Frequent Hemodialysis Network (FHN)

Nocturnal Trial Protocol

Version 3.3 October 15, 2009

Table of Contents

Executive Summary

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.

Because no previous randomized trials of nocturnal dialysis have been conducted, the first calendar year after the initiation of enrollment has been designated as a "Vanguard" phase during which feasibility of randomization and conduct of the interventions will be evaluated. If pre-defined benchmarks for establishment of feasibility are achieved during the Vanguard phase, the trial will proceed to its primary objective of determining if nocturnal HD results in clinically significant improvements in physiological, health-related quality of life (HRQL) and functional outcomes, as compared with home conventional HD.

The initial target sample size was 250 randomized patients. This was reduced to 150 in October 2007 and further reduced to 90 in December 2008 as recommended by the Data, Safety and Monitoring Board. The consortium of Clinical Centers will randomize patients in a 1:1 allocation to either six times per week home nocturnal hemodialysis or home hemodialysis conducted according to a conventional three times per week treatment schedule (subsequently referred to as conventional home hemodialysis). This consortium has extensive experience with nocturnal home hemodialysis (more than 300 patient-years) and standard home hemodialysis and includes the largest nocturnal home hemodialysis programs in the United States and in Canada. Patients for this trial will be drawn from a universe of more than 11,000 patients from Clinical Centers located in the Eastern and Midwestern United States and in Canada.

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 3 times per week home 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 home hemodialysis on two co-primary outcomes:
    i) A composite of mortality with the change over 12 months in LV mass as measured by cardiac MRI
    ii) A composite of mortality with the change over 12 months in the SF-36 RAND physical health composite (PHC)
5) The effects of the interventions on seven secondary outcome domains: 1) cardiovascular structure and function (change in LV mass), 2) health-related quality of

life/physical function(change in the PHC), 3) depression/burden of illness (change in Beck Depression Inventory), 4) nutrition and inflammation (change in serum albumin), 5) cognitive funtion (change in the Trailmaking Test B), 6) mineral metabolism (change in average predialysis serum phosphorus), and 7) 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 home hemodialysis, including measures of solute clearance, treatment time, volume removal, and non-dialytic components of the interventions

7) 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 six times per week nocturnal home HD compared to conventional three times per week home HD will be estimated, and cost-effectiveness and cost-utility ratios of the two therapies will be compared.

Patients assigned to the conventional three times per week home 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, 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 4.2 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 conventional home three times per week hemodialysis groups including a standardized Kt/V of 5.21 versus 2.30; an equivalent renal clearance of β_2-microblogulin (relative to time-average concentration) of 9.03 versus 4.73 ml/min/35 L; a standardized phosphorus removal of 1281 versus 299 mg/day; a total weekly treatment time of 45.6 versus 10.50; and an ultrafiltration rate of 3.32 versus 13.48 ml/min.

Data to be obtained in the trial includes kinetic modeling visits held at baseline and monthly throughout the 12 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, IV iron dose, and vitamin D). Measures of quality of life, depression, physical function, and cost-effectiveness will be obtained at baseline and months 4 and 12. Bioelectric impedance will be performed at baseline and at months 4 and 12. Cardiac MRI will be obtained at baseline and month 12. Medical comorbidity assessment will be obtained at baseline.. 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.

1. Background and Rationale

1.1 Scope of the Problem

Although there has been an improvement in mortality rates in hemodialysis patients in the United States during the past ten years, these rates remain unacceptably high. The first year mortality rate in hemodialysis patients has declined only 10% in the past ten years and has not improved significantly since 1996. Second year death rates have declined only 15% in this same time span, with a similar lack of improvement since 1996. Despite these modest improvements, the annual mortality rate for hemodialysis patients remains above 15%. [USRDS, 2001] Therefore, new innovative therapies are needed to improve the mortality and morbidity rates in chronic dialysis patients.

1.2 Increasing Dialysis Dose on Conventional Hemodialysis Does Not Improve Outcomes

Previous observational studies had suggested that the high mortality and morbidity of ESRD patients on HD might be improved by increasing the delivered dose of dialysis. [Port, 2002;Wolfe, 2000] It was thus hypothesized that increasing doses beyond current standards may result in decreased mortality. This hypothesis was recently tested in one of the largest randomized controlled trial ever conducted in hemodialysis patients, the HEMO Study. [Eknoyan, 2002] Patients on conventional, 3 times weekly in-center hemodialysis were randomized in a 2 x 2 factorial design to receive an eKt/V_{urea} of 1.45 versus 1.05 and high-flux versus low-flux dialyzers. The increased dose was delivered primarily by increasing dialysis session time. There were no significant differences between the two dose groups with respect to mortality, hospitalizations, or other secondary endpoints.

One theory explaining the negative results of the HEMO Study is based on dialysis kinetics. The rate of urea and other small toxic solute removal with hemodialysis is proportional to the concentration of solute (figure 1a). [Depner, 1998] Consequently, most solute removal occurs at the start of hemodialysis, with decreasing removal rates as the hemodialysis session proceeds (figure 1b). [Depner, 1994] During the last hour of a 4.5 hour hemodialysis session, relatively little solute is removed in comparison to the first 3 hours. Thus, increasing dialysis dose by increasing dialysis session time on conventional hemodialysis results in minimal increments in total small toxic solute removal. In addition, once the hemodialysis session is terminated, small solutes sequestered in the intracellular compartment and/or bound by proteins continue to enter the blood, causing the blood concentration of these solutes to rise rapidly after hemodialysis (rebound effect). Minimal increases in time on conventional hemodialysis have little effect on decreasing the degree of rebound.

Similarly, the relatively short increases in time on conventional HD do not result in substantial increases in removal of toxic middle molecules, [Pierratos, 2001] such as β2-microglobulin, implicated in dialysis amyloidosis, [Floege, 2001] nor in phosphate, implicated in cardiovascular risk and death. [Block, 1998; Ganesh, 2001; Goodman, 2000] Removal of phosphate initially follows a first order kinetic process, but the removal rate soon plateaus, with further removal requiring prolongation of the HD session. In addition, rebound is even more pronounced for molecules like phosphate which have low diffusibility, than for highly diffusible small solutes, such as urea.

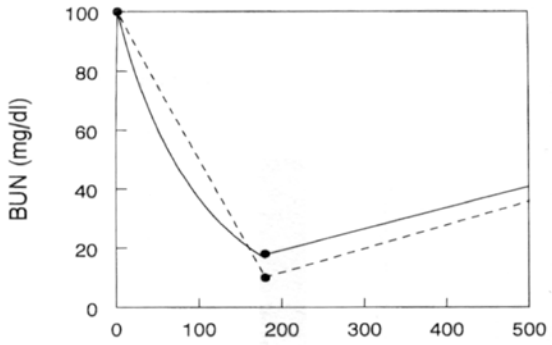


Figure 1a: First order kinetics of urea removal. The rate of urea removal is proportional to the instantaneous urea concentration, as indicated by the solid line. This results in less solute removal than a theoretical dialysis in which urea removal is constant (dotted line - zero order kinetic). Single compartment, fixed volume model (Depner TA, Nephrology Dialysis and Transplantation 1998).

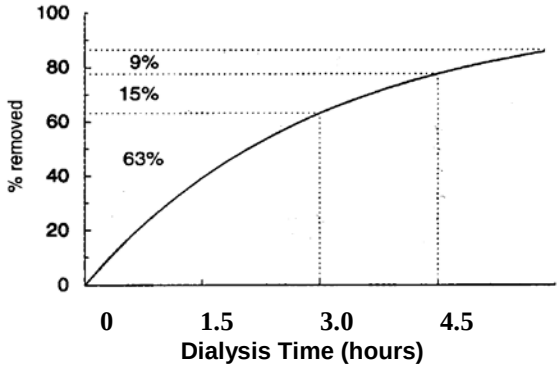


Figure 1b: Relationship between total solute removal and dialysis session time. The rate of solute removal decreases as session time increases. Percentages shown are the incremental removals associated with an increase in time between the dotted lines. (Depner TA, Kidney International, 1994)

Nocturnal daily home hemodialysis thus has several significant advantages compared to a standard three times per week hemodialysis treatment schedule. The increased frequency of HD treatments improves the control of interdialytic weight gain and hypertension. The long duration of therapy for each treatment allows for the patient to reach true dry weight and thus minimizes the need for anti-hypertensive medications. This long-therapy also improves the clearance of middle molecules, allowing for a decrease or discontinuation of phosphate binders in most patients on nocturnal daily home hemodialysis. Finally, small studies have shown significant improvements in quality of life in patients on this modality. These studies are reviewed in more detail in the subsequent section.

1.3 Observational Studies Show Improvements in Health with Nocturnal Daily Hemodialysis

There are several alternative dialytic therapies that have the potential to decrease mortality and morbidity in dialysis patients. Nocturnal home hemodialysis performed six times per week provides a dose of dialysis that is about two to three times greater than the dose provided by standard thrice weekly hemodialysis. As of July 2001, more than 70,000 nocturnal home hemodialysis treatments have been performed in North America. [Lockridge, Jr., 2001] The demographics of this patient population includes 66% male; 73% white, 20% black and 6% other; 7^{th} – 12^{th} grade education in 9%, high school graduate in 45%, some college in 31% and post-graduate education in 8%. Cause of ESRD includes diabetes mellitus in 14%, hypertension in 18%, chronic glomerulonephritis in 11%, polycystic kidney disease in 9% and other causes of ESRD in 37%. [Lockridge, Jr., 2001]

The Clinical Centers in our six times per week nocturnal hemodialysis consortium include the two largest nocturnal programs in the United States, Dr. Robert Lockridge in Lynchburg VA and Dr. Christopher Hoy in Saratoga Springs, NY. Based on observational data these and other investigators have reported significant improvements in nocturnal hemodialysis patients in regard to calcium-phosphorus balance, blood pressure control, nutritional intake and quality of life. The changes in several important intermediate outcomes when patients change from conventional three times per week hemodialysis to six times per week nocturnal home hemodialysis are shown in Table 1. These improvements seen in patients receiving six times per week nocturnal home hemodialysis were not seen in patients in either the high dose or high flux arm of the HEMO Study. [Eknoyan, 2002]

Table 1 – Improvement in Patient Parameters with Daily Nocturnal Home Hemodialysis

Variable	Change from 3X per week HD	References
Pre-dialysis serum creatinine level (mg/dl)	Decrease by 52-68%	[O'Sullivan 1998, McPhatter 1999]
Serum albumin level (g/dl)	Increase by 0.4 - 20%	[O'Sullivan 1998, McPhatter 1999, Pierratos 1998, Cacho 2000]
Dry weight	Increase of 0.1 - 3.0 kg	[McPhatter 1999, Pierratos 1998, Williams 1998, Buoncristiani 1999, Kooistra 1998]
Protein and energy	Increase into recommended intake	[Lacson 2001]
Serum bicarbonate (meq/l)	Increase into normal range	[O'Sullivan 1998, Cacho 2000}
Serum phosphate	Normalization without the need for phosphate binders	[O'Sullivan 1998, McPhatter 1999, Cacho 2000, Kooistra 1998, Pierratos 1999, Musci 1998, Lockridge 1999, Pierratos 1999]
Systolic blood pressure	Decrease of 30 mm Hg, decrease in number of anti-hypertensive medications	O'Sullivan 1998, Pierratos 1998, Cacho 2000, Pierratos 1999, Mohr 1999, Chan 2002]
Hemoglobin level (g/dl)	Increase of 0 - 10%, decrease in EPO dose	[Pierratos 1998, Cacho 2000, Lockridge 1999, Pierratos 1999, Chan 2002]
Beta – 2 microglobulin	Decrease of 50 – 67%	[Gotch 1999, Raj 2000, Clark 1999]
Quality of life	Improvement in SF-36 scores	[McPhatter 1999, Kooistra 1998, Lockridge 1999, Mohr 1999, Brissenden 1998]
Sleep apnea	Decrease in sleep apnea	[Hanly 2003]

Although these improvements seen with nocturnal daily hemodialysis are promising, large gaps exist in our knowledge of the potential benefits of nocturnal home hemodialysis. For example, the improvement in serum albumin levels, an intermediate outcome strongly associated with mortality and morbidity has not been seen in all studies of nocturnal daily hemodialysis. Similarly, hemoglobin levels, which have also been associated with morbidity and mortality, have not improved in all studied patients and erythropoietin dosing does not consistently decrease with nocturnal hemodialysis. Finally, only two small non-randomized studies have investigated the potential for a decrease in hospitalization rates in patients receiving nocturnal hemodialysis. It is therefore not known if patient selection may be at least partially responsible for the decrease in hospitalization rates seen with this modality. Therefore, <u>if a substantial increase in the dose of dialysis can improve patient outcomes, then six times per week nocturnal hemodialysis is an ideal modality that can be used to test this hypothesis.</u>

1.4 Limitations of Existing Nocturnal Hemodialysis Studies

While reported improvements in outcomes after starting nocturnal daily home hemodialysis have often been dramatic, evidence from these prior observational studies is limited by a lack of adequate control groups, selection and dropout bias, and small sample size. [Diaz-Buxo, 2001]

Lack of control groups: All previous studies are pre-post case-series with analyses of changes in parameters from a baseline measurement on conventional HD to follow-up measurements after initiating nocturnal daily home hemodialysis. Because the comparative evaluations are at different times, confounding due to changes in extraneous factors, regression to the mean, and period and carry-over effects influencing the results cannot be ruled out.

Selection bias: Home hemodialysis patients are a select group generally characterized by exceptional compliance, motivation, and social support, and have been reported to have lower mortality risk compared to in-center patients after adjusting for co-morbid factors [Woods, 1996]. Such selection bias may partly account for reports of improved outcomes and lower rates of mortality and hospitalizations in patients on nocturnal daily home hemodialysis. On the other hand, some centers have reported using nocturnal hemodialysis as a salvage therapy [personal communications, Drs. Christopher Hoy and Robert Lockridge]. Although these patients may be expected to have higher mortality, longitudinal improvements in intermediate outcomes may represent regression to the mean rather than true improvement, as non-dialysis factors precipitating the adverse conditions that led to salvage therapy may resolve spontaneously or because of increased medical attention and co-interventions.

Dropout bias: Patients who die or who are otherwise lost to follow-up may fare more poorly than patients who complete the designated follow-up. In the presence of such "informative censoring", standard analyses limited to available data may give spuriously positive results.

Small sample size: The largest home hemodialysis program in the United States has less than 50 patients while the largest program in Canada has fewer than 75 patients. Thus, these small sample sizes limit the ability to detect infrequent, yet clinically significant, potential adverse events. Possible adverse events associated with nocturnal daily home hemodialysis include increased risk of vascular access complications; increased blood losses; provocation of immune and inflammatory responses due to increased exposure to venipuncture, tubing, dialyzers, and dialysate water; increased blood losses; malnutrition due to missed meals while dialyzing; as well as patient burn-out and fatigue due to a more demanding treatment schedule.

It is unlikely that any one of these biases explain the extensive benefits reported for nocturnal daily home hemodialysis, but it is possible that their combined effect may be substantial. Thus, given its promise, the potential benefits of nocturnal daily home hemodialysis must now be established in a rigorous experimental design. A randomized controlled trial which examines the effects of nocturnal daily home hemodialysis on intermediate outcomes, improves our knowledge of the physiology and delivery of nocturnal daily home hemodialysis, and establishes the cost of this therapy, is the logical next step in this staged program of research. Therefore, a well-designed study of six times per week home nocturnal hemodialysis with rigorous methods for data collection and interpretation will help to alleviate the limitations of prior studies.

1.5 Potential Significance of the Results

This trial will determine the feasibility of randomizing patients and carrying out a randomized multi-center clinical trial comparing nocturnal daily home hemodialysis to conventional three times

per week home hemodialysis. If feasibility is demonstrated, the trial will also establish the safety of nocturnal daily home HD, and confirm or refute the benefits of nocturnal daily home hemodialysis on intermediate physiological outcomes and health-related quality of life seen in previous observational studies. It will also quantify the incremental cost of delivering nocturnal daily home hemodialysis in North America. If significant improvements are demonstrated with nocturnal daily home hemodialysis, this trial may lead to further implementation of nocturnal daily home hemodialysis as an alternative treatment option for patients with ESRD.

2. Objectives and Trial Design

2.1 Trial Objectives

The objectives of the study are as follows:

Feasibility

1) To determine the feasibility of recruiting and retaining patients in a randomized trial of six times per week nocturnal -home hemodialysis versus conventional three times per week home hemodialysis.

2) To determine patient adherence and acceptance of nocturnal hemodialysis, and to identify reasons for discontinuation or noncompliance to the interventions.

Safety

3) To determine the safety of the nocturnal hemodialysis intervention, with a particular emphasis on vascular access and patient burden.

Efficacy

4) To evaluate the efficacy of nocturnal HD compared to conventional three times per week home HD on two co-primary outcomes: i) a composite of mortality with the change over 12 months in left ventricular mass by magnetic resonance imaging, and ii) a composite of mortality with the change over 12 months in the SF-36 RAND physical health composite score (PHC).

5) To determine the effect of nocturnal HD on nine secondary outcome domains: i) cardiovascular structure and function, ii) physical function, iii) depression/burden of illness, iv) nutrition, v) cognitive function, vi) mineral metabolism, vii) clinical events, viii) hypertension, and ix) anemia.

Characterization of Interventions

6) To characterize the six times per week nocturnal hemodialysis intervention in comparison to conventional three times per week home hemodialysis, including evaluation of small and middle molecule solute clearance, treatment time, and volume removal.

Implementation

7) To determine the feasibility of implementing six times per week nocturnal hemodialysis in practice, including evaluation of barriers to implementation such as the home environment and any potential incremental costs of nocturnal hemodialysis compared to three times per week conventional home hemodialysis. An evaluation of the cost effectiveness of nocturnal HD relative compared to conventional home three times per week hemodialysis will be performed.

2.2 Overview of Study Design

This will be a randomized, unblinded study of six times per week nocturnal home hemodialysis versus three times per week conventional home hemodialysis. A target of 90 patients will be enrolled into this study with equal allocation in each arm, stratified by Clinical Center and diabetic status. All patients will be assessed for suitability for nocturnal home hemodialysis using a standardized method prior to patients entering the baseline portion of this protocol. The minimum dialysis dose in the conventional home arm will be an equilibrated Kt/V of 1.1.In the nocturnal arm there will be a minimum prescription of six hours per session for six days per week AND a minimum achieved standard Kt/V of 4.0. Patients will be followed for 12 months.

Because no previous randomized trials of nocturnal dialysis have been conducted, the first calendar year after the initiation of enrollment has been designated as a "Vanguard" phase during which feasibility of randomization and conduct of the interventions will be evaluated. If pre-defined benchmarks for establishment of feasibility are achieved during the Vanguard phase, the trial will proceed to its primary objective of determining if 6 times per week nocturnal hemodialysis results in clinically significant improvements in physiological, health-related quality of life (HRQL) and functional outcomes, as compared with three times per week conventional home hemodialysis.

Since the intervention, by necessity, is unblinded, significant efforts will be made to reduce bias. These include: standardization of interventions, blinding interviewers, blinding the assessment of subjective outcomes, in addition to collecting objective outcomes. Patients will be treated and followed for 12 months. Two co-primary outcomes are designated: 1) a composite of mortality with the change over 12 months in the SF-36 RAND physical health composite, and 2) the change over 12 months in left ventricular mass. In addition, first priority secondary outcomes have been designated for seven outcome domains: 1) cardiovascular structure and function (change in LV mass), 2) physical function (change in the PHC), 3) depression/burden of illness (change in Beck Depression Inventory), 4) nutrition (change in serum albumin), 5) cognitive function (change in the Trailmaking Test B), 6) mineral metabolism (change in average predialysis serum phosphorus), and 7) clinical events (rate of non-access hospitalization or death). Hypertension and anemia are also main outcome domains, but without designation of single first priority outcomes. The cost-effectiveness of the two interventions will also be compared.

2.2.1 Modification of Standard Arm

The protocol was initially conceived as a comparison between six times per week nocturnal home hemodialysis and conventional three times per week in-center hemodialysis. This design had the advantage that the in-center hemodialysis control arm represented the current standard hemodialysis therapy, but also had the disadvantage that the effect of the duration or intensity of the dialysis treatment (6 times per week for six to seven hours overnight vs. 3 times per week for about 2.5 to 4.5 hours) was confounded with the location where the hemodialysis occurred (at home vs. in-center). Thus, using the original protocol design, it would not have been possible to distinguish between the effects of dialysis intensity versus dialysis location.

Several months after initiating enrollment, the Steering Committee determined that it would not be possible, using the original study design, to randomize an adequate number of patients to achieve the necessary sample size for adequate statistical power. Patients were reluctant to consider an intervention where there was only a 50% chance that they would be randomized to home hemodialysis therapy. Therefore, in accordance with the philosophy of the trial's Vanguard study design (see Section 4), the Steering Committee elected to change the location of dialysis in the

control arm from in-center hemodialysis to home hemodialysis. All other aspects of dialysis care in the control arm, including the frequency and dose of dialysis delivered, are unchanged form the original protocol (V 2.1). Once the revised protocol was approved by the Clinical Center's local IRB:

1) All new patients not previously randomized into the FHN study under version 2.1 will be randomly assigned to either six times per week nocturnal home hemodialysis or to three times per week conventional home hemodialysis.
2) Patients who consented to the original version (2.1) of the protocol and were already randomized to the home nocturnal arm prior to approval of the revised (V 3.0) protocol will remain with their assigned treatment group and original protocol, but will be asked to sign a new consent form to indicate that the design of the trial has changed for new patients.
3) Patients who consented to the original version (2.1) of the protocol and were already randomized to the conventional in-center arm prior to approval of the revised (V 3.0) protocol were asked to sign a consent for the revised protocol (V 3.0). Once this consent was signed, these patients were given the choice to either continue with conventional in-center hemodialysis three times per week or convert to home conventional hemodialysis three times per week (see Section 6 for additional details).
4) Patients who consented to the original version (2.1) of the protocol and were not already randomized will be required to re-consent with version 3.0 of the protocol if they want to participate in the revised protocol. They will not be permitted to continue in version 2.1 of the protocol that allows them to be randomized in the standard arm of the trial to in-center hemodialysis three times per week.

The revised study design will therefore not include a control group undergoing conventional in-center three times per week dialysis. Since hemodialysis will be performed in the home in both treatment arms, however, the study will now specifically address the question of whether increasing the quantity of dialysis from a conventional 3 times per week treatment schedule (9 to 15 hours per week) to a 6 times per week nocturnal schedule (36 to 42 hours per week) improves patient outcome. The confounding between treatment schedule and dialysis location will be limited to the small fraction of projected patients who were randomized prior to the protocol change, and thus is expected to have little effect on the study's findings. In addition, the dropout rate during training should be substantially reduced as randomization will now occur towards the end of the home hemodialysis training period, instead of prior to the initiation of home hemodialysis training.

2.3 Study Timeline

This trial will be carried out in 5 phases. The first 24 months (Phase I) will be used to finalize the study protocol, secure Institutional Review Board approval, and create procedures manuals, data collection forms, program the trial database and train study personnel (Pre-trial planning). Subject enrollment then began under a Vanguard phase (Phase 2a) that was designed to last for 12 months. Four months into this Vanguard phase, it was determined that it would be difficult to meet recruitment goals with the current protocol. Thus, with NIH and DSMB input, a revised protocol was developed and implemented. Enrollment in the original protocol (V 2.1) of patients was frozen on 9/27/06 and was reopened using the revised (V 3.0) protocol once two of the eight clinical centers received local IRB approval for the revised protocol. The first 12 months of the recruitment period with the revised protocol (V3.0) (Phase 2b) will be referred to as the "New Vanguard" phase

of the trial. This New Vanguard phase will be used to identify process factors that can be modified to improve recruitment and adherence, and subsequently to evaluate the feasibility of recruitment and conduct of the interventions according to pre-established benchmarks. If the New Vanguard phase demonstrates feasibility, recruitment will continue over a further 16 months (Phase 3) of the 29 month accrual period of the revised protocol. Each subject will be treated and followed for 12 months and followed for up to 2 or more months for limited data collection (Phase 4). The last three months will be allocated to final data analysis, reporting of the results, and preparing of the trial database for archival (Phase 5).

