be encouraged to dialyze 5x/week with a treatment time sufficient to maintain the minimum dose of sKt/V. If the 5x/week schedule is also unattainable, the participant will be permitted to dialyze 4x/week. If a reduced time schedule is adopted (one of options 1-4), the study staff will periodically discuss the treatment options with the participant to determine if the participant is willing or able to return to the full 6x/week nocturnal regimen specified in the protocol. Participants will continue to be followed for all data collection, irrespective of their adherence to the randomized therapy (intent to treat analysis).

Please remember to document the reason (i.e. burnout/fatigue, home social situations, etc.) and the newly adapted dialysis schedule.

Table 1: Stepped Options for Modifying 6x/week Nocturnal Hemodialysis Schedule

Option #	Description of Options
1	Maintain 6x/week treatment schedule, but reduce treatment time to the projected total weekly treatment time or an amount acceptable to the participant, subject to: a) minimum session length ≥ 6 hours.
2	Adopt a 5x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the participant's such that the projected weekly sKt/V approximates the participant's target sKt/V as closely as possible.
3	Adopt a 5x/week treatment schedule, without increasing the time per treatment, so long as a) minimum session length ≥ 6 hours.
4	Adopt a 4x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the participant such that the projected weekly sKt/V approximates the participant's target sKt/V as closely as possible.

Complete **Form 309**-Planned Therapy Deviation prior to planned reduction dialysis treatment schedule if

a) The participant plans to miss more than 4 treatments during the next month **OR**
a) The participant plans to miss an average of at least 30 minutes or more treatment time for a period of at least a week **OR**
b) Both a) and b)

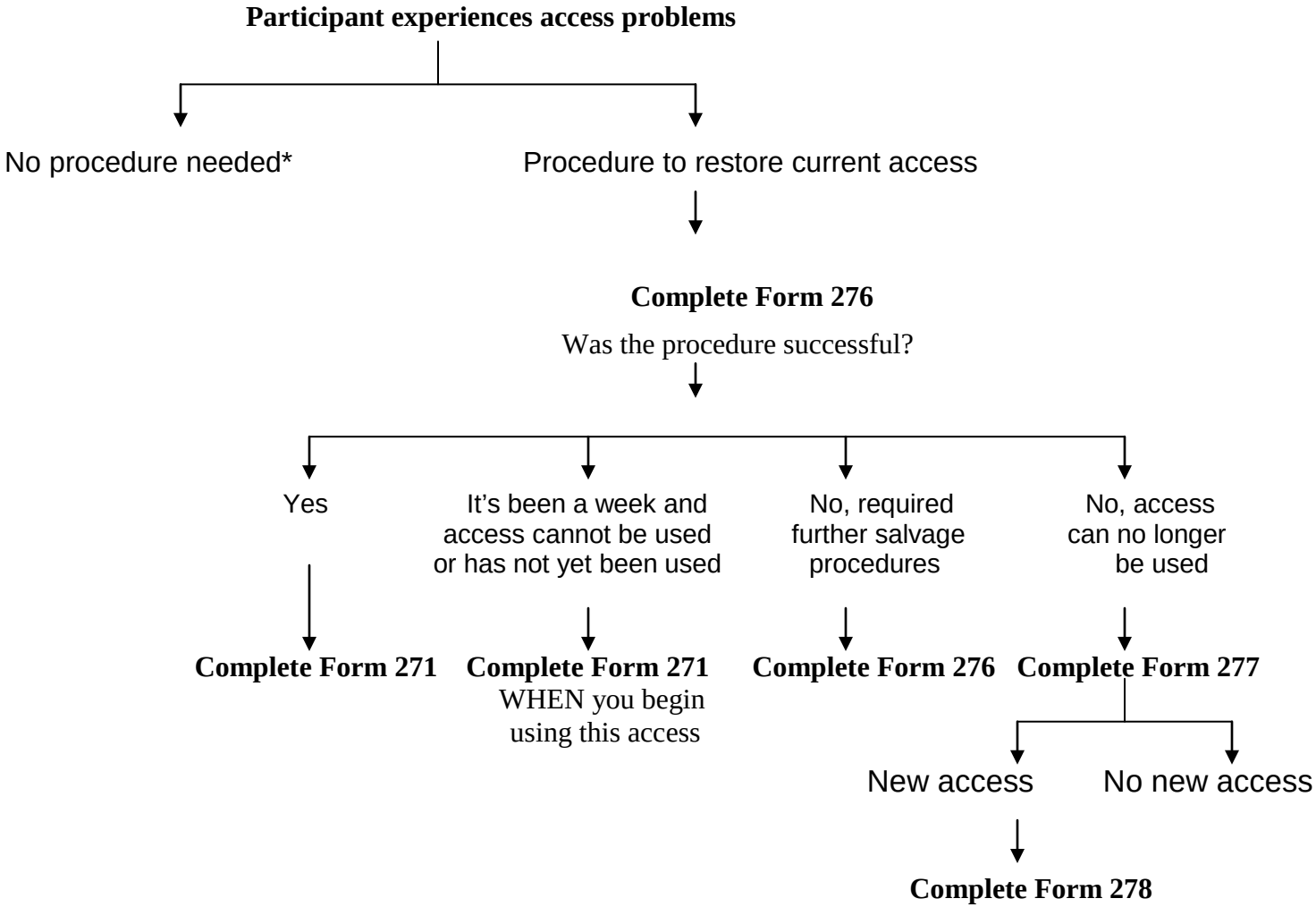
Complete **Form 310-**Detected Therapy Deviation Form if the database has identified that
a) The participant has missed a scheduled dialysis treatment **OR**

b) The participant has shortened the prescribed length of a dialysis treatment

Speak with participant and rectify problem(s) (if any) as soon as possible!!