2.4 Recruitment Strategy

2.4.1 Description of Centers and Available Patient Pool

The target sample size for this trial is 90 patients, of whom 50% will be randomized to nocturnal home six times per week hemodialysis. Patients will be recruited from designated Clinical Centers in the United States and Canada (See Figure 2), which have a combined pool of more than 11,000 prevalent dialysis patients. Each Clinical Center will have the capacity to recruit a minimum of 20 patients into the trial. Data from the Lynchburg and Saratoga Springs nocturnal home hemodialysis programs suggest that between 5 to 10% of patients within their dialysis units have been trained and started on nocturnal home hemodialysis. Other programs have noted that a similar percentage of patients have initiated nocturnal home hemodialysis. [Piccoli, 2002]

Several programs in our consortium have accepted patients from outside of their own dialysis units for home hemodialysis training purposes. In Saratoga Springs, NY, patients travel from as far as 300 miles away for training and for the monthly follow-ups required of home training patients. This situation is similar to that described in Iowa City, IA, where home hemodialysis patients travel up to 300 to 400 miles for training and for monthly follow-up.

Each of the Clinical Centers in this consortium has contacted adjacent nephrology programs and dialysis units and has obtained permission to recruit patients from these units for a study in home nocturnal dialysis. Based on information provided from the Clinical Centers and the adjoining dialysis units, we have provided below in Table 2 a summary of the number of patients that will be available for recruitment into the nocturnal study from this clinical trials consortium.

Table 2 – Patients with ESRD at Each of the Clinical Centers in the Nocturnal Consortium

Clinical Center	Number	Blacks	Whites	Males	Females	Other*	Total
Lynchburg, VA	336	210	126	184	152	400	736
Saratoga Springs, NY	333	27	296	173	160	1020	1353
New York City, NY (Rogosin Inst.)	565	245	149	283	282	600	1165
St. Louis, MO (Washington U)	683	499	118	311	372	730	1413
Kansas City, MO	367	145	220	194	183	400	767
Winston-Salem, NC (Wake Forest)	1169	625	517	596	575	650	1819
London, Ontario, Canada	566	17	515	300	266	0	566
Indianapolis, IN (Indiana U)	441	309	128	216	225	30	741
Iowa City, IA (U of Iowa)	186	10	166	93	93	680	866
U of Toronto -Toronto General Hospital	445	50	185	267	178	180	625
Humber River Regional Hospital	303	77	151	161	124	0	303
University of British Columbia	580	2	313	342	238	726	1306
TOTAL	**5974**	**2216**	**2884**	**3110**	**2848**	**5686**	**11660**

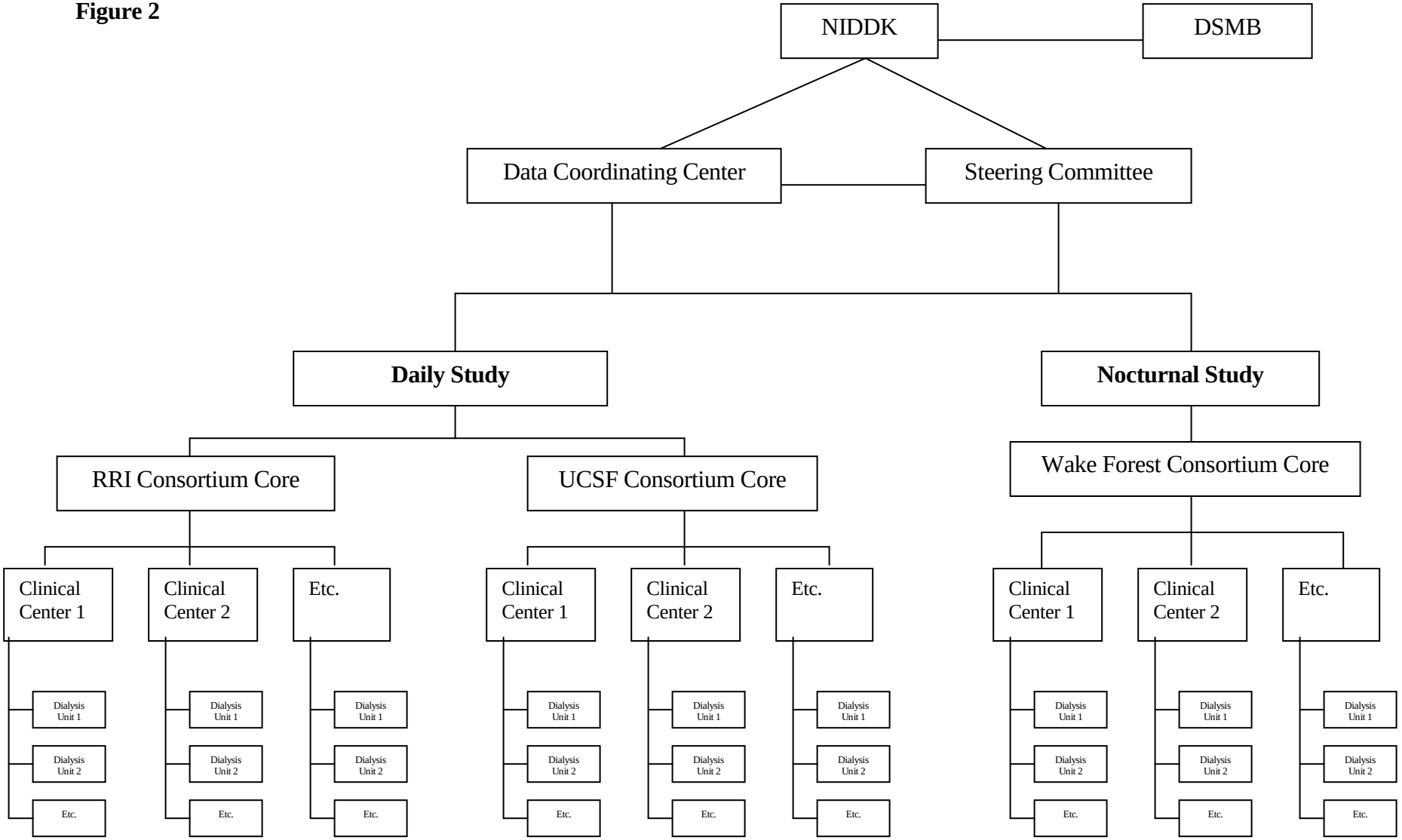
*"Other patients" refers to other dialysis units that have either provided patients for nocturnal home hemodialysis or have provided letters of agreement to supply patients for the study.

Thus, more than 11,000 chronic hemodialysis patients are available for recruitment for the nocturnal home hemodialysis clinical trial. Assuming a conservative estimate of interest among patients, at the 5% level, we will have more than 550 patients in our consortium who should be interested in a home nocturnal hemodialysis program and will complete the nocturnal home HD training procedure.

In addition, talks are underway with several other centers that are initiating nocturnal home hemodialysis programs to assess their interest in joining the consortium in 2006.

FHN ORGANIZATION

Figure 2



2.4.2 Recruitment Initiatives

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 home hemodialysis 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. We have already obtained permission to provide information to one of these websites.
2) Development of a recruitment brochure that will summarize the protocol of the randomized 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).

2.4.3 Retention Techniques

In the HEMO Study, the use of patient incentives, recognition of patient milestones such as birthdays and anniversaries, and frequent interactions with the study coordinator, were important tools used for patient retention at Wake Forest and Washington University. We will use similar techniques for patients who are randomized into this study.

2.5 Study Population

We will include in this study any eligible adult patient with end-stage renal disease who meets the inclusion and exclusion criteria without regard for race, ethnicity or national origin.

2.5.1 Inclusion Criteria

1) Patients with end stage renal disease requiring chronic renal replacement therapy
2) Age $\geq$ 18 years,

3) Achieved mean eKt/V of ≥ 1.0 for at least two baseline sessions

4) Willing to perform hemodialysis at home

We have excluded patients less than 18 years of age from this trial due to the complex emotional and psychosocial factors that may interfere with successful hemodialysis at home.

2.5.2 Exclusion Criteria

Exclusion criteria include:

1) GFR greater than 10 ml/min/1.73 m^2 as measured by the average of urea and creatinine clearances obtained from a urine collection of at least 24 hours

2) Expectation that native kidneys will recover kidney function

3) Current access is temporary non-tunneled catheter

4) Unable to follow the nocturnal home hemodialysis training protocol for any reason, including inability to train the patient or the patient's caregiver

5) Non-compliance with hemodialysis or peritoneal dialysis treatments in the past

6) Medical conditions that would prevent the patient from performing the cardiac MRI procedure (e.g., inability to remain still for the procedure, a metallic object in the body, including cardiac pacemaker, inner ear (cochlear) implant, brain aneurysm clips, mechanical heart valves, recently placed artificial joints, and older vascular stents)

7) Unable to verbally communicate in English or Spanish

8) Current requirement for hemodialysis more than three times per week due to medical comorbidity (ultrafiltration session on fourth day per week not an exclusion criteria)

9) Currently on nocturnal HD, or less than 3 months since the patient discontinued daily or nocturnal HD

10) Scheduled for living donor kidney transplant, change to peritoneal dialysis, or plans to relocate to an area outside of the referral area of one of the Clinical Centers within the next 12 months

11) Expected geographic unavailability for > 2 consecutive weeks or > 5 weeks total during the next 12 months (excluding unavailability due to hospitalizations)

12) Less than 3 months since patient returned to HD after rejection resulting in allograft failure from a kidney transplant.

13) Currently in acute care or chronic care hospital

14) Life expectancy less than six months

15) A medical history that might limit the individual's ability to take trial treatments for the 12 month duration of the study, including: currently receiving chemo or radiotherapy for a malignant neoplastic disease other than localized non-melanoma skin cancer, active systemic infection (including tuberculosis, disseminated fungal infection, active AIDS but not HIV), and cirrhosis with encephalopathy

16) Current pregnancy or planning to become pregnant within the next twelve months (patients require a higher dose of dialysis if pregnant). All female patients that have not gone through menopause will need to use an effective contraceptive method while enrolled in the study.

17) Contraindication to heparin, including allergy or heparin induced thrombocytopenia

18) Current use of investigational drugs or participation in another clinical trial that contradicts or interferes with the therapies or measured outcomes in this trial

19) Unable or unwilling to follow the study protocol for any reason (including mental incompetence)

20) Unable or unwilling to provide informed consent or sign IRB-approved consent form

Patients currently receiving nocturnal home hemodialysis at the Clinical Centers in this consortium have a wide range of comorbid medical conditions, including malignancy, severe chronic obstructive pulmonary disease and heart failure. These patients have had significant improvements in their overall health since starting nocturnal home hemodialysis. Thus, such comorbid medical conditions are not designated as exclusion criteria for this clinical trial.

The liberal residual renal function threshold for exclusion if GFR > 10 ml/min/1.73m^2 reflects reports of the study investigators that 20 - 30% of patients who choose nocturnal hemodialysis do so at the initiation of dialysis therapy, so that a lower threshold would compromise recruitment. It is estimated that nocturnal hemodialysis six times per week provides a clearance (average of urea and creatinine clearances) of approximately 25 – 30 ml/min. Thus, even in those patients with a GFR of 10 ml/min at the initiation of standard hemodialysis therapy, there will be adequate separation of the dose of dialysis in the treatment versus the control groups. Table 3 below shows the separation between groups for several different uremic solutes.

Table 3 – Separation Between Study Arms for Different Levels of Residual Renal Function

Solute	Residual GFR (ml/min)	3X/week HD	6X/week HD	% separation
Urea (std Kt/V)	0	2.46	5.87	139%
Urea (std Kt/V)	10	3.85	7.29	89%
Beta-2 microglobulin	0	4.35	7.39	70%
Beta-2 microglobulin	10	11.95	13.93	17%

2.6 Screening Evaluation

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.

A trained study coordinator at each Clinical Center will review charts of patients on both hemodialysis and peritoneal dialysis to determine potential trial eligibility. The coordinator will

approach potentially eligible participants and provide them with verbal and written information regarding the study. The patient will be provided with literature on the clinical trial and be given the contact number for the Clinical Center and the patient will visit the Clinical Center. The study will be presented to the patient in detail by a trained study coordinator. The study coordinator will answer any questions the patient may have regarding the study. If the patient is agreeable, the patient will be asked to sign an Institutional Review Board - approved consent form for this study. In addition, a consent will be obtained for the storage of blood.

2.7 Baseline Evaluation

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. *[2014 FHN Archive Note: FHN Executive Committee dropped prognostic covariates from the analyses.]* The length of the baseline evaluation is 4 to 18 weeks (except for patients in baseline at the time of the protocol change - see Section 6.1 for more details). Those patients who have not previously received chronic hemodialysis treatments (defined in the protocol as "incident dialysis patients") will need to receive at least one week of hemodialysis (three treatments) prior to providing any baseline data, with the exception of the urine collection to determine residual kidney function.

Suitability for Home Hemodialysis

Several evaluations will be performed by the Clinical Center 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 home hemodialysis 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. 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 of the costs for necessary modifications to the home may be borne by the patient. This issue will vary at individual clinical centers and will depend on the extent of the needed renovations. These centers will provide specific information to the patient regarding possible reimbursement for home modifications.

Based on the information obtained above, the Clinical Center will determine if the patient is a suitable home hemodialysis candidate.

FHN Study Baseline Data Collection

There will be an 18 week window for completion of all baseline studies, including all laboratory data, questionnaires, functional assessments and cardiac MRI (except for patients in baseline at the time of the protocol change - see Section 6.1 for more details). The expectation, however, is that the patient will complete all baseline studies prior to the completion of the generic home hemodialysis

training by the clinical center, a process that typically takes 4 - 6 weeks to complete. All baseline case report forms, including valid results for each of the primary and main secondary endpoints must be entered into the database prior to the patient being randomized into the nocturnal study.

The baseline assessment will include two kinetic modeling sessions, (see Section 3.1), labeled as the B1 and B2 visits. 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. A timed urine collection (minimum 24 hours) will be obtained during the interdialytic interval preceding a dialysis session, preferably midweek for patients producing urine prior to a baseline 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 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.

2.8 Home Hemodialysis Training

It is anticipated that 4 - 6 weeks will be allotted for home hemodialysis training during the baseline phase, although patients will be able to take more time, if needed, to complete the training process. During the training period, patients will receive hemodialysis treatments three times per week. All patients in the trial will initially be trained in the generic requirements for home hemodialysis. These processes include the following major tasks:

1) Vital signs, including BP measurement
2) Setting up and tearing down the dialysis machine without assistance
3) Recognizing machine problems and troubleshooting them appropriately
4) Able to access dialysis vascular access consistently and independently
5) Machine disinfection
6) Water treatment maintenance

At the end of the training process for generic home HD, the study coordinator will ascertain that the patient is still willing to be randomized to either conventional three times per week home HD or nocturnal daily home HD. If the patient is willing to be randomized, then the randomization protocol below will be implemented. After randomization, patients randomized to either arm of the study will receive additional training that is specific to the assigned home HD modality. It is anticipated that this additional training will take approximately one to two weeks.

2.9 Randomization of Trial Participants

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.

Consenting subjects will be randomly allocated in a 1:1 allocation to 6 times per week nocturnal home hemodialysis or three times per week conventional home hemodialysis. The randomization schedules will be prepared by the Data Coordinating Center (DCC) prior to the start of recruitment. Randomization will be stratified by Clinical Center and by diabetic status. Randomly permuted blocks of random sizes will be used to help balance numbers of participants assigned to both treatment regimens. This method guarantees that at no time during randomization will the participants in the individual groups be grossly unequal.

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

Once the patient has completed training for the generic portion of the home hemodialysis training process and all baseline studies have been completed and the forms corresponding to these studies have been received and checked to verify eligibility by the Data Coordinating Center,, the Principal Investigator or the study coordinator shall access the interactive randomization program. The program will verify through a defined set of questions that the participant is ready to be randomized and provide a randomized treatment assignment for that participant based upon his or her stratum. The randomization assignment will be displayed on the screen and emailed to the Clinical Center.

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

After randomization occurs, patients will begin training for the unique aspects of the assigned home hemodialysis modality. For patients assigned to nocturnal home hemodialysis, this will include training for the enuresis or leak detectors, access safety devices, addition of phosphate to the dialysate, etc). For patients assigned to the conventional home HD arm, this will include training in the handling of volume status and blood pressure, etc. It is anticipated that it will take one to two weeks to train an individual patient for these unique aspects of their assigned home hemodialysis modality. An individual patient will have no limit, however, on the time needed for training for these modality specific aspects of home hemodialysis.

3. Intervention Plan

3.1 Description of the Intervention: Dialysis Frequency and Dose

3.1.1 Summary of the Dose Intervention

Consenting patients meeting eligibility criteria will be randomized to 1 of 2 hemodialysis regimens, as shown in Table 4:

i) *Conventional home 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 standard Kt/V (sKt/V) of 4.0

This design is intended to achieve a large separation in a wide range of treatment parameters related to small and middle molecule solute clearance, total weekly treatment time, and ultrafiltration, as shown in Tables 4 and 5.

3.1.2 Rationale for Choosing Target Doses

a) Conventional Home Hemodialysis Group

Hemodialysis dosing is based on clearance of urea, quantified as the Kt/V (K is the clearance of urea, t is time of dialysis session, and V is the volume of distribution of urea in the patient). Traditionally the single-pool Kt/V (spKt/V) has been used to define and measure dose in conventional hemodialysis. [Gotch, 1985] However, because the spKt/V overestimates true clearance due to the phenomenon of urea rebound, this trial will use equilibrated Kt/V (eKt/V). [Daugirdas, 1995; Pedrini, 1988]

The recently completed HEMO Study demonstrated that there was possible benefit of a higher dose of dialysis in women, but there was no recommendation to increase the dose of dialysis. [Eknoyan, 2002] The average dose of dialysis, as measured by the Daugirdas II equation in the CMS ESRD Clinical Performance Measures Project was 1.46 ± 0.27 in 2000. [USRDS, 2001; USRDS, 2000; USRDS, 2002] This single pool Kt/V is equivalent to an equilibrated Kt/V of 1.25. In order to assure adherence to current national standards, a minimum delivered eKt/V of 1.10 will be required in the conventional home hemodialysis group. However, consistent with its designation as a conventional three times per week home hemodialysis arm, the dialysis prescriptions will be otherwise unspecified (subject to a minimum treatment time of 2.5 hrs).

Table 4: Summary of the Interventions*

Parameter	**Conventional 3X/week HomeHD** (control group)	**Nocturnal Home HD** (intervention group)	% Difference in medians; Nocturnal HD vs. Conventional HD
Sessions per week	3	6	+ 100%
Target delivered	**minimum eKt/V of 1.1**,	**minimum sKt/V of 4.0**	
Hours per session [median (mean = SD)]	$\geq$ 2.5 (median = 3.50)	6.0 to 8.0 (median =7.0)	+ 100%
Maximum interdialytic interval during treatment week (median, hours)	68.5	41.0	- 40%
Average interdialytic interval during treatment week (median, hours)	52.5	21.0	- 60%
Hours per week (median, 5^{th} – 95^{th} percentile)	10.5 (9.0 – 13.1)	42.4 (36.6 – 47.6)	+ 304%

* See Table 5 footnote for details of simulation.

Table 5: Clearance of Selected Solutes*

Parameter	Conventional 3X/week Home HD (control group) (median, 5th – 95th percentile)	Nocturnal Home HD (intervention group) (median, 5th – 95th percentile)	% Difference in medians; Nocturnal HD vs. Conventional HD
eKt/V urea per treatment	1.39 (1.12 – 1.75)	1.56 (1.10 – 2.30)	+ 22.3%
Weekly sKt/V urea	2.46 (2.16 – 2.80)	5.60 (4.26 – 6.64)	+ 128%
Equivalent β2 microglobulin clearance (ml/min). Includes estimated extrarenal elimination rate of 3 ml/min	4.73 (4.12 – 5.32)	8.68 (7.66 – 9.99)	+ 84%
Estimated standard phosphate removal (mg/day). Assumes a pre-dialysis phosphorus level of 5 mg/dl	299 (254 - 374)	1191 (1028 - 1338)	+ 298%

* The median values and 5th and 95th percentiles given in Tables 4 and 5 were obtained from simulations with the following assumed distributions of treatment parameters based on a survey of the investigators from the Clinical Centers in the Nocturnal trial: Treatment time is distributed uniformly between 6 and 8 hours; dialysis blood flow is distributed uniformly from 300 to 500 ml/min for 50% of patients on single needle dialysis and uniformly from 200 to 300 ml/min for the other 50% assumed to be using double needle dialysis; dialysate flow is distributed uniformly from 200 to 300 ml/min, and urea KoA is 450 ml/min.

b) Nocturnal Hemodialysis Group

Numerous conference calls with the nocturnal Clinical Center PIs have been held to discuss various aspects of the protocol. It was noted from these discussions that patients perceive less of a benefit from nocturnal dialysis when they dialyze for less than 30 – 35 hours per week. Based on this observation, the dose of dialysis will be prescribed by time and will include a minimum time of six hours six nights per week. The exception to this time prescription will be that the time will need to be increased if the measured standard Kt/V urea is less than 4.0. This exception is present to ensure an adequate separation between the standard and nocturnal groups in regard to urea kinetic modeling.

Simulation results indicate that the median sKt/V with 6 times per week nocturnal hemodialysis will be 5.12, with the 5th and 95th percentiles at 4.12 and 6.02, respectively. It is estimated that less than 5% of patients will have a sKt/V of < 4.0. To ensure that there is excellent separation between the conventional and experimental arms of the trial in regard to urea kinetics, a minimum delivered sKt/V for the nocturnal arm has been set at 4.0.

3.1.3 Calculation of Single Pool, Equilibrated and Standard Kt/V

Single pool Kt/V (sp Kt/V) will be calculated by applying the 2-BUN algorithm [Depner, 1989] to the predialysis and post-dialysis ureas collected according to current KDOQI (2006 dialysis update) [National Kidney Foundation', 2006] standards. The modification of the method of the Tattersall

rate equation will be used to estimate the equilibrated Kt/V (eKt/V) from spKt/V according to the formula:

$$eKt/V = spKt/V \times (T/(T + 30.7))$$

where T denotes treatment time.

3.1.4 Data Collection, Determining the Initial Prescription and Monitoring Dose

Data to be obtained during the kinetic modeling sessions are summarized in Table 6. Although kinetic modeling data will be obtained monthly in order to fully characterize the interventions, the protocol for establishing and updating dialysis prescriptions is designed to minimize the number of prescription modifications and to be as unobtrusive as possible. The protocol for measurement of residual renal function is described in Section 3.1.5.

a) Baseline Kinetic Modeling Session

Two kinetic modeling sessions will be conducted during the baseline evaluation phase of the trial.

In order to prevent randomization of prevalent patients who are unable to achieve a delivered eKt/V close of at least 1.10 in the three times per week home HD arm, patients must achieve an average delivered eKt/V of at least 1.0 for the two baseline kinetic modeling sessions in order to be randomized. If the average delivered eKt/V for the two baseline kinetic modeling sessions is less than 1.0, then an additional kinetic modeling session may be scheduled, and the mean delivered eKt/V recomputed from the last two baseline sessions. This process may be repeated up to 4 times, and the minimum eKt/V requirement will be met if at any of these tries the average eKt/V for the final two assessments exceeds 1.0.

b) Determining and Monitoring the Trial Prescription during Follow-up

i) Conventional Home Hemodialysis Group

Patients randomized to the three times per week conventional home HD group may follow any dialysis prescription provided their delivered eKt/V is at least 1.10 and treatment time is at least 2.5 hours. Modeling data will be obtained monthly, and prescribed eKt/V will be computed centrally based on the patient's current running median V over the preceding 4 months, and the patients current blood flow, dialysate flow, dialyzer type, single or double needle dialysis and ultrafiltration rate. (During the first months following randomization, the running medians will actually be obtained over 1-3 months, depending on the number of prior modeling sessions which have been conducted to that point in the trial.) If the delivered eKt/V falls below 1.10, using study ID numbers the Data Coordinating Center (DCC) will e-mail a warning to the study coordinator at the patient's Clinical Center, and provide alternative prescription options for a prescribed eKt/V of at least 1.10.

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. Data from these run sheets will be provided to the DCC on a monthly basis.

Table 6: Data Collected at Kinetic Modeling Sessions*

Treatment date
Start and end times (recorded)
Actual treatment time recorded on the dialysis machine, if available
Dialysate flow
Blood flow
Dialyzer type
Reuse number
Single or double needle dialysis
Interruption status (was total interruption time >30 min?)
Intradialytic hypotensive episodes and other symptoms requiring saline or reduced UF
Pre and Post HD systolic and diastolic blood pressure
Pre and Post HD weight
Pre and Post HD urea (local laboratory measurement)
Pre and post HD creatinine (local laboratory measurement)
Pre and post HD phosphate (local laboratory measurement)
Predialysis serum β_2-microglobulin (to be measured in reposited serum specimens)
Predialysis serum albumin (local laboratory measurement)

ii) Nocturnal Hemodialysis Group

After the first follow-up kinetic modeling session during the training period for nocturnal home dialysis, the Data Coordinating Center will determine if the minimum prescribed time on dialysis of six hours six times per week will achieve a target sKt/V of at least 4.0 If the minimum dose is insufficient, then the DCC will send an array of dialysis prescription options for a target sKt/V of 4.0. Subsequently, modeling data will be obtained monthly, and revised dialysis prescriptions will be provided if the running median V (over 4 months) increases by an amount that leads to a decrease in the updated prescribed sKt/V to a value less than 4.2. Failure to implement the revised prescriptions will be regarded as non-adherence to the protocol. This procedure is designed to minimize the chance that the running median achieved sKt/V would fall below the minimum delivered sKt/V of 4.0.

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. Data from these run sheets will be provided to the DCC on a monthly basis.

3.1.4.1 Other Measures of Dialysis Adequacy

All patients in both arms of the study will have dialysis dose measured by a number of different methods, including urea kinetics, creatinine kinetics, phosphate kinetics and beta-2-microglobulin kinetics. Phosphate clearance will be calculated by the method of Gotch. [Gotch, 2003] Beta-2-microglobulin clearance will be calculated by the same method used in the HEMO Study. [Cheung, 2003] Pre and post dialysis blood samples will be obtained according to current National Kidney Foundation KDOQI™ Hemodialysis Adequacy (2006 update) guidelines.

3.1.5 Residual Renal Function

Residual renal function will be measured prior to the baseline kinetic modeling session, and at months 4 and 12 of follow-up for all patients who produce urine. Timed urine collections of at least 24 hours will be obtained during the interdialytic interval preceding a dialysis session, preferably midweek prior to a midweek dialysis treatment. For patients undergoing nocturnal dialysis, the collection period extends from the beginning of one dialysis to the beginning of the next dialysis. For patients undergoing conventional home hemodialysis (i.e., the baseline assessment for all patients, and month 4 and 12 assessments for patients assigned to the three times per week arm), the collection is performed during the interdialytic interval prior to a dialysis session. Predialysis blood samples from the dialysis following the collection will be shipped to the dialysis units local laboratory for determination of pre-dialysis concentrations of urea, creatinine, and phosphorus. The time-averaged concentrations of these solutes in the blood will be obtained using kinetic modeling methods for calculation of the solute clearances. If the total volume of the collected sample is 100 ml or more, then an aliquot of the sample will be shipped to the local laboratory of the dialysis unit for measurement of urea, creatinine, and phosphorus. If the urine sample is less than 100 ml, then the patient will be considered to be anuric.

3.1.6 Non-adherence and Deviations from the Protocol

If during follow-up a patient's randomized to the nocturnal home HD 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.

3.2 Duration of Treatment and Follow-up

Each patient will be treated in his/her respective group for 12 months, or until death, recovery of renal function or a stop-point is met (transplant, change to peritoneal dialysis, relocation to a non-study center – see Section 7.3). Except for those subjects who are transplanted, change to peritoneal dialysis, or die, data collection and follow-up will continue for all patients for a minimum of 12 months. For patients who relocate to a non-study dialysis unit or transfer to home hemodialysis during their 12 months of follow-up, all attempts will be made to collect vital status, the two co-primary outcomes (see Section 3.1), and the centrally administered quality of life questionnaires. When possible, the complete data collection procedures designated in the protocol will be maintained for subjects who switch to in-center HD. Those patients who are transplanted or switch to peritoneal dialysis will no longer be followed. Otherwise, no matter what happens to a patient, it is recommended that all attempts be made to encourage any subject who misses the two co-primary outcomes to provide these data for up to six months past his or her F12 window. Patients who need to switch from home HD to in-center HD due to an acute complication, new comorbid medical condition(s), patient or partner burnout or patient desire will continue to be followed in his/her respective group. Re-evaluation of each of these patients will be performed at regular intervals to determine if the patient is able and willing to restart home HD therapy. Adverse events hospitalizations and serious adverse events should be recorded for an additional 30 days after the patients' F12 month ends. Starting with the first dialysis session held at least 30 days after the patients' F12 month ends, one week of data should be recorded from the dialysis unit's run sheets. This data will include start time, end time, and pre and post weight and blood pressure for each dialysis session held during the week.

3.3 Methods to Protect Against Bias

Guidelines for dialytic and non-dialytic co-interventions have been stipulated (see Section 3.4) to reduce the risk that health care team enthusiasm for the novel therapy of nocturnal hemodialysis may lead to differences in care between the treatment groups. To reduce the risk that study personnel may influence patient responses to questionnaires, the HRQL, depression, and utility questionnaires will be administered centrally over the telephone by trained interviewers who are blinded to the patient's treatment assignment. Secondary outcomes that require in-person interviewer survey assessment will be administered by a study coordinator using standard scripts.

Patients on nocturnal home hemodialysis may perceive improvements in their HRQL which have more to do with the novelty of the therapy than to its true benefits ('honeymoon effects'). For this reason, the HRQL outcomes will be assessed at months 4 and 12. HRQL benefits due solely to the novelty of nocturnal hemodialysis would not be expected to persist over one year.

Due to increased opportunity for ultrafiltration, patients on nocturnal hemodialysis may have lower extracellular volume (ECV) than patients receiving HD three times per week. As a result, increases in blood concentrations of albumin, hemoglobin and biochemical parameters may be the result of normalization of ECV rather than true changes in these parameters. To limit volume-related confounding, left-ventricular mass will be assessed by MRI as this method is less subject to volume effects than is echocardiography.

Kt/V calculations may be affected by temporal proximity and amount of protein ingested before dialysis. To account for the possibility of this factor, the study will collect limited information about meal habits before and during dialysis.

3.4 Co-intervention Protocols not Related to Dialysis Dose

3.4.1 The Dialysis Prescription

a) Dialysis machines

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

b) Water quality

All Clinical Centers in the consortium will follow current AAMI standards for water, elemental and ionic purity. AAMI standards will be monitored in each home hemodialysis patient 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 home 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. We 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 home hemodialysis units will receive ultrapure dialysate. Individual hemodialysis units that are not part of the nocturnal consortium of Clinical Centers (i.e., outlying dialysis units) will be encouraged to use ultrapure dialysate. It is recognized, however, that individual hemodialysis units not part of the nocturnal consortium may not be able to achieve this goal due to 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.

c) 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 will not reuse dialyzers after they have been randomized. Patients who receive dialysis at one of the nocturnal Clinical Center's home hemodialysis units will be prescribed high flux dialysis and will not reuse during follow-up. Individual centers that are not part of the nocturnal consortium of Clinical Centers (i.e., outlying dialysis units) 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.

d) Dialysate Composition

In the conventional home hemodialysis group, standard dialysis baths will be used per local protocol and based on the patient's monthly laboratory values. In the nocturnal home 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 KDOQI (2006 dialysis update) 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 are completed twice during baseline.

Ongoing Treatment Once Patient Starts Nocturnal 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.

In addition, it is recommended but not required 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 KDOQI (2006 dialysis update) 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 home 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.

e) Ultrafiltration

In the conventional home 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.

3.4.2 Co-interventions and Standards of Care Not Related to Dialysis Prescription

These co-interventions are divided into 2 tiers.

Tier 1 co-interventions include those aspects of medical care that are unrelated, or only indirectly related to management of ESRD. These aspects are unlikely to be applied differentially between groups and thus should not introduce confounding. Recommendations based on clinical practice

guidelines will be made for items in this tier, but implementation of these recommendations will not be monitored and no data will be collected. Interventions in this tier include immunizations, diabetes and lipid management.

Tier 2 co-interventions include those aspects of medical care specifically related to ESRD for which there is evidence-based treatment recommendations, and that directly affect the clinical outcomes of this trial. Recommendations based on KDOQI (2006 dialysis update) guidelines will be made for items in this tier, and attempts will be made to monitor the implementation of these recommendations via regular data collection and feedback. Laboratory data from selected local labs will be optionally entered into the database on a monthly basis. For subjects who have values that fall outside the recommended ranges, feedback will be provided to the Clinical Center's research coordinator and treating nephrologist via automated reports generated by the DCC.

See the Manual of Operations for additional details regarding recommendations for each of the 2 tiers.

4. Vanguard Phase

4.1 Early Monitoring and Process Adjustments

Because this is the first randomized trial of six-times per week home nocturnal hemodialysis, it is possible that unforeseen obstacles may hamper the ability of the study to accomplish its objectives. Accordingly, the first 12 months of recruitment and follow-up in the trial have been designated as the Vanguard phase of the trial. During this period, automated weekly reports will monitor the progress of the study in achieving the following benchmarks: a) 80 randomized patients within one year of the start of enrollment, b) at least 95% of randomized patients successfully complete the modality specific post-randomization component of the training program for their assigned therapy and initiate home hemodialysis, c) 80% of patients attend at least 80% of scheduled dialysis treatments within each treatment arm, and d) 80% of patients attain 80% of their total prescribed weekly treatment time. If shortfalls in meeting these benchmarks are identified, processes for achieving recruitment and adherence targets will be modified to improve performance. The objective of the Vanguard phase is to identify and correct problems as rapidly as possible to increase the likelihood that the study will achieve its targeted recruitment and adherence goals, and to assure that any protocol changes are implemented very early in the trial so that a stable protocol will be in effect for the majority of the study. After the first year of the trial is completed, the Data Safety and Monitoring Board will review the success of the trial in meeting these benchmarks to determine if the trial should continue to completion. Specific plans for monitoring and implementing adjustments to meet the benchmarks are summarized below.

Recruitment:

Trends in enrollment patterns will be summarized by Clinical Center to determine if recruitment targets and resources allocated to specific centers should be modified. In particular, resources initially allocated to poorly recruiting Clinical Centers will be re-allocated to more successful centers. Reasons for exclusions prior to randomization will be monitored to determine if entry criteria should be modified to increase the randomization rate. A subcommittee of the Steering Committee (the Recruitment/Adherence Committee) has been designated and assigned the task of monitoring logistical impediments to recruitment at each participating Clinical Center. This committee will attempt to identify recruitment strategies which are successful at a specific Clinical Center and facilitate the implementation of these strategies at other Clinical Centers.

At the 1 year feasibility review by the DSMB, consideration will be given to revision of recruitment targets with a corresponding reallocation of resources between the in-center daily trial and the nocturnal dialysis trial if it is clear that one or the other of the trials will fall substantially short of its recruitment target.

Successful Completion of Training:

Trends in the successful completion of training will be summarized by Clinical Center to determine if training completion targets overall are being obtained. Thus Clinical Centers with low levels of training completion will be identified and efforts will be made to determine the reasons for the low rate of training completion. Members of the Recruitment/Adherence Committee will assist with ascertaining the reasons for low training completion and will suggest strategies to increase the rate of successful training.

Missed Dialysis Treatments:

Trends in the rate of missed dialysis treatments will also be monitored for each Clinical Center and related to patient characteristics. The Recruitment/Adherence Committee will monitor logistical impediments to adherence, and will attempt to identify successful strategies for maintaining adherence. As for recruitment, when a successful strategy is identified at a particular Clinical Center, the Recruitment/Adherence Committee will facilitate the implementation of these strategies at other centers. Consideration will be given to terminating recruitment at a Clinical Center if the level of adherence at that center is deemed to be unacceptable.

5. Outcomes

5.1 Outcome Measures

5.1.1 Summary of Primary and Secondary Outcome Measures

Sample size limitations prevent the specification of mortality as the single primary outcome measure in this trial. In addition, no single surrogate intermediate outcome measure is likely to adequately reflect the potential impact of nocturnal hemodialysis on the multiple aspects of ESRD morbidity. Thus, the efficacy of the treatment interventions will be evaluated for each of nine conceptually distinct therapeutic outcome domains. First priority outcome measures have been designated to be given primary emphasis in the interpretation of the trial results for seven of these nine domains (Table 7). Composite endpoints based on mortality and two of these measures, the change over 12 months in the SF-36 RAND physical health composite (PHC), and the change over 12 months in left ventricular mass, will serve as the co-primary outcomes of the trial. Mortality is included as a component of the primary composite outcomes in order to avoid the risk of bias that would have resulted were diseased patients excluded from the analysis. The changes over 12 months in LV mass and the PHC score, without the mortality component, along with the other 6 first prior outcomes in their respective domains, are the main secondary endpoints for the trial.

Table 7: Primary and Main Secondary Outcomes

Domain:	***Co-Primary Outcome***:
Cardiovascular Structure and Function	Composite of 12 month Mortality and change in Left-Ventricular Mass by cine-MRI
Health-related quality of life and physical function	Composite of 12 month Mortality and change in SF-36 RAND Physical Health Composite score (PHC)
Domain:	***Main Secondary Outcome Measure:***
Cardiovascular Structure and Function	Change in Left Ventricular Mass by cine-MRI
Health-related quality of life/physical function	Change in SF-36 RAND Physical Health Composite score
Depression/Burden of Illness	Change in Beck Depression Inventory score
Cognitive funtion	Change in Trailmaking Test B score
Nutrition and inflammation	Change in serum albumin concentration
Mineral metabolism	Change in pre-dialysis serum phosphorus concentration
Survival and hospitalizations	Rate of non-access hospitalization or death
Hypertension	-
Anemia	-

* All changes are meaured over 12 months of follow-up.

The composites of mortality with LV mass and of mortality with the PHC score were designated as co-primary endpoints in part due to the complementary nature of the information provided by LV mass and the PHC score. LV mass is an objective physiological marker of cardiovascular function but is not a clinical endpoint, while the PHC score is an important clinical endpoint, but as a self-reported outcome it may be affected by the subjects' knowledge of their treatment assignments in this unblinded study. Mortality is included as a component of the primary composite outcomes because of its clinical importance, and to avoid the risk of bias that could result if there are different rates of death between the 2 study groups and deceased patients are excluded from the analysis. However, due to the relatively short one year follow-up period, the number of deaths is expected to be limited, so the composite endpoints are expected to be determined by the LV mass and PHC score for most patients. A demonstration of positive effects on both of the primary composite outcomes will be interpreted as providing strong evidence of an overall benefit of the intervention to the patient. A significant positive effect on one but not both of the two co-primary composite endpoints, or significant effects in opposite directions for the two endpoints, would establish the effects of the intervention within the specific domains of the respective outcomes, but the implications regarding an overall benefit to the patient would be ambiguous.

The effects of the interventions on the two primary outcomes will each be evaluated using a variation of the Bonferroni procedure due to Hochberg [Hochberg 1998] to assure that the studywise Type I error rate for both of the co-primary out comes is no greater than 0.05. Statistical significance for each of the 7 main secondary outcomes will be set at a two-tailed alpha of 0.05. The results for the main secondary outcomes will be interpreted in the context of the trial results for the co-primary outcomes, with awareness that multiple hypothesis tests are being conducted. Following completion of the trial, the probabilities of obtaining 1, 2, or more positive results for the main secondary outcomes under the joint null hypothesis of no treatment effects on any of these outcomes will be evaluated based on the observed pattern of associations among the outcome measures.

Single main secondary outcomes are not designated for the hypertension and anemia domains because the intertwined effects of multiple factors within these domains makes it difficult to adequately represent treatment effects with individual outcomes. Key outcomes to be assessed for evaluation of the hypertension domain include pre- and post-dialysis blood pressures and antihypertensive medications; key outcomes for the anemia domain are EPO dose, iron stores, and hemoglobin level.

Additional outcomes will also be measured within each of the designated domains, such as bioelectric impedance measures for the nutrition domain and objective functional tests for the physical function domain. The change in the QALY score will be evaluated as part of the evaluation of cost-effectiveness analyses.

5.1.2 Primary Outcomes

The co-primary surrogate outcomes selected for the study are a composite of mortality with left ventricular mass measured by cardiac MRI, and a composite of mortality with the SF-36 RAND physical health composite score. Mortality is included in the primary composite outcomes because death is a fundamentally important clinical endpoint, and because incorporating mortality into the co-primary outcomes avoids the risk of biases associated with censoring of deaths. The LV mass and PHC components of the co-primary endpoints satisfy the following criteria which were used in selecting the primary outcomes:

1. Biological plausibility that the intervention will influence the parameter;
2. The parameter can be assessed in the study population;
3. A proven correlation between the parameter and mortality (and/or hospitalization, preferably the former), with a change in the parameter being associated with a change in mortality (and/or hospitalization)
4. Hypothesized responsiveness of the parameter to interventional changes;
5. Measured reliability and validity (face, construct, and criterion).

Details of these outcomes are provided below.

(1) Left Ventricular Mass

The change in the left ventricular mass (LVM) from baseline to 12 months will serve as the basis of the first of the two co-primary outcomes. The hypothesized treatment effect of the daily nocturnal

intervention on the mean change in LVM is 15 g. LVM will be assessed by the cine-magnetic resonance imaging (cine-MRI) technique at baseline and at 12 ± 2 months before termination of the study. It is assumed that at least 80% of all study participants will undergo a follow-up cine-MRI examination.

Left ventricular hypertrophy (LVH) is very common in the ESRD population, at the time of dialysis initiation LVH is found in over 80% of patients. Longitudinal studies have shown that LVH is a potent marker of cardiovascular death risk in patients with ESRD [Nakamura, 2002;Paoletti, 2004;Silaruks, 2000;Silberberg, 1989;Stack, 2002;Zoccali, 2001a;Foley, 1995] and thus serves as a good surrogate marker for mortality. Changes in LVM have been associated with clinically relevant differences in outcomes even over a relatively short one-year period [Foley, 2000]. In a recent study a 10% change in LVM correlated with a 22% improvement in all-cause mortality and a 28% improvement in cardiovascular mortality [London, 2001].

The major biological causes for LVH, volume overload and elevated blood pressure, may be positively influenced by increasing the frequency of hemodialysis. Volume overload and hypertension are pathophysiologically connected by expanded extracellular fluid volume which is caused by increased sodium and water retention in ESRD, particularly in patients without significant residual renal function [Lins, 1997;London, 2003;Onesti, 1975]. Furthermore, there is increased arterial stiffness and lack of vascular compliance in uremic patients that manifest both as increased systolic pressures and widened pulse pressures [Chaignon.M, 1981;Horl, 2002;Lins, 1997]. Development of LVH is also influenced by metabolic factors such as hypoalbuminemia, hyperhomocysteinemia, glycation end products, disturbed calcium-phosphate metabolism and secondary hyperparathyroidism [Blacher, 1999;Ganesh, 2001;Moon, 2000;Rostand, 1999;Scharer, 1999;Zoccali, 2001b]. Daily dialysis may affect each of these factors by improving volume control and increasing removal of uremic toxins. Data by Chan et al. in 28 nocturnal HD patients showed that LV mass decreased over 2 years from 147 ± 42 to 114 ± 40 g/m2 ($p = 0.004$) while a control group of 13 patients on conventional hemodialysis showed no change in LV mass during this same time period. [Chan 2003]

(2) SF-36 RAND Physical Health Composite (PHC)

The RAND Physical Health Composite (PHC) from the SF-36 will be used to define the second of the two co-primary outcomes for the trial. The short-form 36 (SF-36) is one of the most commonly used instruments to measure patient-reported health related quality of life in the world, and its 36 items making 8 subscales and 2 summary scales (physical and mental components) have been tested extensively for reliability, validity, and responsiveness in HD patients. [Allen, 2002;Beusterien, 1996;Cagney, 2000;DeOreo, 1997;Diaz-Buxo, 2000;Edgell, 1996;Levin, 1993;Merkus, 1997;Meyer, 1994;Rettig, 1997] The survey is well-accepted by HD patients, taking only 5 to 10 minutes to complete. [Kurtin, 1992; Rettig, 1997]. Studies in nocturnal hemodialysis patients have shown an improvement in both PCS and MCS scores from baseline [Brissenden, 1998;Kooistra, 1998;Lockridge, 1999;McPhatter, 1999;Mohr, 1999]. The minimal clinically important difference for a change in each of these scores has been suggested to be 3 to 5 points. [Hays, 2001; Samsa, 1999]

The RAND PHC score is used as a component of a co-primary outcome rather than one of the SF-36 summary scales (PCS, MCS) because the PCS and MCS can in some cases produce distorted results. [Simon, 1998] In one study, for example, the MCS failed to detect major clinical differences associated with disease progression, despite significant differences in its component

subscales. [Norvedt, 2000] The RAND PHC is based on the same SF-36 scales as the PCS score (physical function, role-physical, pain, general health perceptions). Unlike the PCS, however, the scoring algorithm used to calculate the PHC is based on non-orthogonal factor rotation. [Hays, 1998] This allows the PHC to correlate with mental health, unlike the PCS.

Because self-administered questionnaires may be more difficult to complete for the elderly, minority groups, and those with high comorbidity from trial participation [Unruh, 2003], all questionnaires will be administered by trained interviewers using computer-assisted interviewing (CAI). HRQL will be assessed at baseline, 4, and 12 months by interviewers blinded to treatment allocation through a central telephone service.

5.1.3 Main Secondary Outcomes

The secondary outcomes of the study are summarized in Table 8 below. Note that the change from baseline to 1 year in the LV mass score, without mortality, will serve as the main secondary outcome for the cardiovascular structure and function domain. In addition, the change from baseline to 1 year in the SF-36 PHC score, without mortality, is the main secondary outcome in the health related quality of life and physical function domain. The details for both of these measures are provided in Section 5.1.2.

5.1.3.1 Depression/Burden of Illness (Beck Depression Inventory)

Main Secondary Outcome:

The 12-month mean change in the Beck Depression Inventory v1 will be used as the main secondary outcome measure.

The Beck Depression Inventory, a 21 question well validated survey presented in multiple choice format, measures the presence and degree of depression in adults. Each of the answers is scored on a 0 to 3 scale, and inventory items correspond to a specific category of depressive symptom and/or attitude. It is frequently used to assess depression in patients with ESRD [Craven, 1988;Kimmel, 1995;Kimmel, 1998;Peterson, 1991;Sacks, 1990], and is associated with mortality in this patient population. [Kimmel, 2000] In addition, it has been previously used in daily HD patients. [Troidle, 2003]. The BDI will be measured at baseline, 4 months and 12 months.

5.1.3.2 Cognitive Function (Trailmaking Test B)

Main Secondary Outcome:

The change from baseline to 12 months in the Trailmaking Test B completion time will be the main secondary outcome to assess cognitive function.

Trailmaking Test B (Trails B) evaluates the ability to visually search, sustain attention, and perform cognitive shifting as the activity is completed. This test is brief, sensitive to subtle neuropsychological impairments, can be compared with age-adjusted norms, and is useful in monitoring the progression of neuropsychological dysfunction. Test-retest reliability, construct validity, and concurrent validity have been previously documented. The Trails B has been used in studies of ESRD and CKD and in patients following kidney transplantation [Kramer, 1996;Kurella, 2004;Umans, 1998]. In addition, this test works well over a wide range of cognitive function and is not subject to floor or ceiling effects.

In the Trails B test, the subject draws lines, connecting 25 circles that contain numbers from 1 to 13 and letters from A to L. The subjects must draw lines alternating from number to letter. The total time to complete the task is recorded. Errors are not counted, but the subject is alerted to mistakes made. They are instructed to correct them which increases the amount of time needed to complete the task. For this trial, Trails B has been selected as the main secondary outcome for evaluation of the cognitive function domain, as it assesses higher order "executive" functions in addition to attention and the skills necessary to complete Trails A. The Trails B test will be performed at baseline, months 4 and 12.