******Treatment deviations due to hospitalizations are not counted******

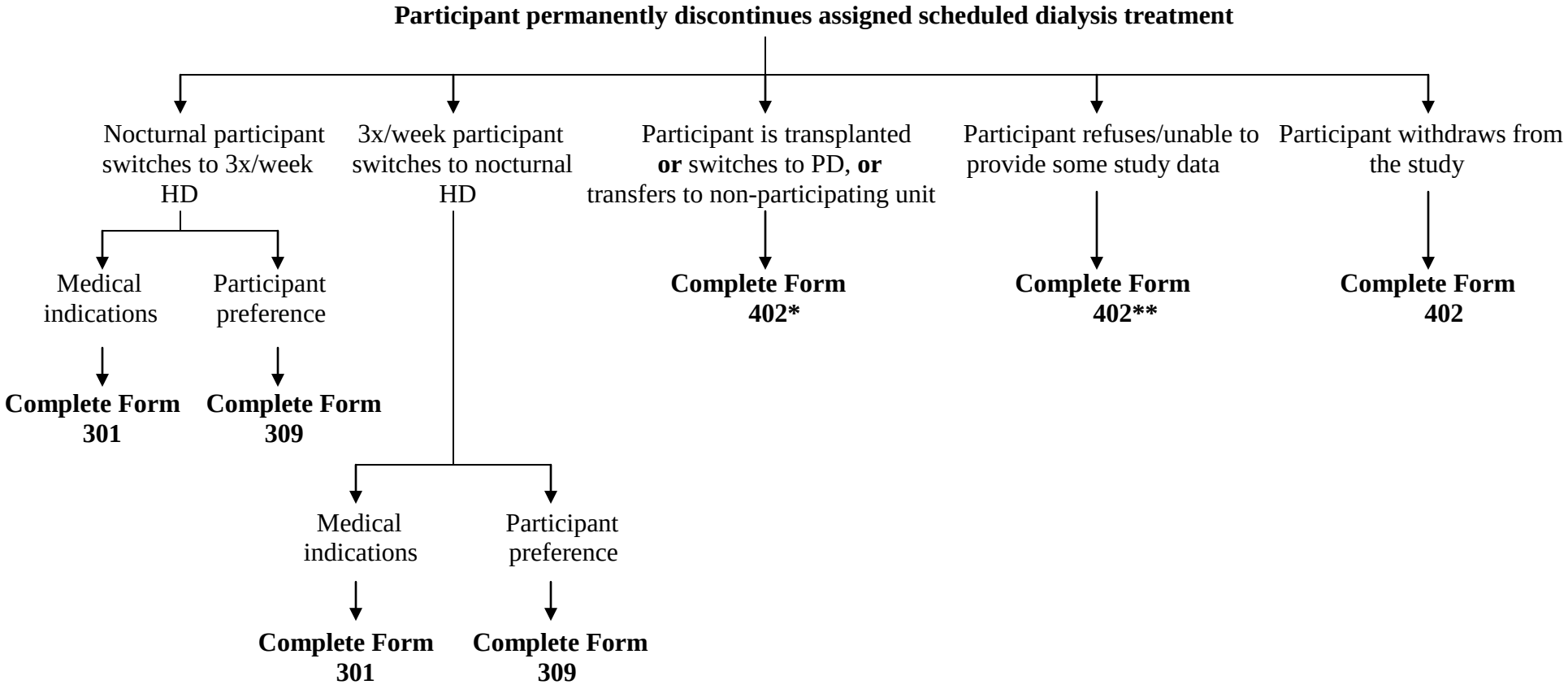
PARTICIPANT ACCESS PROBLEMS



*The following **DO NOT** count as access repair procedures: diagnostic venogram without any other procedures, tPA administration, line reversal, procedures done in the dialysis unit, angioplasty of a central vein or stent placement on a central vein

If participant is hospitalized, complete Forms 303 and 308.
If participant dies, complete Forms 306 and 308.

PARTICIPANT PERMANENT DISCONTINUATION/SWITCH OF THERAPY DUE TO MEDICAL INDICATION



*Participants relocating to non-participation dialysis units during their 14 month follow-up, all attempts will be made to collect vital status, the two co-primary outcomes, and the centrally administered QOL questionnaires. If participant transfers to participating dialysis unit – complete Form 400

**Prior to completing Form 402 for participant's refusing to provide study data, a physician should speak to the participant and explain that these data are valuable whether the participant is adhering to his or her randomized treatment group or not.