Table 8: Summary of Outcome Measures

Category	Outcome
Co-Primary Outcomes:	
Cardiovascular Structure and Function	Composite of 12 month Mortality and change in Left-Ventricular Mass by Cine-MRI
Health-related Quality of Life and Physical Function	Composite of 12 month Mortality and change in SF-36 Physical Health Composite Score
Secondary Outcomes: **(<u>9 domains</u> – those in bold are designated as main "priority" outcomes within the domain)**	
Cardiovascular Structure and Function	**Left-ventricular mass by cine-MRI** End-diastolic, end-systolic, and stroke volumes, ejection fraction, cardiac output Rate of intradialytic hypotension episodes Interdialytic weight gain
Health-related Quality of Life/Physical Function	**SF-36 Physical Health Composite score** Health Utilities Index score Feeling Thermometer score Medical Outcomes Study Sleep Scale Lower Extremity Performance Battery* score
Depression/Burden of Illness	**Beck Depression Inventory, v1 score**
Cognitive Function	**Trailmaking Test B score** Modified Mini-Mental Status score
Nutrition and Inflammation	**Serum albumin** Normalized protein catabolic rate Body mass index Lean body mass by single frequency bioimpedance analysis

Mineral Metabolism	**Predialysis serum phosphate**
	Predialysis serum calcium
	Calcium-phosphate product
	Parathyroid hormone
	Phosphate binder dose
Survival and Hospitalization	Rate of non-access hospitalizations or death
	Rate of access hospitalizations
	Rate of all hospitalizations or death
	Rate of cardiovascular hospitalizations or death
	Total hospital days (over 12 months)
Hypertension	Average pre-dialysis blood pressure
	Average post-dialysis blood pressure
	Average pulse pressure
	Proportion of patients with wkly average predialysis systolic blood pressure <110 mmHg
	Number of prescribed antihypertensives
Anemia	Pre-dialysis hemoglobin
	Erythropoietin dose
	Cumulative intravenous iron requirements (over 12 months)
	Serum ferritin and transferrin saturation
Adverse Events and Risks:	
Vascular Access Complications	Time to first access intervention
	Rate of access interventions
	Time to first access failure
	Rate of access failures
	Rate of infection related failures
Patient Burn-out	Proportion of patients requiring dialysis modality change over 12 months
	Monthly average number of missed treatments (baseline and monthly)
	Weekly average number of shortened treatments (baseline and monthly)
Treatment Burden:	
Patient Burden	Minutes to recovery
	Proportion of patients wishing to continue, or switch to nocturnal HD at 12 months

*gait speed, time to stand, standing balance

5.1.3.3 Nutritional Status (Serum Albumin)

Main Secondary Outcome:

The mean change in serum albumin from baseline to 12 months will be the main secondary outcome measure of nutrition and inflammation.

Malnutrition is common in maintenance dialysis patients [Allman, 1990; Alvestrand, 1996; Bansal, 1980b; Bellizzi, 2000; Centers for Medicare & Medicaid Services: 2001 Annual Report: End Stage Renal Disease Clinical Performance Measures Project, 2002] and interventions that successfully treat malnutrition are uncommon. A lower serum albumin level is strongly associated with increasing mortality rates [Leavey, 1998; Lowrie, 1990; Pifer, 2002] and even a 10 – 15% decrease in serum albumin level is associated with an increase in mortality rates. [Combe, 2001; Culp, 1996] In the HEMO Study, the mean serum albumin level declined by 0.21 g/dL and this decline was not significantly affected by either the high dose or high flux interventions. [Rocco, 2004]

In addition to being influenced by protein and energy nutritional status and changes in hydration status, serum albumin is also an acute phase protein whose synthesis is suppressed in the presence of inflammation. [Kaysen, 1995; Kaysen, 1997a; Kaysen, 1997b] The association between serum albumin and mortality may thus be magnified by its dual status as a marker of both malnutrition and disease (inflammation) even when hydration status is constant. [Stenvinkel, 1999; Zimmermann, 1999] It is also not surprising that there is ample evidence linking hypoalbuminemia with atherosclerotic disease [Bergstrom, 1998;Stenvinkel, 1999;Zimmermann, 1999] congestive heart failure [Bergstrom, 1998] and infectious complications. [Churchill, 1992; Bansal, 1980a; Mattern, 1982]

Despite the numerous advances in hemodialysis therapy in the past ten years, including higher doses of dialysis and better anemia control, there has been no significant change in serum albumin levels during the past ten years, as measured by the Centers for Medicare and Medicaid Clinical Performance Measures project. [Centers for Medicare & Medicaid Services: 2001 Annual Report: End Stage Renal Disease Clinical Performance Measures Project, 2002] In the HEMO Study, neither the high flux nor high dose interventions affected the slow progressive decline in serum albumin levels seen in this patient cohort. [Eknoyan, 2002] Using a basic informative censoring model, there was a decline in serum albumin levels of approximately 0.21 g/dL over a follow-up period of three years in the HEMO Study cohort. [Rocco, 2004] Clearly, if daily nocturnal home hemodialysis patients have a statistically significant increase in serum albumin levels compared to patients in the control group, this will be one of the few therapies that demonstrate such a result.

For all of these reasons, the change in serum albumin levels from baseline to 12 months will be the primary nutritional outcome for this study. Serum albumin levels will be obtained monthly by the Clinical Center's local laboratory. The method used to measure the serum albumin level and the normal range for the lab will also be obtained.

5.1.3.4 Mineral Metabolism (Predialysis Serum Phosphorus Concentration)

Main Secondary Outcome:

The mean change from baseline to 12 months in pre-dialysis serum phosphate has been selected as a main secondary outcome based on its potential role in cardiovascular disease in ESRD.

Hyperphosphatemia is an independent risk factor for death among patients on chronic hemodialysis, especially cardiovascular deaths.[Block, 1998;Block, 2004;Ganesh, 2001] Block et al reported that the risk for all cause mortality increased when the baseline serum phosphorus was more than 6.6 mg/dl while Ganesh et al reported that patients with a serum phosphorus level more than 6.5 mg/dl had an increased risk of death due to coronary artery disease. A more recent publication by Block shows that the association between hyperphosphatemia and increased risk of death is progressive, with higher serum phosphorus levels associated with a higher risk of death [Block, 2004]. Although the mechanisms by which hyperphosphatemia cause cardiovascular mortality and morbidity is not completely understood, vascular calcification is likely to be one of these mechanisms. [Safar, 2002] There is a correlation between elevated serum phosphorus levels and elevated coronary calcium scores, [Raggi, 2002] a surrogate measure of coronary artery disease. It is no longer believed that vascular calcification is a passive process due to deposition resulting from an elevated calcium phosphorus product. [Moe, 2002] Hyperphosphatemia may cause calcification via the induction of genes for bone protein formation by vascular smooth muscle cells. [Jono, 2000] In addition, vascular calcification is also influenced by both tissue-specific cellular mechanisms and plasma components. [Bostrom, 2000; Schinke, 2000; Schinke, 1998]

The extent of arterial calcification in patients on chronic dialysis therapy far exceeds that of persons in the general population. [Braun, 1996; Goodman, 2000; Raggi, 2002] and the progression of arterial calcification is more rapid in patients treated with dialysis than in subjects from the general population. [Chertow, 2002; Goodman, 2000] Arterial calcification in adults with CKD is associated with an increased risk of death as well as adverse clinical outcomes such as myocardial infarction, congestive heart failure, endocarditis, and valvular heart disease. [Blacher, 2001;Raggi, 2002] Due to financial constraints, it will not be possible to measure coronary calcium scores in this patient cohort.

It has been difficult to achieve normal serum phosphorus levels in chronic hemodialysis patients receiving three times per week in-center hemodialysis. The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Improvement (K/DOQI) bone guidelines recommendation that the serum phosphorus level be maintained between 3.5 mg/dl and 5.5 mg/dl. In a national database with more than 40,000 patients, 20% of patients had a serum phosphorus level between 6 and 7 mg/dl, 11% had a level between 7 and 8 mg/dl and 9% had a level greater than 8 mg/dl. [Block, 2004] Clearly, new methods are needed to help decrease serum phosphorus levels. Preliminary studies suggest that patients on nocturnal dialysis can achieve normal serum phosphorus levels without the need for phosphate binders. [Mucsi, 1998]

In sum, hyperphosphatemia is a common biochemical abnormality in chronic hemodialysis patients and is a potentially preventable cause of serious adverse clinical outcomes. Thus, even though the serum phosphorus level is influenced by the number of phosphate binders prescribed, it was decided that the serum phosphorus level, and not the number of phosphate binders prescribed, would be the primary outcome for mineral metabolism. The use of phosphate binders by patients will be tracked at baseline, months 4 and 12. Physicians will be encouraged to follow KDOQI (2006 dialysis update) guidelines for the management of hyperphosphatemia. Serum phosphorus levels will be obtained at least once per month. If there is more than one value per month, then the first value of the month will be used for analytic purposes.

5.1.3.5 Clinical Events (Rate of Non-Access Hospitalizations/Death)

The rate of non-access hospitalizations or death has not been designated as a main secondary outcome since there is insufficient power to detect treatment differences. Also, the rate of all hospitalizations was not used as a main secondary outcome because:

a) The evidence supporting a beneficial effect of frequent dialysis on access hospitalizations is not regarded by the Steering Committee as being as compelling as the evidence of a beneficial effect on non-access hospitalizations. Hence, the assessment of the Steering Committee is that inclusion of access hospitalizations would have reduced the power to detect a beneficial effect,

b) The mechanisms by which the interventions are hypothesized to influence access and non-access hospitalizations are distinct,

c) The expanded use of outpatient procedures to perform access repairs was expected to complicate the identification of access hospitalization.

A non-access hospitalization will be defined as an inpatient stay in an acute care hospital that includes an overnight stay. This is the same definition used for the HEMO Study.

5.1.4 Other Main Secondary Outcome Domains

5.1.4.1 Hypertension Domain

Hypertension is an important comborbidity in the hemodialysis population, and high levels of systolic (SBP) blood pressure are strongly associated with total mortality, coronary events, and stroke in the general population. Some studies have shown that pre-dialysis systolic blood pressure is a good predictor of cardiovascular events [Tozawa, 2002] and correlates well with mean ambulatory 24-hour systolic blood pressure and left ventricular mass in hemodialysis patients [Conion, 1996]. In this study comparing different home hemodialysis treatment schedules, the interpretation of the results for the hypertension domain must take into account the interplay between several complicating issues, including:

a) the intertwining of blood pressure level with the level of anti-hypertensive medication,

b) declining blood pressures in dialysis patients experiencing worsening cardiac function,

c) the dependence of the shape of the curve defining blood pressure levels vs. time on the dialysis treatment schedule, so that the difference between predialysis blood pressure levels and the time-averaged blood pressure may differ between the treatment groups,

Due to issue (a), a treatment that improves hypertensive status may either reduce blood pressure or the level of antihypertensives that are prescribed to control blood pressure within standards of care goals. This second issue (b) is especially evident in observational studies in dialysis patients which have reported that both lower and higher levels of blood pressure are associated with increased risk of cardiac and cerebrovascular mortality [Foley, 2002;Port, 1999;Tozawa, 2002;Zager, 1998]. The elevated mortality risk associated with low pre-dialysis SBP probably reflects a high prevalence of cardiac failure and cardiomyopathy rather than adverse effects of lower blood pressure *per se* on outcome. In the context of this randomized trial, it is possible that an intervention that improves cardiac health may reduce the proportion of patients with declining blood pressures resulting from declining cardiac function, thus potentially masking beneficial effects of that intervention on the mean blood pressure level. The third issue (c) refers to the fluctuating pattern of blood pressure

levels in hemodialysis patients, which decline during dialysis treatments and increase between treatments. Due to these variations in blood pressure level in association with the dialysis treatment schedule, it is possible that a comparison of blood pressures in patients on a 6 times per week intervention vs. patients on a 3 times per week intervention may yield different results depending on the timing of the blood pressure measurements in relation to the dialysis treatments.

Two strategies will be used to address these issues. First, in both treatment arms the primary assessment of blood pressure level will be based on the average of a sequence of 12 home blood pressure readings obtained over a mid-week 2-day period obtained in the home and the average of 12 home blood pressure readings obtained over a weekend 2-day period obtained in the home.(see Section 6.2). Blood pressure readings are obtained mid-week and on the weekend in order to capture the potential difference in blood pressure readings that may occur on the weekend due to the longer interdialytic interval. The protocol for the home blood pressure readings should avoid bias from white-coat effects, and by averaging over multiple times points is intended to minimize confounding due to factor (c). Second, rather than designating a single main blood pressure outcome, the effects of the interventions on the hypertension domain will be evaluated based on three different outcomes related to changes in blood pressure over time. In addition to the 48-hr home blood pressure measurement protocol, pre- and post-dialysis blood pressures and the use of antihypertensive medications will be recorded at baseline, and then at months 4, and 12 during follow-up. As described in Section 9.11, the effects of the interventions will be evaluated primarily based on three different outcomes: i) the change from baseline to 12 months in the 48-hour average systolic blood pressure, ii) change from baseline to 12 months in the number of antihypertensives prescribed, and iii) change from baseline to 12 months in the proportion of patients with 48-hour average pre-dialysis systolic blood pressure less than 110 mmHg.

In addition to consideration of systolic blood pressure, pulse pressure will be used as a further secondary cardiac outcome parameter. Pulse pressure is correlated with objective measures of vascular calcification in patients with hyperlipidemia [Miwa, 2004] and both systolic and pulse pressure are associated with measures of vascular stiffness [Izzo, 2004;London, 2004].

5.1.4.2 Anemia Domain

Anemia is present in the vast majority of patients with end-stage renal disease (ESRD) and is caused primarily by an inadequate production of endogenous erythropoietin (EPO), although recent evidence suggests that there is a component of EPO resistance as well, likely reflecting a state of chronic inflammation. While debate continues over the appropriate target hemoglobin, partial correction of anemia in ESRD patients has been shown to decrease mortality [Ma, 1999] and hospitalizations [Xia, 1999], and improve quality of life [Evans, 1990], cognitive and brain function [Pickett, 1999]. Achieving efficient treatment of anemia requires the use of recombinant forms of EPO (Epogen™ or Aranesp™ in the US), as well as administration of iron (Infed™, Dexferrum™, Ferrlecit™ or Venofer™ in the US), generally parenterally, in hemodialysis patients.

The use of nocturnal dialysis has been reported to improve anemia, determined by higher hemoglobin levels at a fixed or lower EPO dose, or a stable hemoglobin, but at a lower EPO dose. Use of the EPO index (weekly EPO dose in units divided by the hemoglobin in g/dL) provides a quantitative measure of the impact of more frequent dialysis on the “efficiency” of EPO administered. Klarenbach et al reported a 39% reduction in EPO dose after 15 months of quotidian dialysis, with patients on either daily nocturnal or daily short dialysis [Klarenbach, 2002]. Chan et al noted a significant decrease in EPO dose in 28 patients on nocturnal daily dialysis from 10,372 to

8,090 U/week [Chan, 2002]. Pierratos more recently reported that 26% of patients on daily nocturnal hemodialysis were not receiving EPO but were maintaining target hemoglobin levels [Pierratos, 2004]. In an earlier analysis of this patient population the reduction of EPO use was associated with a 40% decrease in costs for EPO [McFarlane, 2002].

A number of other parameters are important in anemia management, including the achieved hemoglobin level, the iron status of the patient, and the amount of IV iron that is needed to maintain adequate iron stores. For this study the following parameters will be tracked related to anemia:

1. Hemoglobin
2. EPO dose and route of administration
3. Ferritin
4. Transferrin saturation
5. IV Iron administered (formulation, route of administration, total monthly dose).

EPO dose will be calculated as units used per month, and obtained at baseline and follow-up months 4, 8 and 12.

Due to the intertwining of EPO dose and hemoglobin level, the effect of the interventions on anemia will be evaluated by considering both of these endpoints rather than designating a single main outcome for the anemia domain. See Section 9.11 for details.

5.1.5 Other Secondary Outcomes

5.1.5.1 Cardiac Function, Hypertension and Volume

a) Additional Measurements by Cardiac MRI. In addition to the determination of left ventricular mass, the cine MRI technology allows for the measurement of cardiodynamic parameters including end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, ejection fraction (EF), and cardiac output (CO). Some of these measures are influenced by volume status (EDV, ESV), whereas others are indicators of cardiac function and atherosclerotic changes (stroke volume, EF, and CO). The change in these parameters between baseline and termination of the study at 12 months will be used as additional secondary outcome parameters.

b) Intradialytic Hypotension. Intradialytic hypotensive episodes (IDHE) occur in approximately 20% of standard 3x/week dialysis treatments. In addition to complicating delivery of an adequate treatment, repeated IDHE might conceivably cause micro-ischemia to critical body organs, including brain, heart, intestines, and thereby contribute to an increased risk of hospitalization and death. Only recently has it been shown that hemodialysis associated hypotension is an independent risk factor for mortality. In one study the effect was no longer present after adjusting for comorbidity [Tisler, 2003]. In another paper, mortality was increased, especially when SBP falls from pre-dialysis levels of $\leq$ 140 mmHg to below 100 mmHg [Shoji, 2004]. In the HEMO Study IDHE episodes were clearly related to increased mortality risk [Daugirdas, 2003], although, similar to Tisler et al., the mortality effect was no longer present after adjusting for predialysis SBP. It is hypothesized that more frequent HD will reduce the rate of IDHE. In nocturnal hemodialysis, the weekly ultrafiltration volume may actually increase, since patients may drink more, however, the ultrafiltration volume per session as well as the ultrafiltration rate (ml/hour) will likely decrease. In addition, since plasma volume refilling during the first 2 hours of a dialysis session is generally faster than later in the dialysis treatment, it is hypothesized that IDHE will be reduced with

nocturnal hemodialysis. If more frequent HD substantially reduces IDHE, this therapy may reduce mortality and other hard CV outcomes. Data will be collected during baseline dialysis sessions pre-randomization, while the patient is undergoing 3x/week dialysis, and then during a midweek dialysis session each month. The rate of IDHE will be computed as fraction of reported sessions during which IDHE occurred. Factors associated with IDHE (as identified in the HEMO Study) will be tested to see if they predict IDHE in either group. Subanalyses will include weekly ultrafiltration volume and its dependence on dialysate sodium concentration.

c) Interdialytic Weight Gain. A decrease in interdialytic weight gain has been hypothesized to be one mechanism by which improvements in LV mass can be seen. Thus, interdialytic weight gains will be determined each month for the 48 and 72 hour dialytic interval in the standard arm and for the 24-hour and 48-hour dialytic interval in the nocturnal arm of the trial. The collection of this data will be performed during the same week that the pre-dialysis blood pressure data is collected.

5.1.5.2 Physical Function and HRQL

5.1.5.2.1 Physical Function

a) Lower extremity performance battery. Muscle size, quality and function may be altered in the face of uremia. It is unknown whether uremia contributes to impaired physical function directly (i.e., via toxicity of retained solutes), or indirectly, because of associated malnutrition, hyperparathyroidism, vitamin D deficiency or other factors. In a cross-sectional study, age, serum albumin, and Kt/V_{urea} were associated with gait speed and time to stand testing, explaining 52% and 46% of variability [Johansen, 2001].

In addition to the PCS of the SF-36, several objective measures of physical function will be included as secondary outcomes. The strengths and limitations of self-reported vs. objective measures of physical function were deliberated. Since it was anticipated that many study subjects would be unable to complete objective tasks, and the link between these tasks and mortality have not been established, the PCS was selected as the primary outcome for the physical function domain. However, it was recognized that the SF-36, being self-reported, might be biased, particularly as the study intervention is not blinded. Therefore, the Investigators believed that the inclusion of objective measures of physical function was vital to understanding the effects of nocturnal hemodialysis on this domain. The tasks selected include: gait speed, time to stand, and balance. Tasks will be assessed at baseline, 4 months and 12 months.

A lower extremity performance battery (LEP) designed for use in a large epidemiological study, the Established Populations for Epidemiological Study of the Elderly (EPESE) is the measurement of choice for this study [Guralnik, 1994]. The LEP consists of 3 tasks that represent activities necessary to be mobile: standing balance, walking speed, and timed chair stands. The LEP combines gait speed, chair rise time, and balance skills into a cumulative score of function. The LEP score shows excellent reliability [Ostir 2002] and it is also highly responsive to change [Onder, 2002]. The tests discriminated risk of death and nursing home placement in the total older population in the EPESE study [Guralnik, 1994]. In a subset of older adults with no self-reported disability reported from EPESE studies, the LEP also predicted functional decline and hospitalization over 4 years. Recently, the LEP was used in a clinical setting as a quantitative estimate of future risk for hospitalization and decline in health and function in a population of older adults [Studenski, 2003]. In that clinical setting, the physical performance measures were independent predictors of use, change in health status, and decline in function in a primary care

clinical environment, after accounting for baseline status, age, a hospital risk estimator, and primary physician's risk estimate. Performance measures alone, or in combination with self-report measures also predicted outcomes better than self-report alone [Studenski, 2003].

Performance testing will be conducted prior to a dialysis treatment since performance scores on the LEP can be affected after a single dialysis treatment [Tawney, 2004]. Performance scores will be derived for each test (balance, walk, and chair stands); with a score of 0 representing the inability to complete the test and 4 the highest level of performance. Ordinal categories for the 4 meter walk, chair stands, and balance tests will assigned based on reference tables developed for elderly people who participated in the EPESE study [Guralnik, 1994]. The individual balance, walk, and chair stands scores category scores will also be summed to create am overall LEP (0 –12). The LEP incorporates missing data into the tests results by assigning a 0 score while those who are able to complete the test are assigned a score according to the quartile of performance. This means that patients who were not capable of performing a test were still assigned a score.

All physical function tests will be performed at baseline, 4 months and 12 months.

5.1.5.2.2 Cognitive Function

a) Modified Mini-Mental Status. In addition to the Trailmaking Test B (Trails B), the Modified Mini-Mental Status (3 MS) will be performed. The 3 MS is a widely used tool to determine global cognitive function. Although likely to be less sensitive to change than the Trails B, its broad use, acceptance in the cognitive function literature, and the availability of age-matched, population norms makes it attractive to apply in the nocturnal HD Study. Published studies suggest that approximately one-quarter of patients with ESRD have evidence of global cognitive impairment, as defined by a 3 MS score <80 [Kurella, 2004;Sehgal, 1997]. Adjusted mean scores tend to decline with declining kidney function, suggesting a relation between uremia and global cognitive impairment. Anemia, hyperparathyroidism, hypertension and hyperlipidemia may be associated with cognitive impairment; these factors be modified by nocturnal HD, and may mediate some of the potential benefit of SDHD on cognitive function if one exists. The 3 MS requires approximately 5-10 minutes to complete. These tests will be performed at baseline, months 4 and 12. The main analyses will compare changes in the 3 MS scores from baseline to month 12.

5.1.5.2.3 Other Quality of Life Related Secondary Measures

a) Health Utilities Index (HUI). The Health Utilities Index, Mark 3 (HUI3) is a 21-item generic health instrument for determining overall utility associated with particular health states [Furlong, 2001]. The HUI questionnaire is composed of eight attributes of high importance to members of the general population: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. A preference-based scoring function, based on multi-attribute utility theory, allows one to converts questionnaire responses into a measure of overall health utility, which can then be used to calculate quality-adjusted life years (QALYs) in clinical trials.

   The Health Utilities Index (HUI) has been validated and used in many observational studies and clinical trials sponsored by NIH. A number of ongoing CKD and ESRD studies are using the HUI, including Intensive vs. Conventional Renal Support in Acute Renal Failure: Economic Analysis, Assessing QALY in Chinese renal failure patients (Hong Kong), Pilot Study of Chronic Renal Insufficiency and Functional Abilities in Renal Subjects (F.A.I.R.S.). Cost effectiveness is commonly used to determine the potential advantage of a new technology

compared to standard therapies. The Health Utilities Index will be obtained at baseline, and months 4 and 12.

b) Feeling Thermometer. The feeling thermometer is a single question that asks patients to rate their own health on a visual analog scale from 0 to 100 with 0 being dead and 100 being perfect health [Baldassarre, 2002;Schunemann, 2003]. The feeling thermometer has been used in numerous studies to permit patients to provide preference ratings of their own health status (health utilities). Although it has not been shown to discriminate between dialysis modalities [Churchill 98], it has demonstrated responsiveness to therapy in multiple health states[Baldassarre, 2002;Schunemann, 2003]. Thus, the change from baseline to month 12 in feeling thermometer score will be used as an additional secondary outcome in this trial. The feeling thermometer will be obtained at baseline, months 4 and 12.

c) Sleep. The Medical Outcomes Study (MOS) Sleep Scale is an 12-item measure that includes items on sleep initiation and maintenance, sleep adequacy, daytime somnolence, and respiratory disturbance; 10 items of the instrument are summed to obtain an overall sleep score (Sleep Problems Index) [Unruh, 2003]. Subjects are instructed to relate responses to sleep habits over the previous month. The SPI showed good internal consistency reliability (Cronbach's alpha = 0.70) and discriminative validity, with lower (worse) overall sleep scores in HD patients versus patients without known kidney disease [Unruh, 2003]. Self-reported sleep complaints have been noted to have similar frequency between different dialysis modalities [De Vecchi, 2000]. The MOS Sleep Scale will be performed at baseline, months 4 and 12.

5.1.5.3 Nutritional Status

There is no ideal nutritional marker, due to the lack of a single variable that is easily performed, reproducible, inexpensive and can predict outcomes. Thus, most studies rely on a combination of nutritional markers to assess nutritional status. Some of the markers that have been used include the Subjective Global Assessment (SGA), normalized protein catabolic rate (nPCR), measures of body size, including height, weight and body mass index (BMI) and measures of lean body mass such as duel energy x-ray absorptiometry (DEXA), multifrequency bioimpedance (BIA), anthropometrics and creatinine kinetics and. In addition, nutritional status is affected by the presence of inflammation and a variety of markers have been used to measure inflammation. C-reactive protein (CRP) is the most commonly measured inflammatory marker in dialysis patients.

The normalized protein catabolic rate has been used in dialysis patients for many years as a measure of dietary protein intake. It is much easier to determine dietary protein intake from nPCR than from diet records, interviews by dietitians or by using food frequency questionnaires. [Panzetta, 1990] The use of the nPCR assumes, however, that the patient is in neutral nitrogen balance, an assumption that is not always met and an assumption that has not been tested in nocturnal hemodialysis patients. In addition, there is now evidence that a low nPCR is not associated with an increased risk of mortality in chronic hemodialysis patients. [Pifer, 2002;Rocco, 2004] Therefore, in this study, nPCR will be used as a surrogate for dietary protein intake. The change in nPCR over 12 months will be determined. The same method used in the HEMO Study will be used to determine nPCR values. nPCR will be calculated on a monthly basis.

Higher BMI has been shown to be protective in chronic dialysis patients, a finding that is contrary to that found in the general population. [Cheung, 2000; Hakim, 1999;Kopple, 1997;Sarnak, 2000] In the HEMO Study, the mean post-dialysis weight declined by about 2.7 kg at three years under the informative censoring model, with no significant differences between the randomized treatment groups through year 3. [Rocco, 2004] In addition, there was an association between an increased risk of mortality and a lower cross-sectional BMI level in the range below 25 $kg/cm^{2.}$ Also, declining BMI was associated with an increased risk of mortality, on average, regardless of either the patient's current or 12 month prior BMI level. The measurement of BMI is confounded in dialysis patients, however, by the presence of both muscle wasting and excess fluid weight. In CKD patients with residual renal function that allowed for the collection of 24 hour urine for creatinine excretion, the survival advantage for patients with high BMI was found only in those patients with low body fat and in the low BMI group, high body fat and low muscle mass were associated with an increased risk of death. [Beddhu, 2003] These data imply that maintenance or increasing muscle mass and/or lowering body fat may be important in decreasing mortality rates in dialysis patients and that measurement of lean body mass will be an important outcome to measure in this study (see below). BMI will be calculated on a monthly basis.

Of the several measures that can be used to assess lean body mass, DEXA is the most reliable. [Kerr, 1996] DEXA is not routinely available, [Jones, 2002] however, and no studies have been performed to determine if lean body mass, as measured by DEXA, is predictive of outcome in dialysis patients. Single frequency bioimpedance has been shown to be associated with both morbidity and mortality in dialysis patients. [Chertow, 1997;Ikizler, 1999] However, all bioelectrical impedance methods employ some form of predictive modeling to obtain estimated outcomes. Thus, large errors in individual limit its clinical use, especially when persons are monitored repeatedly. The predictive errors for an individual are large so that repeated estimates are insensitive to small responses to treatment. [Chumlea 2004, in press] In addition, BIA may not be very precise for measuring body composition in both underweight and obese patients since height and weight are major sources of variation in the BIA prediction models [Guida, 2001].

Anthropometrics were used to measure body composition in the HEMO Study. In this study, the mean levels of both upper arm and calf circumference declined throughout three years of follow-up in all treatment groups, although the decline was less in the high flux group for upper arm and calf circumferences (by 0.35 ± 0.16 cm ($p = 0.031$) and 0.31 ± 0.13 ($p = 0.015$) respectively, representing 1.2% and 0.9%, respectively of the mean baseline values for these factors). [Rocco, 2004] Anthropometrics can also be used to obtain information on subcutaneous fat thickness on the limbs and trunk (triceps and subscapular skinfolds), internal adipose tissue (abdominal circumference), [Després, 1991] midarm muscle area (combination of midarm circumference and triceps skinfolds), frame size (elbow breadth) [Chumlea, 2002] and knee height (to estimate stature in amputees or patients unable to stand) [Chumlea, 1994;Chumlea, 1998]. Calf circumference is an indirect measure of muscle mass [Patrick, 1982] and fat free muscle mass can be calculated when the measurements for biceps, triceps, subscapular and suprailiac skinfolds are obtained [Heymsfield, 1982]. These latter calculations are also susceptible to the same criticisms noted above for bioimpedance for specific patient subgroups such as obese and underweight patients. In addition, anthropometry is more time-consuming than bioimpedance and the calculation of fat free mass cannot be done if one of the four skinfold measures is unable to be obtained. This situation occurred in about 10% of the HEMO Study patients [Rocco, 2004]. For this study, single frequency BIA should be performed at baseline, 4 months and 12 months. The BIA is not required for

randomization. All measurements should be carried out immediately prior to a mid week dialysis treatment (Wednesday or Thursday) in the recumbent position for patients in the standard arm of the study.

5.1.5.4 Mineral Metabolism

Three other aspects of mineral metabolism will be measured in this study: Changes in the use of phosphate binders, change in serum calcium level and change in serum PTH level. As noted in 5.1.3.4 above, the serum phosphorus level can be influenced by the use of phosphate binders. The type and amount of phosphate binders will be collected at baseline, months 4 and 12 in all patients. This information will be important since the rate of progression of coronary artery and aortic calcification was greater in patients receiving large oral doses of calcium-containing compounds versus sevelamer. [Chertow, 2002; Chertow, 2003] It is anticipated that there will be a decrease in the number of phosphate binders prescribed in patients in the nocturnal arm of the study. [Mucsi, 1998] Although there is also likely to be an increase in protein and thus phosphorus intake in nocturnal study patients, financial constraints do not allow for the determination of phosphorus intake over time in this patient cohort.

Hypercalcemia is a risk factor for mortality in chronic hemodialysis patients [Block, 2004;Foley, 1996]. The use of calcium-based phosphate binders increases the risk of hypercalcemia, [Chertow, 2002;Chertow, 2003] and hypercalcemia is also a risk factor for vascular calcification. [Raggi, 2002] Conversely, most studies have not shown a relationship between hypocalcemia and mortality. Nocturnal dialysis patients are at risk for hypocalcemia, and a higher dialysate calcium level is needed to help prevent this problem. [Al Hejaili, 2003] Thus, serum calcium levels will be obtained on a monthly basis. If there is more than one value in a particular month, then the first value of the month will be used for analytic purposes. The percentage of patients with normal serum calcium levels will be determined at baseline and months 1 and 2 and compared to the percentage of patients with normal serum calcium levels during months 4 – 6 and months 10 - 12.

There is evidence that both hyperparathyroidism and hypoparathyroidism is associated with an increased risk of death. Dialysis patients with hyperparathyroidism are more likely to develop myocardial fibrosis [Amann, 1994] and patients with an elevated PTH level have an increased risk for all cause and cardiovascular mortality. [Block, 2004; Ganesh, 2001] More recent studies have also shown an association of hypoparathyroidism (defined differently by each investigator) and cardiac morbidity and mortality. [Guh, 2002; Tsuchihashi, 2000] One hypothesis for this observation is that hypothyroidism leads to adynamic bone disease that prevents the uptake of serum calcium. This loss of bone buffering results in the availability of calcium for deposition into blood vessels and soft tissues. Thus, the percentage of patients with normal serum PTH levels will be determined at baseline and months 1 and 2 and compared to the percentage of patients with normal PTH levels during months 4 - 6 and months 10 - 12. In addition, the use of vitamin D analogues will be ascertained during these same time intervals.

5.1.5.5 Hospitalization/Death

In addition to the main secondary outcome defined by the rate of non-access hospitalizations or death, the rates of the following additional hospitalization related outcomes will be obtained and compared between the treatment groups:

a) Rate of access hospitalizations

b) Rate of all hospitalizations or death

c) Rate of cardiovascular hospitalizations or death.

5.1.5.6 Vascular Access Events

Vascular access events will be tracked for both study endpoints and for safety. All vascular access procedures, including both inpatient and outpatient procedures, will be tracked on a monthly basis using a modification of the HEMO Study form 6. Vascular access procedures will include angioplasty, stenting, use of thrombolytics in fistulas or gortex grafts, removal of a permanent access (and reason for removal) and placement of a new permanent access.

5.1.5.7 Treatment Burden and Experience with Nocturnal Hemodialysis

The primary assessment of treatment burden will be based on the question: "How long does it take you to recover from a dialysis session in minutes?" This question was asked as part of a "Dialysis Symptom and Fatigue" questionnaire given to patients participating in the London Daily/Nocturnal HD Study [Heidenheim, 2003]. The other components of the "Dialysis Symptom and Fatigue" questionnaire had previously been validated [Lindsay, 1994] and were part of a battery of established QOL tools used in the London Study. The investigators of the London Daily/Nocturnal HD Study have reported that this question was successfully answered on 313 of 314 occasions. This single question instrument was positively correlated with subscales evaluating fatigue, disease stress, and psychosocial stress, and was negative correlated with the SF-36 physical and mental component summary scores. The instrument also had a high test-retest correlation of $r = +0.86$ over a 3-month time interval. The London Daily/Nocturnal HD Study indicated large reductions in recovery time were observed on both the daily and nocturnal dialysis therapies after patients switched to these therapies from conventional 3 times per week dialysis. This question will be asked at baseline, months 4 and 12.

5.2 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after randomization into the study, even if the event is not considered to be related to enrollment into the study. Medical conditions/diseases present before enrollment in the study are only considered adverse events if they worsen after enrollment into the study. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (Including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

All adverse events must be recorded on the Adverse Events Form (Form 307) with the following information:

a) The severity grade (mild, moderate, severe)
b) Relationship to the study drug(s) (suspected/not suspected)
c) Duration (start and end dates or if continuing at final exam)
d) If it constitutes a SAE, a Serious Adverse Events Form (Form 308) should be completed.

A serious adverse event is defined as an event which:

a) Is fatal or life-threatening
b) Results in persistent or significant disability/incapacity
c) Constitutes a congenital anomaly/birth defect
d) Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
e) Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    i) Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    ii) Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    iii) Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    iv) Social reasons and respite care in the absence of any deterioration in the patient's general condition.

5.3 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.

In addition, there is a risk that there will be either a disconnection of the blood tubing or 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 home dialysis patients will need to have a home partner who can assist with any alarms that may occur during the hemodialysis treatment.

The protocol for monitoring other potential complications is noted below.

a) Vascular Access Complications: Access infection, stenosis, thrombosis, and intervention will be defined, and a detailed protocol developed to monitor and treat these complications in both groups. The primary measure of vascular access complications will be primary unassisted patency rate (time to first access intervention). Groups will also be compared with respect to: number of access interventions per patient years, time to first thrombosis related access failure, and number of thrombosis related access failures per patient years,

number of access infections per patient years, number of infection related access failures per patient years, time to first infection related access failure.

b) Iron Losses: Patients on daily hemodialysis have been shown to have increased iron losses compared with conventional patients. Iron utilization will be documented in both groups.

c) Malnutrition: Although it is anticipated that nutritional status will improve with nocturnal hemodialysis, the potential for malnutrition exists. There may be increased dialytic losses of amino acids due to increased clearances provided with nocturnal hemodialysis. Thus, nutritional status, as outlined in Sections 5.1.3.3 and 5.1.5.3, will be monitored on a regular basis.

d) Patient Burn-Out: Patient fatigue is a potential concern with the increased frequency of treatments with nocturnal hemodialysis, especially with the requirement that the patients perform the dialysis treatments themselves. The proportion of patients who require a change in dialysis modality lasting more than 2 weeks (back to conventional hemodialysis or to peritoneal dialysis) will be assessed along with reasons for modality change.

e) Calcium and phosphorus balance: Nocturnal hemodialysis is known to decrease serum phosphate and even lead to hypophosphatemia. Persistently low serum phosphate may lead to weakness, osteomalacia and severe hypophosphatemia (defined as a serum level < 1.0 mg/dl) may cause hemolysis, acute respiratory failure, myocardial depression, or seizures. In addition, nocturnal hemodialysis can lead to negative calcium balance due to calcium loss through ultrafiltration. This may lead to increase of PTH and alkaline phosphatase. These laboratory parameters will be monitored on a regular basis as outlined in Section 3.4.1.d.

6. Data Collection and Monitoring

6.1 Frequency of Measurements

For those patients who were randomized in version 2.1 of the protocol to the conventional in-center hemodialysis arm of the study, they will be given a choice to either continue with conventional in-center HD three times per week or convert to conventional home hemodialysis three times per week. For all these patients, data will continue to be collected as indicated in version 2.1 of the protocol regardless of whether they convert to home hemodialysis. That is, the main data collection periods will be at 5 months of follow-up and 14 months of follow-up and the schedule for data collection in protocol version 2.1 will be followed. Baseline data that can be obtained by chart review only for the newly added second baseline visit will also be entered into the database. This data will likely consist only of baseline laboratory data.

All patients who were randomized under version 2.1 of the protocol into the conventional in-center arm of the study will need to sign a new consent form for the revised protocol. For all patients who consent to the study with the version 3.0 or higher protocol, data will be collected as summarized in Table 9.

For those patients who were in baseline at the time of the protocol change, the period for baseline was extended from 12 weeks to 24 weeks for all baseline variables except for the two co-primary outcomes of the change in Left-Ventricular Mass by Cine-MRI and the change in SF-36 Physical Health Composite Score. For these two co-primary outcomes, the data will need to be obtained no more than 12 weeks prior to randomization; otherwise the measurement(s) will need to be repeated. Each of these patients will need to sign a consent form for the revised protocol prior to the

resumption of data collection. Those baseline data collection items that do not result in patient burden (e.g., routine lab test data, chart review data) can be updated at the discretion of the clinical center prior to randomization.

Most questionnaires (including HRQL, depression, cognitive function, and treatment burden) and objective tests of physical function will be performed at baseline, and at 4 and 12 months post-randomization. The purpose of the 4-month (F4) assessment is to allow evaluation of short-term effects prior to significant attrition, while the 12-month (F12) assessment is intended to allow evaluation of longer-term effects. The cardiac cine-MRI will be performed at baseline and 12 months (B, F12) only.

Kinetic modeling sessions will be performed twice in the baseline period and monthly after randomization through month 12. 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 9 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. Twice during baseline and monthly during follow-up, start and end times, pre- and post-dialysis blood pressures, and pre- and post-dialysis 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 3 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 4, 8, and 12 during follow-up.

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 baseline kinetic modeling sessions are designated as "B" visits and are numbered sequentially. The follow-up visits are designated as F1 (month 1), F2 (month 2), and so on through the F12 visit.

6.2 Details on Measurements

6.2.1 Cardiac MRI

The cardiac MRI will be performed at baseline and at the month 12 visit. The most commonly used method to measure LVM is two-dimensional (2D) Doppler echocardiography. Since the method assumes a geometric shape of the normal heart, it is less accurate for dilated or extremely hypertrophic hearts. Furthermore, the results are heavily operator dependent and the variability of the measurement for LVM was found to be wider than originally thought [Collins, 1989;Palmieri,

1999]. Cine-MRI has been shown to be more accurate and less volume and operator dependent than 2D-echocardiography. In addition to determination of LVM, the cine MRI technology allows for measurement of various cardio-dynamic parameters, such as end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, ejection fraction, myocardial mass and cardiac output [Kramer, 2004]. We believe that the relative superiorities of MRI over echocardiography are compounded in ESRD patients who not only have a high prevalence of LVH, but who also suffer from volume expansion between dialysis sessions [Stewart, 1999].

Cine-MRI assessment of LVM showed a good interstudy reproducibility of 7.8 g (mean weighted values from 11 studies), intraobserver reproducibility of 4.8 g, and interobserver reproducibility of 9.0 g in mainly normal subjects. This is contrasted by a mean weighted interstudy SD for 2D-echo of 19.2 g [Myerson, 2002]. For these reasons cardiac cine MRI will be used for the assessment of LVM in all study patients.

Availability of MRI centers experienced in performing standard cine-MRI examinations has been verified by the Clinical Centers using a standardized questionnaire. MRI scans will be performed at designated MRI centers close to each patient's study dialysis unit. Scans will be digitized and provided to a Cardiac Core MRI reading center where they will be analyzed in a standardized way by a trained person, blinded to the patient's treatment allocation.

6.2.2 Home Blood Pressure Readings, Dialytic Blood Pressure, Interdialytic Weight Gains, and Intradialytic Hypotensive Episodes

Home blood pressure readings will be obtained at baseline and at months 4 and 12. Home blood pressure will be measured using the Omron HEM-705CP blood pressure monitor which meets the standards of the Association for the Advancement of Medical Instrumentation. This device is capable of storing 28 measurements and has been extensively used in research. Calibrated devices will be distributed to the Clinical Centers. Subjects will be trained on its use with a published protocol [O'Brien, 2001]. Study subjects will take 12 home self blood pressure measurements during a 48-hour midweek interval and an additional 12 home blood pressure measurements on the weekend. Subjects will also be asked to bring their medication to the study Clinical Center for their scheduled visits. Blood pressure measures will be taken at least two hours after a dialysis session, or one hour prior to a dialysis session. The start and end times of any dialysis session during the 2-day measurement session will be noted.

Pre and post-dialysis systolic and diastolic blood pressures, the nadir recorded intradialytic systolic and diastolic blood pressures, pre and postdialysis weights, and the presence of intradialytic hypotension requiring intravenous saline will be recorded from the HD run sheets for each HD session over a 1-week interval prior to and including the kinetic modeling session once during baseline and at months 4, 8 and 12 during follow-up. Interdialytic weight gains will be calculated from the pre and post weights. See Table 11 C.

6.2.3 Bioelectric Impedance

Single frequency bioelectric impedance (BIA) assessments should be performed at baseline and at months F4, and F12 visits. BIA is not required on randomization. All measurements should be conducted in the recumbent position, and should be performed immediately prior to a mid-week HD treatment (i.e., Wednesday or Thursday) and after at least two consecutive dialysis treatments for patients in the nocturnal arm of the study. . BIA is not required for patients with bilateral amputations or who have metallic implants such as a pacemaker.

6.2.4 Medications

All medications will be recorded using the WHO DRUG system at baseline and at months 4, 8 and 12. Dose levels and frequency of use will be recorded for EPO and phosphate binders at these same time points. For other medications the name of the medication (but not dose or frequency) will be recorded.

Table 9. 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
SF-36 Survey, v2	Yes	✓				✓								✓
Health Utilities Index –3	Yes	✓				✓								✓
Feeling Thermometer	No	✓				✓								✓
MOS Sleep Scale	Yes	✓				✓								✓
Beck Depression Inventory, v1	Yes	✓				✓								✓
Trailmaking Test 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	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Cardiovascular and blood pressure														
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	✓				✓								✓
Nutrition														
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 monthly during follow-up.

C. Laboratory Measurements and Medications

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

[1]These local labs to be entered into database <u>at least</u> once every 3 months (center may optionally enter these labs at additional time points)

D. Mineral Metabolism and Anemia Measures – see Labs and Medications Table 11C

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

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

Measurement	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Adherence to Therapy													
Number of missed sessions (over 1 month)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Number of shortened treatments (over last week)	✓				✓				✓				✓
Burden of Treatment													
Minutes to recovery question	✓				✓								✓
Modality preference question	✓				✓								✓
Characterizing the Non-dialytic aspects of the Intervention													
Patient interviews/questionnaires	✓				✓								✓

6.2.5 Local Laboratory Measurements from Kinetic Modeling Sessions

Blood will be drawn pre- and post-dialysis at each kinetic modeling session. Samples will be refrigerated and then shipped to the local laboratory associated with the dialysis unit. See Section 6.1 and Table 11 B for frequency with which various labs will be drawn. In addition, at baseline, and at the F4 and F12 visits, the patient's urine will be collected for the period in between HD sessions along with the time of collection for assessment of urea, creatinine, and phosphate excretion rates.

It is recommended that serum albumin will be measured using the bromcresol green assay, as this is the most widely used measure of albumin in the US. Laboratory parameters which are not obtained as part of the dialysis units usual patient care will be specifically ordered, and costs will be paid by the Study.

It is anticipated that most patients will have all labs in baseline and follow-up drawn at the home training unit where the clinical center is located. However, if it is anticipated that a patient will have baseline and/or follow-up labs drawn at a site other than the home training unit (for example, due to travel considerations), then those patient's labs instead will be sent to the central laboratory for analysis.

6.2.6 Questionnaires

The SF-36, Beck Depression Inventory, sleep scale, and other quality of life questionnaires will be administered centrally by trained telephone interviewers blinded to treatment allocation. Patients will be contacted in their homes at baseline and at months 4 and 12. Questionnaires that cannot be administered by telephone due to the need for visual cues (i.e., Feeling Thermometer, Trails B, Modified Mini-Mental Status, burden of treatment) will be administered by the local study coordinator.

6.2.7 Objective Tests of Physical Function

The Lower Extremity Battery (LEP: timed 4-meter walk, timed chair stand, and balance test) will be performed at baseline, 4 months and 12 months (Table 11 A). This test will be conducted by the study coordinator before the HD session since performance scores can be affected after a single HD treatment [Tawney, 2004]. The study coordinators will be trained by an experienced person familiar with the methods of this test prior to study start.

For the LEP, performance scores will be derived for each test with a score of 0 assigned to those unable to complete the test, and 4 indicating the highest level of performance. Ordinal categories for the 4-meter walk, chair stand, and balance test will be assigned based on reference tables developed for elderly people who participated in the EPESE study [Guralnik, 1994]. In addition, the individual scores for each of the 3 tests will be summed to create an overall LEP score (0-12). The LEP score incorporates missing data into the test results by assigning a score of 0 for missing values and for those unable to complete the test, while those who are able to complete the test are assigned a score according to a quartile of performance.

6.2.8 Samples for Biorepositories

Additional biological samples will be obtained to be stored to use in future studies of hemodialysis patients. In particular, β_2-microglobulin and C-reactive protein will measured from samples obtained at baseline, 4 and 12 months. Patient consent will be obtained to specifically address the collection of these specimens. Among those participants who consent for storage of biological specimens, serum and plasma specimens will be shipped to the National Institute of Diabetes and

Digestive and Kidney Diseases Biosample Repository at Fisher BioServices at study baseline, months 4 and 12. During the course of the trial, all studies using the biorepository samples must receive the approval of the FHN Ancillary Studies Committee and follow the study policies of the trial regarding ancillary studies.

6.3 Definitions, Monitoring and Reporting of Patient Events

6.3.1 Outcome Classification Committee

An Outcome Classification Committee will be composed of the Clinical Center Principal Investigators, who will review all deaths and 100 hospitalizations to verify cause of death or hospitalization (see below). The members of the Outcome Committee will be trained by the Data Coordinating Center in order to provide a standard classification system for patient deaths and hospitalizations. The Data Coordinating Center will remove any information that can identify the randomization status of the patient being reviewed so that members of the Outcome Committee will be blinded to the patient's treatment allocation.

6.3.2 Hospitalizations

All hospitalizations will be categorized by the Clinical Center (Site) PIs by access versus non-access hospitalization and by primary and secondary reason for hospitalization using one of a number of hospitalization categories by system, coded with a modification of the HEMO Study code list.

The detailed hospitalization discharge form will be completed by the Site PI, Co-Investigator or Collaborator from the patient's Clinical Center and reviewed by the Consortium Center PI (Dr. Rocco) or his designee. After each hospitalization that does not lead to a death, a subject will sign a release to allow the hospital to provide the details of the hospitalization to the FHN Clinical Center team. (In addition, each subject will sign a blanket release form annually, to make it easier for the Clinical Centers to obtain details on hospitalizations that lead to death and to obtain details on deaths.) The Clinical Center will contact the hospital involved. Data to be obtained and recorded on the detailed hospitalization discharge form include date of admission, date of discharge, whether the patient was in the intensive care unit during the hospital stay, whether a vascular access procedure was performed during the hospital stay, the primary and secondary reason for hospitalization as coded by the categories on the form, and the standard adverse event questions about the expectedness and relatedness of the hospitalization. The answers to these questions will be based on either the discharge summary associated with that hospitalization or a narrative description of the hospitalization provided by a physician who was responsible for the care of the patient. The FHN detailed hospitalization discharge form will also capture whether the Site PI, Co-Investigator's or Collaborator's categorization was based on an actual discharge summary or some other form of documentation, and this form should be submitted to the Data Coordinating Center within 30 days of the patient's hospital discharge.

For the first 12 FHN Nocturnal Study hospitalizations, the Outcome Committee will be available for consultation but will not do formal reviews. After the first 12 FHN Nocturnal Study hospitalizations have occurred, for the next 52 daily study hospitalizations, the Clinical Center will send a hospitalization packet including the hospitalization discharge form and a discharge summary/narrative description to the DCC. The DCC staff will send create a hospitalization packet including these data and send this packet to one blinded member of the Outcome Committee, and he will complete Outcome Committee Hospitalization Review Form reassessing whether it was a CV or Access hospitalization. (The precise "reason for hospitalization" code associated with the hospitalization is not reassessed.) If the CV and access determination coded by the Outcome

Committee member and the Clinical Center PI, Co-Investigator or Collaborator differ, then the case will be adjudicated by the Outcome Committee during the monthly conference call until resolution can be reached. The final categorization with respect to CV and Access will be recorded in the "final categorization" section at the end of the Outcome Committee Hospitalization Review Form. The hospitalization code chosen by the committee as the "final categorization" will be used for subsequent analyses of these 52 hospitalizations.

The agreement of the Outcome Committee and Clinical Center classifications of the initial 52 hospitalizations will be evaluated as part of the Vanguard assessment of the trial. Subsequently, 12 hospitalizations per year (one hospital admission form per calendar month) will be selected for review by a member of the Outcome Committee and adjudication by the Outcome Review Committee if necessary.

6.3.3 Deaths

The death form will be completed by the Principal Investigator from the involved Clinical Center, who will classify the death using a modification of the HEMO Study coding system. This system will allow for the classification of deaths by organ system, such as cardiac and infection-related. A death packet with the death form and specific patient information will be sent by the Clinical Center to the Data Coordinating Center, who in turn will forward this data to members of the Outcome Committee. For hospitalizations resulting in death, the same information as described above for hospitalizations will be obtained. If the death did not occur in the hospital, then the principal investigator will provide a narrative describing the circumstances of the patient's death and the presumed cause of death based on the patient's history and events leading up to the patient death. One member of the Outcome Committee will review this information and verify the cause of death on the death form. If the death coded by the Outcome Committee member and the Clinical Center PI differ, then the case will be discussed by the Outcome Committee during the monthly conference call. The death code chosen by the committee will be used for subsequent analysis.

6.3.4 Vascular Access Complications

All vascular accesses will be tracked for complications using a modification of the Dialysis Access Consortium (DAC) Study vascular access forms. A form will be completed on each patient at the time of randomization that will classify the type and location of the vascular access in use at that time. A vascular access complication form will be completed whenever the study patient undergoes one or more of the following vascular access procedures: access failure (thrombosis or removal requiring placement of a new access), placement of a new vascular access, access intervention (angioplasty, stenting, surgical revision, fibrin sheath stripping, etc., but not TPA instillation or venogram only). The procedures performed for these access complications will also be noted on this form. Vascular access infections not requiring removal of the access will not be recorded. Information on vascular access complications will be provided to the DSMB to monitor the rates of access complications in each arm of the study.

6.3.5 Withdrawal from Study Protocol

All withdrawals from the study protocol will be tracked and the reason for withdrawal will be ascertained (see Sections 7.3 and 7.4).

7. Deviations from Trial Protocol, Action Items and Stop Points

7.1 Nonadherence

All subjects will be strongly encouraged throughout the study to adhere to the randomized therapy. Deviations from the 3 times per week therapy designated for the conventional home HD arm or the 6 times per week therapy in the nocturnal home hemodialysis treatment arm may occur during the course of the trial, however. Protocols will be developed to treat such deviations in a standardized fashion, with the goal of minimizing the duration and extent of deviations from the planned interventions. Patients will continue to be followed for all data collection, irrespective of their adherence to the randomized therapy (intent to treat analysis).

7.2 Action Items

The DCC will report and the Outcome Committee will review (in conjunction with Kinetic Modeling Committee) any patient who has persistent underdialysis (i.e., for conventional home hemodialysis group, not meeting eKt/V of 1.10 per session for 2 or 3 consecutive measurements; for the nocturnal home hemodialysis group, not meeting a std Kt/V of 4.0 for 3 consecutive measurements)

a) DCC will report and the Recruitment and Adherence Committee will review any patient who has persistent nonadherence to therapy. Persistent nonadherence to be defined and monitored with appropriate action by adherence committee (in conjunction with Kinetic Modeling Committee).

b) DCC will report and the Standards of Care/Clinical Management Committee will review any patient who has persistent hypophosphatemia (serum phosphate level less than the lower limit of the normal range) on 2 or 3 consecutive monthly measurements

c) The Central HRQL Survey Center will report within 24 hours to the research coordinator or treating nephrologist any patient who has potentially life-threatening findings on questionnaires done exclusively for the purpose of the study. These findings will also be reported to the DCC who will report these findings in a timely manner to the study center when received by the database. These findings may include, but are not limited to:

    i) scores above a certain threshold that indicates depression on the Beck Depression Inventory

    ii) answers 2 or 3 on question #9 of the Beck Depression Inventory ("would you kill yourself")

d) The Central Cardiac MRI Core will simultaneously transmit a report to the Clinical Center, Data Coordinating Center and Consortium Core for any patient who has potentially clinically relevant findings on tests done exclusively for the purpose of the study. The DCC will report these findings in a timely manner (approximately 2-3 weeks from MRI Core Physician review) to the study center when received by the database. These findings usually include clinically relevant abnormalities noted during the performance of the cardiac MRI. These will relate to abnormalities noted in the pericardium, myocardium, valvular structures and/or contiguous vascular structures. Clinically relevant abnormalities will be adjudicated based on the best clinical judgment of the reviewing physician at the Central Cardiac MRI Core.

7.3 Stop Points

It is recognized that certain situations may require premature discontinuation of the randomized therapy (stop-points). Provided the subject does not withdraw consent, data collection and follow-up will continue for all subjects meeting any of the following stop-points in order to perform the intent to treat analysis. Wherever possible and clinically appropriate, efforts should be made by the treating physician and principal investigator to get the patient back into their randomized group. **All discontinuations of therapy will be reviewed by the Standards of Care/Clinical Management Committee.** Subjects may discontinue the randomized therapy for the following reasons:

a) **The treating physician determines that the subject requires more frequent or less frequent dialysis** for reasons including, but not limited to, the following: uremic symptoms, uncontrolled hypertension, patient fatigue/burnout, etc.

b) **Home hemodialysis patient requests discontinuation of home hemodialysis** for any reason (e.g., burnout/fatigue, home social situation no longer allows, etc.) and refuses to follow the above "non-adherence protocol" described in Section 7.1. The reason for discontinuation of therapy will be documented and the patient will be switched to an alternative dialytic modality.

c) **Home hemodialysis patient unable to perform the HD treatment safely** for any reason (as determined by treating nephrologist or principal investigator of the Clinical Center or Safety Committee). The reason for discontinuation of therapy will be documented. Whenever possible, the practicing physician, in conjunction with the Clinical Center physician, should reassess the patient periodically to determine if the patient can go back to nocturnal HD after retraining.

7.4 Losses to Follow-up

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

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

a. Subject withdraws consent for data collection

b. Subject changes to peritoneal dialysis

c. Subject receives renal transplant

d. Subject relocates to a non-study center.

For patients who are lost to routine data collection for reasons b - d above, all attempts will be made to collect vital status. For patients who relocate to a non-study dialysis unit or transfer during their 12 months of follow-up, all attempts will be made to collect vital status, the two co-primary outcomes, and the centrally administered quality of life questionnaires.

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

8. Economic Evaluation

8.1 Hypothesis

We hypothesize that savings in non-dialysis health care costs due to better health from nocturnal home hemodialysis will offset its additional dialysis related expenses. That is, we hypothesize that nocturnal home hemodialysis will be a "Dominant Strategy" (better outcomes with reduced costs).

8.2 Purpose

If nocturnal home hemodialysis proves to be effective in improving health outcomes, it will be important to understand:

a) The changes in dialysis center costs to provide this mode of hemodialysis,

b) The changes in overall health care costs to insurers (principally CMS) of patients using this mode of hemodialysis,

c) The cost-effectiveness of the intervention (change in insurer costs per change in quality adjusted life-years)

d) Costs per month for in-center hemodialysis (three times per week) obtained from the Daily Trial will be used to compare the monthly costs of nocturnal home hemodialysis with 3 times per week in-center hemodialysis.

The purpose of the economic analysis in this trial is to provide answers to these questions.

8.3 Data Collection and Methods

Resource use for patients assigned to either arm of this study will be assessed under the various headings, and by the methods listed in the tables below. Additionally, the following data will be available for economic and other analyses:

- Baseline income and employment status
- Follow up income and employment status
- Baseline vascular access
- All follow up vascular access replacement, repair or removal
- Home modification costs for nocturnal study patients

General. To obtain estimates of cost independent of year and geographical differences, we will denominate the use of resources initially in terms of more basic units: hours of nursing or other professional time, outlier adjusted DRG weights for hospitalizations and Medicare allowable charges for other types of payments, specific classes of equipment needed for dialysis and actual supplies used, actual non-injectable drug prescriptions. These will then be given dollar values using consistent references such as published salary scales, national average payments for diagnosis related groups (DRGs) for hospital services and relative value units (RVUs) for professional services, General Services Administration (GSA) contract prices, Red Book average wholesale prescription prices or Average Sales Price (ASP).

Resource use for patients assigned to either arm of this study will be assessed under the various headings, and by the methods listed in the Tables 10 - 13 below.

Table 10: Center Costs per Dialysis of Home Hemodialysis (3 or 6 Times Weekly):

Cost element	Method of assessment	Calculation of standard cost
Training		
Nursing/technician time for training.	Expert judgment and personnel records of the directors of the home training centers.	Published salary scales for hands-on time/% hands-on time. Range of % hands-on time used for sensitivity assessment.
Professional time by other professional personnel: dietitians, social workers, etc.	Record of visits and times spent at same subset of dialysis sessions.	Published salary scales.
Equipment at each dialysis station	Generic list compiled by consensus of dialysis administrators.	GSA price list, with amortization period determined by consensus. Cost per *dialysis* will be computed.
Consumable supplies per dialysis	List will be assembled by Cost Subcommittee.	GSA price list.
Routine laboratory tests included in "bundle."	Published charges by large reference laboratories.	Inflation adjusted average published permitted charge.
Overhead	Average overhead from CMS cost reports.	Applied as a percent to total of above.
Home dialysis itself		
Nursing technician time for clinic visits and troubleshooting	Expert judgment and personnel records of the directors of the home training centers.	Published salary scales for hands-on time/% hands-on time. Range of % hands-on time used for sensitivity assessment.
Professional time by other professional personnel: dietitians, social workers, etc.	Record of visits and times spent at same subset of dialysis sessions.	Published salary scales.
Equipment at each dialysis station	Generic list compiled by consensus of dialysis administrators.	GSA price list, with amortization period determined by consensus. Cost per *dialysis* will be computed.

Consumable supplies per dialysis	List will be assembled by Cost Subcommittee.	GSA price list.
Routine laboratory tests included in "bundle."	Published charges by large reference laboratories.	Inflation adjusted average published permitted charge.
Overhead	Average overhead from CMS cost reports.	Applied as a percent to total of above.

Table 11: Patient Costs per Dialysis of Home Hemodialysis (3 or 6 Times Weekly):

Cost element	Method of assessment	Calculation of standard cost
Home modifications	Data from form 101 and form 260	Accrue to training costs, otherwise TBD.
Unreimbursed costs (phone line, estimated costs of electricity and water, etc.	Periodic costs data	Accrue to maintenance costs, otherwise TBD.

Table 13: Other CMS Covered Medical Care (1):

Cost element	Method of assessment	Calculation of standard cost
Injectable medicines given in dialysis units or at home for nocturnal hemodialysis patients.	Data from Forms 203 and 204 collected at baseline, F4, F8 and F12.	Medicare allowable charges for the various agents and doses.
Hospitalizations (Part A)	Estimated from claims for Medicare primary patients in study cohort. Record of ICD9 Diagnostic and Procedure Codes (or Canadian equivalent) and length of stay for all hospitalizations for patients in Medicare HMOs and Canada.	Consistent assignment of DRGs for each hospitalization (with duration adjustment), using "DRG grouper" and related standardized CMS payments.
Hospitalizations (Part B)	Estimated from claims for Medicare Primary patients in study cohort. Total Part B allowed charges corresponding to known dates of hospitalization.	Attribute charges for Medicare Primary to non-Medicare Primary patients with the same DRGs. Standard CMS payments per RVU.
Outpatient medications (Part D)	Data from Form 205 completed at baseline, F4, F8 and F12. Can be crosschecked with data from pharmacy records maintained for Part D expenditures in Medicare patients.	Assign set cost for each medication based on average wholesale price or average sales price.
Non-hospital Medicare covered services	Estimated from claims for Medicare primary payer patients. Data from forms 208 and 209 collected at baseline, F4, F8 and F12. Can be crosschecked with claims data from CMS.	Assignment of CMS HCPCS codes. Standard CMS payments.

Comments: (1) In principle, it would be possible to obtain non-dialysis Medicare charges directly from the CMS billing data. However, participants in this trial may be Canadian, members of an HMO (in California), or within the first three years of ESRD on other than Medicare Primary insurance coverage. Therefore we draw inferences from hospital stay data collected within the trial itself. These data include major diagnostic group for the stay, which is used in Medicare pricing. We shall check validity of estimation process by comparing estimates with the actual billed charges in the subset of patients that is Medicare Primary.

Table 13: Other Health Care Related Expenses Not Covered by Medicare

Cost element	Method of assessment	Calculation of standard cost
Non-injectable medicines (not covered by Medicare Part D)	Data from Form 205 completed at baseline, F4, F8 and F12 and crosschecked with Part D data.	Prices calculated from "Red Book."
Patient employability or other socially productive activities	Data from Form 105 (at baseline) and Form 233 (at F12).	"Social functional status" recorded and compared.

8.4 Analysis

a) **Intention to treat**: All analyses will be performed on an "intention to treat" basis. That is, the average costs of patients in each arm will be determined retaining all patients in their originally randomized arm, irrespective of the treatment that is ultimately used for that patient. If a patient is lost to the trial by death, transplantation, withdrawal of consent, or move to a non-participating center, that patient will be included in his/her original randomization group, but the costs will be pro-rated for the actual time in the trial.

b) **Sensitivity analysis**: An important component of any economic evaluation is an analysis of the uncertainty surrounding the differences in expected costs and expected utility of the alternative strategies. Our approach to the analysis of uncertainty will be informed by the guidelines of the Panel on Cost-Effectiveness in Health and Medicine (Gold et al, 1996):

- Conduct univariate (one-way) sensitivity analysis for all variables to determine where uncertainty about some key parameters could have a substantial impact on the conclusions. A tornado diagram will be used to sort the variables by their magnitude of effect (sensitivity). The potential major sensitive parameters include rate of hospitalization, cost for a hospital stay, EPO dose and rate of EPO use, nursing time devoted to training and home support, proportion of home nocturnal to all dialysis patients, and various techniques to allocate overhead to each modality. For the lifetime analysis, additional sensitive parameters include technique survival (length of time on randomized modality), patient survival, and discount rate.
- Conduct multivariate (2- or 3-way) sensitivity analysis for important parameters. This explores potential magnitude of effect when two or more key parameters are altered together. The results from univariate sensitivity analysis will serve as a guide to select the variables in multivariate sensitivity analysis. The potential sensitive parameters pairs may include hospital costs and rate of hospitalizations, or EPO dose and rate of EPO use.
- Construct a confidence or credible interval around the cost-effectiveness result. Bootstrap simulation with replacement will be utilized to derive costs and

utilities and associated incremental cost effectiveness ratio (ICERs) with 95% confidence intervals. Acceptability Curves will be constructed to determine the probability of nocturnal hemodialysis being cost-effective over the standard hemodialysis under certain cost-effectiveness thresholds. Conventionally, ICERs of less than $50,000 per QALY are considered very cost-effective whilst those with an ICER of between $50,000 and $100,000 per QALY are considered moderately cost-effective

In addition, the estimates from physician reported utilizations will be incorporated for sensitivity analysis.

c) **Time-frame for analysis**: The economic evaluation will consider two time-frames: a) within trial one-year period, and b) the lifetime of the patient. We recognize specifically that the costs of the non-dialysis component of care may decline over the year of observation, such that the average over the year might underestimate the long-term impact on costs (and benefits). This will be assessed by estimating total costs within the first and the final four months of the study. We shall use a probabilistic economic model to project long-term survival, health benefits, and costs beyond the study period and extend the findings to patients and facilities not included in the trial. Lifetime costs and benefits will be **discounted at a rate of 3%**.

d) **Objective 1 – Costs of dialysis**: Costs per month of dialysis for patients in the two study arms will be determined by summing the per dialysis costs of dialysis as listed in Table 10 - 11 above and multiplying this sum by the average number of outpatient dialysis sessions per month for the patients in each arm of the study. This analysis may be useful to CMS and other payers in setting appropriate payment rates for nocturnal hemodialysis.

e) **Objective 2 – Total CMS covered costs**: Costs per month of CMS covered care will be summed by summing the average per month costs of dialysis (as in (d) above) and of other covered care as in Table 13 above.

f) **Objective 3 – Cost-Effectiveness**: The impact of randomization to nocturnal hemodialysis (compared with standard 3 times weekly home hemodialysis) on life expectancy will be determined directly from survival of patients in the two arms of this trial. Utility (quality of life) will be determined from the Health Utilities Index. The impact of assigned treatment on quality adjusted life years will be calculated from the measures. If as hypothesized, nocturnal hemodialysis is a "dominant" strategy, improving survival/health utility and lowering costs, differences in survival, utility, dialysis costs, and total CMS costs will be presented in a cost-consequences framework. If, conversely, survival/health utility is improved, but total CMS costs are increased, we will calculate the incremental cost-effectiveness ratio (cost per quality-adjusted-life-year), to permit comparison with other possible ways for CMS to spend its health care dollar.

g) **Objective 4 - Comparison of nocturnal with short daily hemodialysis:** While not a primary purpose of this randomized trial, there will be interest in comparing the outcomes of overnight nightly home hemodialysis with the outcomes of short daily in-center dialysis being studied in the companion trial performed by this consortium. These results will not be directly comparable as the patient groups from which patients will be randomized are different. However the degree of difference (or conversely, of

comparability) may be estimated by comparison of the outcomes in the standard arm (conventional home hemodialysis three times weekly) in this trial and in the companion trial. We shall make such comparisons.

h) **Power**: We acknowledge that the power for some of the above proposed analyses is likely to be poor. Specifically, formal power analyses have suggested that there will be low power to detect differences in patient survival and the rate of hospitalizations. The latter will likely be a major component of the total CMS costs of management of a dialysis patient. Therefore a major focus of this economic analysis will be the sensitivity analysis to determine robustness of our analyses.

i) **Objective 5 – Economic and social impact of nocturnal hemodialysis on the patient, his/her family, and society:** Information on these aspects of the economic impact of nocturnal hemodialysis is likely to be considerably more subjective and less quantitative than for the above components of the economic analysis. We shall therefore make no attempt to merge these data with the economic analyses above, but will rather simply list the conclusions together with the other information in the cost-consequences framework.

9. Statistical Analyses

9.1 General Methods for Descriptive Summaries and Baseline Comparisons

Quantitative variables will be summarized with standard descriptive statistics and represented graphically with displays such as box plots, smooth density function estimates [Silverman, 1986] and histograms, and categorical variables will be described by frequency tables and standard graphical displays. Inferential analyses for quantitative variables will be performed using 2-group t-tests and, when appropriate, linear models such as analysis of variance and regression. Highly skewed variables may be transformed prior to inferential comparisons, or nonparametric methods employed. Categorical variables will be analyzed with 2-sample comparisons of proportions, logistic regression, general multinomial response models, and multinomial logistic models for ordered categorical outcomes [Agresti, 2002].

9.2 Analyses of Recruitment Process

Descriptive summaries of clinical and demographic characteristics will be obtained for each of the stages of the recruitment process. The characteristics of each stage will be compared to each other and to the USRDS to address the representativeness of the FHN participants. Reasons for exclusion or dropout during baseline will be tabulated.

9.3 Primary Outcomes

The primary analysis will evaluate the effects of the treatment interventions on two co-primary endpoints: 1) a PHC/Mortality composite endpoint based on mortality during the 12-month follow-up period and the change from baseline to 12 months in the SF-36 Rand Physical Health Composite (PHC) among those who survive to 12 months, and 2) a LV mass/Mortality composite based on mortality during the 12-month follow-up period and the change from baseline to 12 months in the Left Ventricular Mass (LV mass) as estimated by cardiac MRI among those who survive to 12 months.

The analysis of the PHC/Mortality composite will be conducted using a rank-based nonparametric procedure as follows. Patients who die prior to 12 months are ranked from lowest (indicating the poorest outcome) to highest based on their survival time prior to death. Those

who survive to 12 months are ranked based on the change in the PHC score from baseline to 12 months. The patient with the largest decline in the PHC is given the next lowest lowest rank above the patient with the latest death prior to 12 months. The patient with the largest increase in the PHC is given the highest rank, with the others falling in between. Follow-up is censored prior to 12 months if the patient is transplanted or lost to follow-up for mortality prior to the 12 month assessment, and at 12 months if the patient survives to 12 months, but does not provide a 12-month PHC measurement. In this way, if a patient survives to 12 months but has a missing 12-month PHC score he/she is still credited as surving to 12 months. The ranks will be compared between treatment groups using the logrank test.

The LV mass/Mortality composite will be analyzed in an analogous fashion, except that increases in LV mass will be given lower ranks (indicating a less favorable outcome) than decreases.

A variation of the Bonferroni correction due to Hochberg [Hochberg 1998] will be used to maintain a studywise Type I error of 0.05 for the co-primary outcomes. In this procedure both of the co-primary endpoints are regarded as statistically significant if the p-values for both outcomes are not greater than 0.05. If the larger of the two p-values is greater than 0.05, then the outcome with the smaller p-value is regarded as statistically significant if its p-value is not greater than 0.025.

9.4 Main Secondary Outcomes

As described in Section 9.3, the PHC/Mortality and LV mass/Mortality composites are the co-primary endpoints for evaluation of patient benefit in the trial. In addition, as described in Section 5.1.2, main secondary outcomes have also been designated for each of six specific and conceptually distinct physiological or quality of life-related outcome domains. These include: i) change over 12 months in the PHC; and, ii) change over 12 months in LV mass (without the mortality components), which represent the main secondary outcomes for evaluation of the physical function and cardiac structure and function domains, respectively. The remaining outcome domains and associated main secondary outcomes are iii) depression/disease burden (change over 12 months in Beck Depression Inventory), iv) nutrition (change over 12 months in serum albumin), v) cognitive function (change over 12 months in the Trails B), and vi) mineral metabolism (change over 12 months in average pre-dialysis phosphorus). The primary evaluation of the effects of the treatment interventions on each of these seven outcome domains will be based on the designated main secondary endpoints. Analyses of other outcomes within each domain will be regarded as exploratory. Hypertension and anemia are also stipulated as main outcome domains, but are not conducive to the designation of a single main endpoint.

As described in Section 9.3, the PHC/Mortality and LV mass/Mortality composites are the co-primary endpoints for evaluation of patient benefit in the trial. In addition, as described in Section 5.1.2, main secondary outcomes have also been designated for each of seven specific and conceptually distinct physiological or quality of life-related outcome domains. These include: i) change over 12 months in the PHC; and, ii) change over 12 months in LV mass (without the mortality components), which represent the main secondary outcomes for evaluation of the physical function and cardiac structure and function domains, respectively. The remaining outcome domains and associated main secondary outcomes are iii) depression/disease burden (change over 12 months in Beck Depression Inventory), iv) nutrition (change over 12 months in serum albumin), v) cognitive function (change over 12 months in the Trails B), vi) mineral metabolism (change over 12 months in average pre-dialysis phosphorus), and vii) clinical events (rate of non-access

hospitalizations or death). The primary evaluation of the effects of the treatment interventions on each of these seven outcome domains will be based on the designated main secondary endpoints. Analyses of other outcomes within each domain will be regarded as exploratory. Hypertension and anemia are also stipulated as main outcome domains, but are not conducive to the designation of a single main endpoint.

Two-sided tests will be used when testing the effects of the interventions on both the primary and secondary endpoints. The primary and main secondary analyses will be conducted by intention-to-treat in the sense that all patients analyzed according to their randomized assignment, irrespective of whether they adhered to the interventions. As noted above, however, follow-up will be censored at the time of renal transplantation. The analyses of the main secondary endpoints will be tested at the 0.05 level, without formal adjustment for multiple comparisons. However, nominally significant effects on individual secondary outcomes will be interpreted as consistent with Type I errors unless accompanied by significant effects of the interventions on the primary outcomes and a consistent pattern of treatment effects across multiple secondary outcomes.

The intention-to-treat analyses will incorporate all randomized patients, including patients randomized prior to the date at which the standard three times per week intervention was modified from in-center hemodialysis to home hemodialysis. Patients assigned to in-center three times per week therapy prior to the modification will be combined with patients assigned to standard home hemodialysis three times per week therapy after the implementation of the modification. The Steering Committee estimates that more than 50% of the patients initially assigned to standard in-center therapy will elect to transfer to home therapy. If the projected total sample size of 125 randomized patients in the standard three times per week is attained, the total patient years of follow-up on in-center therapy for the few patients randomized to the three times per week arm prior to the implementation of this modification is thus expected to comprise a small proportion of the total patient years of follow-up in this arm.

9.5 General Analytic Strategy for Quantitative Outcomes

The following analytic strategy will be employed for quantitative outcomes, including each of the main secondary outcomes with the exception of the rate of non-access hospitalization or death. The main analysis for each outcome will evaluate the treatment effect on the change from baseline to 12 months. For outcomes evaluated monthly (serum albumin and pre-dialysis phosphorus) the 12 month value will be averaged over the Months 10, 11, and 12 assessments for increased statistical power. For each outcome with multiple follow-up assessments (including the PHC, serum albumin, Beck Depression Inventory, Trailmaking Test B, and pre-dialysis phosphorus), an additional analysis will be conducted to evaluate the change from baseline to Month 4, where the Month 4 value is taken as the average value over months 3, 4, and 5 for serum albumin and pre-dialysis phosphorus. The analysis of change to 4 months will evaluate short term effects, while the analysis of change to 12 months will evaluate longer-term effects. The 4-month comparison is also intended to evaluate treatment effects prior to significant attrition. The "basic model" to be used for quantitative outcomes is:

$$\Delta Y_t = \beta_{0t} + \beta_{1t}\,Trt + \beta_{2t}Y_0 + \Sigma\,\gamma_{it}\,S_i + \Sigma\,\delta_{it}\,F_i + \varepsilon_t, \qquad \text{(Basic Model)}$$

where ΔY_t denotes the change in the response variable from baseline to time t, Trt is an indicator variable for the daily treatment intervention, Y_0 is the baseline value of the response variable, the S_i are indicator variables for the Clinical Centers, the F_i are the following six pre-specified baseline covariates (age, race, years of dialysis, diabetic status, baseline serum albumin, and

baseline GFR), and the ε_t are random residuals at t = 4 and 12 months. The primary focus of the model will be to estimate the treatment effect β_{1t} as accurately as possible; the remaining terms are included to reduce residual variability and reduce bias from missing data. The model will be fit by restricted maximum likelihood [Harville, 1977] assuming an approximate normal distribution and with an unstructured covariance matrix for the residuals at the two time points. The change in the LV mass from baseline to its single follow-up assessment at 12 months will be analyzed by restricting the basic model to one time point, which simplifies to traditional analysis of covariance.

The target sample size of 90 patients is sufficient that inferences for the fixed effect terms in these analyses will remain valid with moderate departures from normality [Verbeke, 1997]. However, standard diagnostics will be performed and simulations conducted to address this issue, and modifications to the model will be made if necessary. In addition to evaluating the effects of the treatment interventions on LV mass, in grams, the effects of the interventions on the percentage change in LV mass will also be considered in secondary analyses.

9.6 Analysis of Non-Access Hospitalization Rate or Death

The effects of the treatment interventions on the rate of non-access hospitalizations or death will be analyzed by treating the non-access hospitalizations and death as correlated event-time outcomes under a semi-parametric survival analytic framework. An Anderson-Gill model for recurrent events will be used to characterize the effects of the interventions on the intensity rate for the non-access hospitalizations, and a Cox-proportional hazards model will be used to characterize the effects of the interventions on the hazard rate for mortality. The joint analysis of both outcomes will be stratified by type of outcome (non-access hospitalization vs. mortality) to allow for potential differences between the baseline hazard function for mortality and the baseline intensity function for non-access hospitalizations. The models for both outcomes will be stratified also by Clinical Center, with treatment group and the pre-specified covariates included as independent variables. A common treatment effect will be modeled for both outcomes in order to produce a pooled estimated treatment effect across the two outcomes. Standard errors will be estimated using robust “sandwich-type” estimates to account for correlations of (possibly) multiple events within the same patient. Follow-up time will be censored at death for the non-access hospitalization outcome and at time of transplantation, transfer to a nonparticipating dialysis facility, or the end of the 12-month follow-up period for both the non-access hospitalization and death outcomes. Censoring at transplant and transfer to nonparticipating dialysis units is necessary because hospitalizations will not be recorded or classified following these events. The incorporation of death as a separate event in addition to non-access hospitalizations is intended, in part, to reduce the risk of bias due to informative censoring.

9.7 Analysis Strategies for Other Outcomes

A modified version of the basic model for Bernoulli response variables will be used to analyze the change in the rates of dichotomous outcomes such as the presence of intradialytic hypotensive episodes [Diggle, 1994]. Primary unassisted patency will be defined as the time from randomization until the first access procedure or thrombosis (including angioplasty), and analyzed by Cox regression stratified by Clinical Center with treatment group and the pre-specified covariates as independent variables [Klein, 1997].

Ordinal variables will be analyzed using longitudinal models adapted for ordinal categorical outcomes with repeated measurements [Liang, 1995;Toledano, 1999].

9.8 Additional Analyses of the Effects of the Interventions

In addition to considering effects of the interventions on outcome at 4 and 12 months, contrasts will be constructed to estimate their effects on the change from 4 to 12 months to determine if treatment effects are changing over time. For quantitative outcomes obtained monthly, the basic model will be extended to evaluate patterns of change incorporating each protocol time point. Due to the larger number of time points, the covariance matrix of the residuals will be estimated under a mixed effects model including random effects (e.g., a random intercept and slope) and additional correlation parameters as needed to fit the serial correlation structure of the data [Littell, 1996;Verbeke, 1998].

Concentrations of serum albumin, hematocrit, and hemoglobin as well as body weight may shift shortly after initiation of nocturnal home hemodialysis due to altered extracellular volume, complicating interpretation of longitudinal changes. Thus, we plan to supplement tests of effects of the treatment interventions on changes from baseline to month 4 or month 12 (which may overestimate beneficial effects of the nocturnal hemodialysis intervention due to hemoconcentration) with contrasts evaluating the changes from the 1-month visit, at which time most hemoconcentration effects should have occurred. Contrasts for changes from baseline to the 1-month visit will be used to estimate the size of the change in extracellular water and the associated hemoconcentration effects.

Analyses will also be used to test for interactions between the treatment interventions and pre-specified baseline factors to evaluate whether certain subgroups experience increased or reduced benefits of the interventions. The Steering Committee has pre-specified the following factors for evaluation of treatment interactions:

History of heart disease, gender, anthropometric volume (Watson volume < 35 L vs. ≥ 35 L), years of dialysis (< 2 years vs. ≥ 2 years), presence of residual renal function (defined by > 100 mL urine volume per 24 hours).

Additional analyses will also be performed to determine if the primary and secondary outcomes differ based on the utilization of single needle versus double needle dialysis in patients randomized to the nocturnal arm of the study.

The primary and main secondary analyses will also be repeated after excluding those patients who were randomized prior to the modification of the conventional hemodialysis arm to stipulate home rather than in-center dialysis. [*2014 FHN Archive Note: These analyses were not done as agreed by FHN Steering Committee.]*

9.9 Missing Data

In spite of the relatively short follow-up of 12 months, a nontrivial loss-to-follow-up is inevitable in a study of HD due to high rates of death, transplant, and patient transfer to non-participating facilities. In the HEMO Study the combined loss-to-follow-up from death, transplant, and transfer was approximately 18% at 1 year.

Because all methods for accounting for missing data are subject to bias depending on untestable assumptions [Verbeke, 2000], efforts will be made to minimize missing data in the study design and conduct of the trials [Allison, 2001]. These include: 1) continuing data collection after safety stop-points or patient-termination of the treatment regimens, 2) provisions to obtain the key outcome results at a later time point should the patient be hospitalized at the target time for the visits, 3) monitoring and feedback regarding missing data throughout the trial, and 4) oral

administration of questionnaires.

Analytically, including prognostic baseline covariates and the early 4-month follow-up assessment should also reduce the chance of significant bias from missing data under the restricted maximum likelihood approach we propose. In this approach, bias from missing data at the 12-month assessment is reduced to the extent that relationships between the unobserved values of missing responses and the probability of missingness can be accounted for by either the baseline factors or the observed 4-month responses. *[2014 FHN Archive Note: FHN Executive Committee dropped prognostic covariates from the analyses.]* Nonetheless, some bias due to informative censoring [Little, 1995] is probably inevitable. Therefore, we plan to use a pattern mixture approach [Little, 1995] to perform sensitivity analyses of the estimated treatment effects under a range of assumptions regarding the association of the censoring times with the values of the missing responses [Daniels, 2000].

9.10 Analyses of Compliance

Rates of action items, stop points, dropouts, individual missed dialysis treatments and other aspects of compliance to the treatment regimens will be summarized by treatment group and related to baseline characteristics to ascertain what factors are associated with successful implementation of the treatment regimens. Reasons for dropouts and for noncompliance to the treatment interventions will also be tabulated by randomized group to assist in determining aspects of the interventions that may need to be altered in the design of a future hard endpoint full-scale trial.

9.11 Statistical Power

Estimates of parameters for determination of study power were obtained primarily based on information from the HEMO Study database, with downward adjustments in mortality and hospitalization rates to account for the expectation of lower comorbidity among patients eligible for nocturnal dialysis. During the first year of follow-up in the HEMO Study, the mortality rate was 12%/year, the transplant rate was 4%/year, the rate of all non-access hospitalizations was 1.19 per year, and approximately 80% of patients remained in active follow-up at the 12 month assessment. To assure the power calculations are conservative, we have projected that mortality and hospitalization rates will be 40% lower in the control group of this trial than in the HEMO Study, and that transplantation rates will be slightly higher (6% per year instead of 4%), reflecting the expectation of a younger average age and inclusion of more incident patients. Data from the HEMO Study was also used to estimate the standard deviation of the change in the PHC, average serum albumin, average serum phosphorus, average pre-dialysis systolic blood pressure after controlling for the baseline value of outcome and pre-specified covariates. The standard deviation estimate of 24 g for the change in LV mass was estimated from the standard deviation of the change in LV mass by MRI obtained in 153 patients over 9 months by Pitt et al (2003).

The minimum detectable effect sizes for the co-primary PHC/Mortality and LV mass/Mortality composite endpoints of were estimated under the following assumptions: a) the target sample size of 90 randomized patients is achieved, b) exponentially distributed survival, with a 7%/yr mortality rate in the control group, c) exponentially distributed transplantation, with a 6%/yr transplantation rate in both treatment groups, d) measurements at 12 months of the PHC and LV mass outcomes will be obtained in 80% of randomized patients, e) normally distributed changes in the PHC and LV mass in those patients with 12-month measurements, with standard deviations (without covariate adjustment) of 9.12 PHC units and 24.0 g, respectively, f) utilization of the log rank test as described in Section 9.3, without covariate adjustment, and g) use of Hochberg's procedure to maintain an overall Type I error rate of $\leq 5\%$.

The minimum detectable treatment effects under the above assumptions were estimated by statistical simulation, and are presented in Table 14. Two calculations of the minimum detectable effect are provided for each scenario. The first calculation (without parentheses), represents the minimum detectable overall treatment effect among all randomized patients, averaging over both the nocturnal group patients who successfully complete the training program and those who do not. The second calculation (in parentheses), represents the minimum detectable treatment effect among those who successfully complete the training program an implement the nocturnal therapy, assuming i) that 95% of patients randomized to the nocturnal arm successfully complete the final two weeks of the training program specific to nocturnal therapy, and ii) that the treatment effect is 0 among those who do not complete the training program. Under Hochberg's procedure the threshold used to test the significance of each of the two co-primary endpoints depends on the other; hence, as indicated in the table, the minimum detectable effect size for the PHC/Mortality composite depends in part on the magnitude of the treatment effect on LV mass, and the minimum detectable effect size for the LV mass/Mortality composite depends on the size of the treatment effect on the PHC. Under a hypothesized treatment effect leading to a 20% reduction in the mortality rate, the target sample size of 90 patients has 90% power to detect overall treatment effects ranging from 8.38 to 8.64 points for the change in SF-36 PHC score, depending on the size of the treatment effect on LV mass. Similarly, the study has 90% power to detect treatment effects ranging from 22.0 to 22.7 g for the change in LV mass, depending on the size of the treatment effect on the PHC. Under the stated assumptions, these overall minimum detectable effects translate to treatment effects ranging from 8.82 to 9.09 points for the PHC and from 23.2 to 23.9 g for LV mass among the 95% of randomized patients who successfully complete the training program.

Table 14

Estimated Detectable Effect Sizes for 80% or 90% Power for the Primary Outcomes[1]

Outcome	Treatment Effect on Other Primary Outcome	80% power	90% power
LV mass - Mortality	0	*19.8 (20.8) g*	*22.7 (23.9) g*
	2.28 g	*19.6 (20.6) g*	*22.6 (23.8) g*
	4.56 g	*19.0 (20.0) g*	*22.0 (23.2) g*
PHC - Mortality	0 units	*7.52 (7.92) units*	*8.64 (9.09) units*
	6 units	*7.44 (7.83) units*	*8.59 (9.04) units*
	12 units	*7.23 (7.61) units*	*8.38 (8.82) units*

[1] As described in the text, under the Hochberg procedure the statistical power for each of the two primary outcomes depends in part on the effect size for the other outcome. Thus, the minimum detectable effect on the LV mass-Mortality composite is evaluated assuming treatment effects on the change in the PHC of either 0, 2.28 (corresponding to 25% of the estimated standard deviation of the change in the PHC score after covariate adjustment), or 4.56 units (corresponding to 50% of one standard deviation). Similarly, the treatment effects on the PHC-Mortality composite are evaluated assuming effects of either 0, 6 (25% of 1 SD) or 12 g on the

change in LV mass. The simulation results indicate the above calculations are accurate if the correlation between the change in LV mass and the change in the PHC score is between 0 and +0.5.

Table 15 provides the estimated minimum detectable effect sizes for each of the quantitative main secondary outcomes under the following assumptions: a) measurements obtained at 12 months in 80% of patients for each outcome, b) the standard deviations of the changes in each outcome (with covariate adjustment) are as indicated in Table 15, c) two-sided significance levels of 0.05 are applied to each outcome, without adjustment for multiple tests, d) utilization of the parametric analysis of changes with covariate adjustment outlined in Section 9.5. The power calculations do not take into account information provided by the 4 month measurements for patients with missing data at 12 months; thus, in this respect the values are slightly conservative. As in Table 14, the minimum detectable effects are provided both overall (without parentheses), and among the assumed 95% of patients who complete the post-randomization component of the nocturnal training program (with parentheses), assuming no treatment effect among those not successfully completing the training program.

Table 15

Estimated Detectable Effect Sizes for 80% or 90% Power for the Main Secondary Outcomes[1]

Outcome Variable	Assumed SD of 1 Yr Change	80% power	90% power
PHC (points)	8.310	*5.54* *(5.83)*	*6.40* *(6.74)*
LV mass (g)	24.00	*16.0* *(16.8)*	*18.5* *(19.5)*
Average Albumin (g/dL)	0.296	*0.198* *(0. 208)*	*0.229* *(0.241)*
Average serum phosphorus (mg/dL)	1.636	*1.08* *(1.14)*	*1.26* *(1.33)*
Beck Depression Inventory (1 SD)[2]	-	*0.67* *(0.71)*	*0.77* *(0.81)*
Trailmaking Test B (1 SD)[2]	-	*0.67* *(0.71)*	*0.77* *(0.81)*

[1] Treatment effect tested at alpha = 0.05 using a 2-sided test.

[2] Detectable treatment effects expressed per 1 standard deviation of the changes in the Beck Depression Inventory and Trailmaking Test B because pilot data on 1-year changes in these

outcomes in dialysis patients is not available.

10. Safety and Monitoring

10.1 Data Safety and Monitoring Board

The External Advisory Committee/Data Safety and Monitoring Board (DSMB) will meet regularly to review the safety of the participants during the course of the study. In addition, the DSMB will monitor the operational progress of the trial and evaluate interim analyses of treatment efficacy performed by the Data Coordinating Center.

The specific activities of the DSMB will vary during the course of the trial. Prior to the start of the trial, the DSMB will review and approve the protocol and template informed consent form. During the Vanguard phases, the DSMB will review quarterly reports summarizing the operational conduct of the study, including analyses of recruitment, success of the training program for nocturnal dialysis, retention, adherence, adherence, and quality control. The quarterly reports will include specific assessments of the success of the trial in meeting the pre-designated benchmarks for the Vanguard phases. The DSMB will also review quarterly tabulations of stop points, action items, and adverse events. The DSMB will meet by teleconference after receiving the second quarterly report, and more often if necessary, to verify the safety of the trials and provide feedback regarding the operational issues.

After the completion of the Vanguard phases, the DSMB will meet in person to determine whether the trial should proceed to completion based on the extent to which the benchmarks established for the Vanguard phase are met. Depending on the success of the Daily HD trial and its parallel Nocturnal HD trial in meeting their operational goals, the DSMB may recommend a revision of the target sample sizes and reallocation of resources between the two trials.

After the New Vanguard Phase, subsequent interim reports will be provided to the DSMB at months 15, 21, 27, and 33. These reports will include summaries of the operational progress of the trial and patient safety, as well as interim analyses of the effects of the treatment interventions on the primary and main secondary endpoints at 4 and 12 months follow-up. The DSMB will meet by teleconference following distribution of the month 15 and month 27 reports, and will hold face-to-face meetings following the month 21 and month 33 reports. If necessary, additional teleconferences and face-to-face meetings will be scheduled.

10.2 Definition and Reporting Safety-Related Adverse Events

A Standards of Care/Clinical Management Committee will oversee that standards of care are being met (see Section 3.4.2). A blinded Outcome Committee will monitor and investigate adverse events that will be reported to the DSMB. The following adverse events will be reported monthly by the DCC to the Outcomes Committee (see Section 7) who will investigate them and complete an assessment of their seriousness and relatedness to the randomized therapy. The frequency of these adverse events and detailed assessments will be reviewed by the DSMB quarterly. The adverse events to be handled in this way are:

i) all deaths which occur during the hemodialysis session itself

ii) all deaths which occur at home

iii) all hospitalizations which result from an event occurring during or immediately after the HD session

iv) any premature discontinuation of the HD session for medical or technical reasons (these include but are not limited to, blood line disconnection, air embolism, leakage of dialysate into blood line, etc.)

Safety analyses presented at annual DSMB meetings will include summary reports of frequency and differences between treatment groups for each of the following:

i) deaths

ii) hospitalizations

iii) vascular access failures (primary and secondary)

10.3 Stopping Rules

A formal stopping rule for efficacy will not be used because none of the intermediate outcomes are judged to be sufficiently definitive to warrant early termination of the trial, and because it is unlikely to be feasible to switch a large proportion of the patients in the conventional arm to nocturnal dialysis therapy until after the scheduled termination of the trial. However, to assist the DSMB in interpreting results from multiple looks at the data, the DCC will provide thresholds for statistical significance for each intermediate outcome based on the O'Brien-Fleming rule.

11. Reference List

Centers for Medicare & Medicaid Services: 2001 Annual Report: End Stage Renal Disease Clinical Performance Measures Project. Am J Kidney Dis 2002;39:S1-S98.

Agresti A: Categorical Data Analysis, ed 2nd Edition. New York, Wiley, 2002.

Al Hejaili F, Kortas C, Leitch R, Heidenheim AP, Clement L, Nesrallah G, Lindsay RM: Nocturnal but not Short Hours Quotidian Hemodialysis Requires an Elevated Dialysate Calcium Concentration. J Am Soc Nephrol 2003;14:2322-2328.

Allen KL, Miskulin D, Yan G, et al.: Association of nutritional markers with physical and mental health status in prevalent hemodialysis patients from the HEMO study. J Ren Nutr 2002; 12:160-169.

Allison P: Missing Data; Sage Publications, 2001.

Allman MA, Stewart PM, Tiller DJ, Horvath JS, Duggin GG, Truswell AS: Energy supplementation and the nutritional status of hemodialysis patients. Am J Clin N 1990; 558-562.

Alvestrand A, Gutierrez A: Relationship between nitrogen balance, protein and energy intake in haemodialysis patients. Nephrol Dial Transplant 1996; 11:S130-S133.

Amann K, Ritz E, Wiest G, Klaus G, Mall G: A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol 1994; 4:1814-1819.

Baldassarre FG, Arthur HM, Dicenso A, Guyatt G: Effect of coronary artery bypass graft surgery on older women's health-related quality of life. Heart Lung 2002; 31:421-431.

Bansal VK, Popli S, Pickering J, Ing TS, Vertuno LL, Hano JE: Protein-calorie malnutrition and cutaneous anergy in hemodialysis maintained patients. Am J Clin Nutr 1980a; 33:1608-1611.

Bansal VK, Popli S, Pickering J, Ing TS, Vertuno LL, Hano JE: Protein-calorie malnutrition and cutaneous anergy in hemodialysis maintained patients. Am J Clin Nutr 1980b; 33:1608-1611.

Beddhu S, Papps LM, Stat M, Ramkkumar N, Samore M: Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol 2003; 14:2366-2372.

Bellizzi V, Cioffi MF, Cianciaruso B: Body weight is a fluctuating parameter in hemodialysis patients. Kidney Int 2000; 58:900-902.

Bergstrom J, Lindholm B: Malnutrition, cardiac disease and mortality: An Integrated point of view. Am J Kidney Dis 1998; 32:834-841.

Beusterien KM, Steinwald B, Ware JEJr: Usefulness of the SF-36 Health Survey in measuring health outcomes in the depressed elderly. J Geriatr Psychiatry Neurol 1996; 9:13-21.

Blacher J, Demuth K, Guerin AP, Vadez C, Moatti N, Safar ME, London GM: Association between plasma homocysteine concentrations and cardiac hypertrophy in end-stage renal disease. J Nephrol 1999; 12:248-255.

Blacher J, Guerin AP, Pannier Bet al: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 2001; 38:938-942.

Block GA, Hulbert-Shearon TE, Levin NW, and Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31:607-617.

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15:2208-2218.

Bostrom K, Demer LL: Regulatory mechanisms in vascular calcification. Crit Rev Eukaryot Gene Expr 2000; 10:151-158.

Braun J, Oldendorf M, Moshage W, et al: Electron beam computed tomography in the evaluation of cardiac calcifications in chronic dialysis patients. Am J Kidney Dis 1996; 27:394-401.

Brissenden, J. E., Pierratos, A., Ouwendyk, M., and Roscoe, J. M. Improvements in quality of life with nocturnal hemodialysis. J Am Soc Nephrol 9, 168A. 1998.

Cagney KA, Wu AW, Fink NE, Jenckes MW, Meyer KB, Bass EB, Powe NR: Formal literature review of quality-of-life instruments used in end-stage renal disease. American Journal of Kidney Diseases 2000; 36:327-336.

Chaignon.M, Chen WT, Tarazi RC, Bravo EL, Nakamoto S: Effect of hemodialysis on blood volume distribution and cardiac output. Hypertension 1981; 3:327-332.

Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A: Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. Kidney Int 2002; 61:2235-2239.

Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62:245-252.

Chertow GM, Jacobs DO, Lazarus JM, Lew NL, Lowrie EG: Phase angle predicts survival in hemodialysis patients. J Renal Nutr 1997;7:204-207.

Chertow GM, Raggi P, McCarthy JT, Schulman G, Silberzweig J, Kuhlik A, Goodman WG, Boulay A, Burke SK, Toto RD: The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. Am J Nephrol 2003; 23:307-314.

Cheung A, Sarnak MJ, Yan G, et al.: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney International 2000; 58:353-362.

Cheung AK, Levin NW, Greene T, et al.: Effects of high flux hemodialysis on clinical outcomes: Results of the HEMO study. J Am Soc Nephrol 2003; 14:3251-3263.

Chumlea WC, Guo SS, Steinbaugh ML: The prediction of stature from knee height for black and white adults and children, with application to the mobility-impaired. J Am Diet Assoc 1994; 94:1385-1391.

Chumlea WC, Guo SS, Wholihan K, Cockram D, Kuczmarski RJ, Johnson CL: Stature prediction equations for elderly non-Hispanic White, non-Hispanic Black, and Mexican American persons: from NHANES III (1988-94). J Am Diet Assoc 1998; 98:137-142.

Chumlea WC, Wisemandle W, Guo SS, Siervogel RM: Relations between frame size and body composition and bone mineral status. Am J Clin Nutr 2002; 75:1012-1016.

Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H: Canadian hemodialysis morbidity study. Am J Kidney Dis 1992; 19:214-234.

Collins HW, Kronenberg MW, Byrd BF: 3rd Reproducibility of left ventricular mass measurements by two-dimensional and M-mode echocardiography. J Am Coll Cardiol 1989; 14:672-676.

Combe C, Chauveau P, Laville M, Fouque D, Azar R, Cano N, Canaud B, Roth H, Leverve X, Aparicio M, and the French Study Group for Nutrition in Dialysis.: Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. Am J Kidney Dis 2001; 37:S81-S88.

Conion PJ, Walshe JJ, Heinle SK, Minda S, Krucoff M, Schwab SJ: Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients. J Am Soc Nephrol 1996; 7:2658-2663.

Craven JL, Rodin GM, Littlefield C: The Beck Depression Inventory as a screening device for major depression in renal dialysis patients. Int J Psychiatry Med 1988; 18:365-374.

Culp K, Flanigan MJ, Lowrie EG, Lew N, Zimmerman B: Modeling mortality risk in hemodialysis patients using laboratory values as time-dependent covariates. Am J Kidney Dis 1996; 28:741-746.

Daniels MJ, Hogan JW: Reparameterizing the pattern mixture model for sensitivity analyses under informative dropout. Biometrics 2000; 56:1241-1248.

Daugirdas, J., Levin, N., Bailey, J., Beck, G., Cheung, A., Greene, T., Leypoldt, J., Martin, A., and for the HEMO Study group. Occurrence of Intradialytic hypotension as a risk factor for mortality in the Hemo Study. J Am Soc Nephrol 14, 711A. 2003.

Daugirdas JT, Schneditz D: Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. ASAIO J 1995; 41:M719-M724.

DeOreo PB: Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. Am J Kidney Dis 1997; 30:204-212.

Depner TA: Benefits of more frequent dialysis: lower TAC at the same Kt/V. Nephrol Dial Transplant 1998; 13:20-24.

Depner TA: Assessing adequacy of hemodialysis: Urea modeling. Kidney Int 1994; 45:1522-1535.

Depner TA, Cheer A: Modeling urea kinetics with two vs. three BUN measurements. A critical comparison. ASAIO Trans 1989; 35:499-502.

Després J, Prud'homme D, Pouliot M, Tremblay A, Bouchard C: Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr 1991; 3:471-477.

Diaz-Buxo JA, Lacson E Jr: Daily hemodialysis: a dialysis provider perspective. Adv Ren Replace Ther 2001; 8:280-285.

Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang H, Lazarus JM: Quality-of-life evaluation using short form 36: Comparison in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 2000; 35:293-300.

Diggle PJ, Liang KY, Zeger SL: Analysis of longitudinal data. Oxford Statistical Science Series 1994; 13:139.

Edgell ET, Coons SJ, Carter WB, Kallich JD, Mapes D, Damush TM, Hays RD: A review of health-related quality-of-life measures used in end-stage renal disease. Clinical Therapeutics 1996; 18:887-938.

Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JWet al.: Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347:2010-2019.

Evans RW, Rader B, Manninen DL, Cooperative Multicenter EPO Clinical Trial Group.: The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. JAMA 1990; 263:825-830.

Floege J, Ketteler M: Beta2-microglobulin-derived amyloidosis: an update. Kidney Int Suppl 2001; 78:S164-S171.

Foley RN, Herzog CA, Collins AJ: Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. Kidney Int 2002; 62:1784-1790.

Foley RN, Parfrey PS, Harnett JD, Kent GM, Hu L, O'Dea R, Murray DC, Barre PE: Hypocalcemia, morbidity and mortality in end-stage renal disease. Am J Nephrol 1996; 16:386-393.

Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: The prognostic importance of left ventricular geometry in uremic cardiomyopathy. J Am Soc Nephrol 1995; 5:2024-2031.

Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE: Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. J Am Soc Nephrol 2000; 11:912-916.

Furlong WJ, Feeny DH, Torrance GW, Barr RD: The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. 2001. Ann Med 2001; 33:375-384.

Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-2138.

Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al.: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000; 342:1478-1483.

Gotch FA, Levin NW: Daily dialysis: the long and the short of it. Blood Purif 2003; 21:271-281.

Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 1985; 28:526-534.

Guh JY, Chen HC, Chuang HY, Huang SC, Chien LC, Lai YH: Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. Am J Kidney Dis 2002; 39:1245-1254.

Guida B, De Nicola L, Pecoraro P, Trio R, Di Paola F, Iodice C, Bellizzi V, Memoli B: Abnormalities of bioimpedance measures in overweight and obese hemodialyzed patients. Int J Obesity 2001; 25:265-272.

Guralnik JM, Simonsick EM, Ferrucci L, et al.: A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home placement. J Gerontol 1994; 49:M85-M94.

Hakim RM, Lowrie E: Obesity and Mortality in ESRD: is it good to be fat? Kidney International 1999; 55:1580-1587.

Harville DA: Maximum likelihood approaches to variance component estimation and to related problems. JASA 1977; 72:320-340.

Hays RD, Morales LST: The RAND-36 measure of health-related quality of life. Ann Med 2001; 33:13-21.

Heidenheim AP, Muirhead N, Moist L, Lindsay RM: Patient quality of life on quotidian hemodialysis. Am J Kidney Dis 2003; 42:36-41.

Hemmelgarn BR, Manns BJ, Quan H, Ghali WA: Adapting the Charlson Comorbidity Index for use in patients with ESRD. Am J Kidney Dis 2003; 42:125-132.

Heymsfield SB, McManus C, Smith J, et al.: Anthropometric measurement of muscle mass: Revised equations for calculating bone-free arm muscle area. Am J Clin Nutr 1982; 36:680-690.

Horl MP, Horl WH: Hemodialysis-associated hypertension: pathophysiology and therapy. American Journal of Kidney Diseases 2002; 39:244.

Ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim RM: Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: A prospective study. Kidney Int 1999; 55:1945-1951.

Izzo JJ: Arterial stiffness and the systolic hypertension syndrome. Curr Opin Cardiol 2004; 19:341-352.

Johansen KL, Chertow GM, DaSilva M, Carey S, Painter P: Determinants of physical performance in ambulatory patients on hemodialysis. Kidney Int 2001; 60:1586-1591.

Jones CH, Akbani H, Croft DC, Worth DP: The relationship between serum albumin and hydration status in hemodialysis patients. J Renal Nutr 2002; 12:209-212.

Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii HGCM: Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 2000; 87:E10-E17.

Kaysen GA, Rathore V, Shearer GC, Depner TA: Mechanism of hypoalbuminemia in hemodialysis patients. Kidney Int 1995; 48:510-516.

Kaysen GA, Stevenson FT, Depner T: Determinants of albumin concentration in hemodialysis patients. Am J Kidney Dis 1997a; 29:6589-6568.

Kaysen GA, Yeun JY, Depner T: Albumin synthesis, catabolism and distribution in dialysis patients. Miner Electrolyte Metab 1997b; 23:218-224.

Kerr PG, Strauss BJG, Atkins RC: Assessment of the nutritional state of dialysis patients. Blood Purif 1996; 14:382-387.

Kimmel PL, Peterson RA, Weihs KL, et al.: Behavioral compliance with dialysis prescription in hemodialysis patients. J Am Soc Nephrol 1995; 5:1826-1834.

Kimmel PL, Peterson RA, Weihs KL, et al.: Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients. Kidney Int 1998; 54:245-254.

Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz Iet al.: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000; 57:2093-2098.

Klarenbach S, Heidenheim AP, Leitch R, and Lindsay RM: Reduced requirement for erythropoietin with quotidian hemodialysis therapy. ASAIO J 2002; 48:57-61.

Klein JP, Moeschberger ML: Survival analysis: techniques for censored and truncated data. New York, Springer-Verlag Inc., 1997.

Kooistra MP, Vos J, Koomans HA, Vos PF: Daily home haemodialysis in The Netherlands: effects on metabolic control, haemodynamics, and quality of life. Nephrol Dial Transplant 1998; 13:2853-2860.

Kopple JD: Nutritional status as a predictor of morbidity and mortality in maintenance hemodialysis patients. ASAIOJ 1997; 3:246-250.

Kramer L, Madl C, Stockenhuber F, Yeganehfar W, Eisenhuber E, et al.: Beneficial effect of renal transplantation on cognitive brain function. Kidney Int 1996;49:833-888.

Kramer U, Wolf S, Fenchel M, Kraft A, Tomaschko K, Stauder N, Risler T, Claussen CD, Miller S: TrueFISP MR imaging to determine the influence of hemodialysis on the myocardial functional parameters in patients with terminal renal insufficiency. Rofo 2004; 176:350-356.

Kurella M, Chertow GM, Luan J, Yaffe K: Cognitive impairment in chronic kidney disease. J Am Soc Geriatrics 2004; 52:1863-1869.

Kurtin PS, Davies AR, Meyer KB, DeGiacomo JM, Kantz ME: Patient-based health status measures in outpatient dialysis. Early experiences in developing an outcome assessment program. Med Care 1992; 30:MS136-MS149.

Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 1998; 31:997-1006.

Levin NW, Lazarus JM, Nissenson AR: National Cooperative rHu Erythropoietin Study in patients with chronic renal failure-an interim report. The National Cooperative rHu Erythropoietin Study Group. Am J Kidney Dis 1993; 22:3-12.

Liang KY, Zeger SL: Inference based on estimating functions in the presence of nuisance parameters. Statistical Science 1995;10:158-173.

Lindsay RM, Heidenheim AP: Measurement of quality of life in international trials involving dialysis patients and the use of recombinant human Erythropoietin in Bauer C., Koch KM, Scigalla P, Wieczorek L, ed: Erythropoietin:Molecular Physiology and Clinical Applications; in Marcel Dekker I (ed): Molecular Physiology and Clinical Applications. New York, 1994 pp 81-92.

Lins RL, Elseviers M, Rogiers Pet al.: Importance of volume factors in dialysis related hypertension. Clin Nephrol 1997; 48:29-33.

Littell RC, Milliken GA, Stroup WW, Wolfinger R: SAS System for Mixed Models. SAS Publishing, 1996.

Little RJA: Modeling the drop-out mechanism in repeated-measures studies. JASA 1995; 90:1112-1121.

Lockridge RS, Jr., Spencer M, Craft V, Pipkin M, Campbell D, McPhatter L, Albert J, Anderson H, Jennings F, Barger T: Nocturnal home hemodialysis in North America. Adv Ren Replace Ther 2001; 8:250-256.

Lockridge RSJr: Nightly home hemodialysis (NHHD), future treatment "option of choice": Fifteen months of experience in Lynchburg, Virginia. Home Hemodial Int 1999; 3:23-28.

London GM, Marchais SJ, Guerin AP: Arterial stiffness and function in end-stage renal disease. Adv Chronic Kidney Dis 2004; 11:202-209.

London GM: Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Semin Dial 2003; 16:85-94.

London GM, Marchais SJ, Guerin AP: Arterial stiffness and function in end-stage renal disease. Adv Chronic Kidney Dis 2004; 11:202-209.

London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, Metivier F, Adda H, Safar ME: Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. J Am Soc Nephrol 2001; 12:2759-2767.

Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990; 15:458-482.

Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol 1999; 10:610-619.

Mattern WD, Hak LJ, Lamanna RW, Teasley KM, Laffell MS: Malnutrition, altered immune function, and the risk of infection in maintenance hemodialysis patients. Am J Kidney Dis 1982; 1:206-218.

McFarlane PA, Pierratos A, Redelmeier DA: Cost savings of home nocturnal versus conventional in-center hemodialysis. Kidney Int 2002; 62:2216-2222.

McPhatter LL, Lockridge RS, Jr., Albert J, Anderson H, Craft V, Jennings FM, Spencer M, Swafford A, Barger T, Coffey L: Nightly home hemodialysis: improvement in nutrition and quality of life. Adv Ren Replace Ther 1999; 6:358-365.

Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT: Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. The Necosad Study Group. Am J Kidney Dis 1997; 29:584-592.

Meyer KB, Espindle DM, DeGiancomo JM, et al.: Monitoring dialysis patients' health status. Am J Kidney Dis 1994; 24:267-279.

Miskulin DC, Athienites NV, Yan G, Martin AA, Ornt DB, Kusek JW, Meyer KB, Levey AS: Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. Kidney Int 2001; 60:536-540.

Miwa Y, Tsushima M, Kawano Y, Sasaguri T: Pulse pressure is an independent predictor for the progression of aortic wall calcification in patients with controlled hyperlipidemia. Hypertension 2004; 43:536-540.

Miwa Y, Tsushima M, Arima H, Kawano Y, Sasaguri T: Pulse pressure is an independent predictor for the progression of aortic wall calcification in patients with controlled hyperlipidemia0. Hypertension 2004; 43:536-540.

Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K: Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int 2002; 61:638-647.

Mohr PE, Neumann PJ, Franco SJ, Marainen J, Lockridge R, Ting G: The quality of life and economic implications of daily dialysis. Policy Anal Brief H Ser 1999; 1:1-4.

Moon KH, Song IS, Yang WS, Shin YT, Kim SB, Song JK, and Park JS: Hypoalbuminemia as a risk factor for progressive left-ventricular hypertrophy in hemodialysis patients. Am J Nephrol 2000; 20:396-401.

Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A: Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int 1998; 53:1399-1404.

Myerson SG, Bellenger NG, Pennell DJ: Assessment of left ventricular mass by cardiovascular magnetic resonance. Hypertension 2002; 39:750-755.

Nakamura S, Sasaki O, Nakahama H, Inenaga T, Kimura G: Left ventricular hypertrophy is a risk factor independent of hypertension in survival of hemodialyzed patients. Ren Fail 2002; 24:175-186.

National Kidney Foundation': *KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy*. Am J Kidney Dis 2006; 48:S1-S90.

O'Brien E, Beevers G, Lip GY: ABC of hypertension: Blood pressure measurement. Part IV-automated sphygmomanometry: self blood pressure measurement. BMJ 2001; 322:1167-1170.

Onder G, Penninx BW, Lapuerta P, Fried LP, Ostir GV, Guralnik JMPMJ: Change in physical performance over time in older women: the Women's Health and Aging Study Gerontol A. Biol Sci Med Sci 2002;57:M289-M293.

Onesti G, Kim KE, Greco JA, del Guercio ET, Fernandes M, Swartz C: Blood pressure regulation in end-stage renal disease and anephric man. Circ Res 1975; 36:145-152.

Ouseph R, Ward RA: Water treatment for hemodialysis: ensuring patient safety. Semin Dial 2002; 15:50-52.

Ouwendyk M, Leitch R, Freitas T: Daily hemodialysis: A nursing perspective. Ad Ren Replace Ther 2001; 4:257-267.

Palmieri V, Dahlof B, DeQuattro V, Sharpe N, Bella JN, de Simone G, Paranicas M, Fishman D, Devereux RB: Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE study. Prospective Randomized Study Evaluating Regression of Ventricular Enlargement. J Am Coll Cardiol 1999; 34:1625-1932.

Panzetta G, Tessitore N, Faccini G, Maschio G: The protein catabolic rate as a measure of protein intake in dialysis patients: Usefulness and limits. Nephrol Dial Transpl 1990; 5:125-127.

Paoletti E, Specchia C, Di Maio G, Bellino D, Damasio B, Cassottana P, Cannella G: The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. Nephrol Dial Transplant 2004; 19:1829-1834.

Patrick JM, Bassey EJ, Fentem PH: Changes in body fat and muscle in manual workers at and after retirement. Eur J Appl Physiol 1982; 14:49-54.

Pedrini LA, Zereik S, Rasmy S: Causes, kinetics and clinical implications of post-hemodialysis urea rebound. Kidney Int 1988; 34:817-824.

Peterson RA, Kimmel PL, Sacks CR, et al.: Depression, perception of illness and mortality in patients with end-stage renal disease. Int J Psychiatry Med 1991; 21:343-354.

Piccoli GB, Bermond F, Mezza E, Quaglia M, Pacitti A, Jeantet A, Segoloni GP: Home hemodialysis. Revival of a superior dialysis treatment. Nephron 2002; 92:324-332.

Pickett JL, Theberge DC, Brown WS, Schweitzer SU, Nissenson AR: Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999; 33:1122-1130.

Pierratos A: Daily nocturnal home hemodialysis. Kidney Int 2004; 65:1975-1986.

Pierratos A, Ouwendyk M: Nocturnal hemodialysis: an update. Int J Artif Organs 2001; 24:1-3.

Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, and Young EW: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS . Kidney International 2002; 62:2238-2245.

Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 2002; 13:1061-1066.

Port FK, Hulbert-Shearon TE, Wolfe RA, Bloembergen WE, Golper TA, Agodoa LYC, Young EW: Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis 1999; 33:507-517.

Raggi P, Boulay A, Chasan-Taber S, et al.: Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002; 39:695-701.

Rettig RA, Sadler JH, Meyer KB, et al.: Assessing health and quality of life outcomes in dialysis: A report on an Insititute of Medicine workshop. Am J Kidney Dis 1997; 30:140-155.

Rocco, M. V., Dwyer, J. T., Larive, B., Greene, T., Cockram, D. B., Chumlea, W. C., Kusek, J. W., Leung, J., Burrowes, J. D., McLeroy, S. L., Poole, D., and Uhlin, L.for HEMO Study Group. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: Results of the HEMO Study. Kidney Int 65, 2321-2334. 2004.

Rostand SG, Drueke TB: Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int 1999; 56:383-392.

Sacks CR, Peterson RA, Kimmel PL: Perception of illness and depression in chronic renal disease. Am J Kidney Dis 1990; 15:31-39.

Safar ME, Blacher J, Pannier B, et al: Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002; 39:735-738.

Samsa G, Edelman D, Rothman ML, et al.: Determining clinically important differences in health status measures: A general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics 1999; 15:141-155.

Sarnak MJ, Levey AS: Cardiovascular disease in Chronic renal disease: a new paradigm. Am J Kidney Dis 2000; 35:S117-S131.

Scharer K, Schmidt KG, Soergel M: Cardiac function and structure in patients with chronic renal failure. Pediatr Nephrol 1999; 13:951-965.

Schinke T, Karsenty G: Vascular calcification-a passive process in need of inhibitors. Nephrol Dial Transplant 2000; 15:1272-1274.

Schinke T, McKee MD, Kiviranta R, et al.: Molecular determinants of arterial calcification. Ann Med 1998; 30:538-541.

Schunemann HJ, Griffith L, Stubbing D, Goldstein R., Guyatt G.H.: A clinical trial to evaluate the measurement properties of 2 direct preference instruments administered with and without hypothetical marker states. Med Decis Makin 2003; 23:140-149.

Sehgal AR, Grey SF, DeOreo PB, Whitehouse PJ: Prevalence, recognition, and implications of mental impairment among hemodialysis patients. Am J Kidney Dis 1997; 30:41-49.

Shoji T, Tsubakihara Y, Fujii M, Imai E: Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int 2004; 66:1212-1220.

Silaruks S, Sirivongs D, Chunlertrith D: Left ventricular hypertrophy and clinical outcome in CAPD patients. Perit Dial Int 2000; 20:461-466.

Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end-stage renal disease. Kidney Int 1989; 36:286-290.

Silverman BW: Density Estimation for Statistics and Data Analysis 6. London, Chapman and Hall, 1986.

Simon GE, Revicki DA, Grothaus L, Vonkorff M: SF-36 summary scores: are physical and mental health truly distinct? Med Care 1998; 36:567-572.

Stack AG, Saran R: Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. Am J Kidney Dis 2002; 40:1202-1210.

Stenvinkel P, Heimburger O, Paultre F, Diczflusy U, Want T, Berglund L, Jogestrand T: Strong association between malnutrition, inflammation and atherosclerosis in chronic renal failure. Kidney Int 1999; 55:1800-1911.

Stewart GA, Foster J, Cowan M, Rooney E, McDonagh T, Dargie HJ, Rodger RS, Jardine AG: Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. Kidney Int 1999;56:2248-2253.

Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, Fox M, Guralnik JM: Physical performance measures in the clinical setting. J Am Geriatr Soc 2003; 51:314-322.

Tawney KW, Kovach JJ, Zaluska A, Handelman GJ, Levin NW: Physical Performance as Affected by Dialysis Treatment. Journal of the American Society of Nephrology 2004.

Tisler A, Akocsi K, Borbas B, Fazakas L, Ferenczi S, Gorogh S, Kulcsar I, Nagy L, Samik J, Szegedi J, Toth E, Wagner G, Kiss I: The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. Nephrol Dial Transplant 2003; 18:2601-2605.

Toledano AY, Gatsonis C: Generalized estimating equations for ordinal categorical data: arbitrary patterns of missing responses and missingness in key covariates. Biometrics 1999; 55:488-496.

Tozawa M, Iseki K, Iseki C, Takishita S: Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis. Kidney Int 2002; 61:717-726.

Troidle L, Wuerth D, Finkelstein S, Kliger A, Finkelstein F: The BDI and the SP36: Which tool to use to screen for depression? Adv Perit Dial 2003; 19:159-162.

Tsuchihashi K, Takizawa H, Torii T, Ikeda R, Nakahara N, Yuda S, Kobayashi N, Nakata T, Ura N, Shimamoto K: Hypoparathyroidism potentiates cardiovascular complications through disturbed calcium metabolism: possible risk of vitamin D (3) analog administration in dialysis patients with end-stage renal disease. Nephron 2000; 84:13-20.

Umans JG, Pliskin NH: Attention and mental processing speed in hemodialysis patients. Am J Kidney Dis 1998; 32:749-751.

Unruh M, Yan G, Radeva M, Hays RD, Benz R, Athienites NV, Kusek J, Levey AS, Meyer KB, HEMO Study Group.: Bias in assessment of health-related quality of life in a hemodialysis population: a comparison of self-administered and interviewer-administered surveys in the HEMO study. J Am Soc Nephrol 2003; 14:2132-2141.

USRDS. US Renal Data Systems. USRDS 2000 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Bethesda MD 2000. 2000.

USRDS. U.S. Renal Data System, 2001 Annual Data Report: Atlas of end-stage renal disease in the United States, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2001. 136-146. 2001.

USRDS. U.S. Renal Data System, USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute if Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 151-164. 2002.

Verbeke G, Lesaffre E: The effect of misspecifying the random effects distribution in linear mixed models for longitudinal data. Computational Statistics and Data Analysis 1997; 23:541-556.

Verbeke G, Lesaffre E, Brant LJ: The detection of residual serial correlation in linear mixed models. Statistics in Medicine 1998; 17:1391-1402.

Verbeke G, Molenbergh G: Linear Mixed Models for Longitudinal Data (Springer series in statistics); New York, Springer, 2000 p 568.

Wolfe RA, Ashby VB, Daugirdas JT, et al.: Body size, dose of hemodialysis and mortality. Am J Kidney Dis 2000; 35:80-88.

Woods JD, Port FK, Stannard D, Blagg CR, Held PJ: Comparison of mortality with home hemodialysis and center hemodialysis: a national study. Kidney Int 1996; 49:1464-1470.

Xia H, Ebben J, Ma JZ, Collins AJ: Hematocrit levels and hospitalization risks in hemodialysis patients. J Am Soc Nephrol 1999; 10:1309-1316.

Zager PG, Nikolic J, Brown RH, Campbell MA, Hunt WC, Peterson D, Van Stone J, Levey A, Meyer KB, Klag MJ, Johnson HK, Clark E, Sadler JH, Teredesai P: "U" curve association of blood pressure and mortality in hemodialysis patients. Kidney Int 1998; 54:561-569.

Zimmermann J, Herrlinger A, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999; 55:648-658.

Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, Seminara G, Stancanelli B, Malatino LS, CREED Investigators.: Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. J Am Soc Nephrol 2001a; 12:2768-2774.

Zoccali C, Mallamaci F, Asahia K, Benedetto FA, Tripepi G, Tripepi R, Nicocia G, Buemi M, Miyata T: Pentosidine, carotid atherosclerosis and alterations in left ventricular geometry in hemodialysis patients. J Nephrol 2001b; 14:293-298.