Frequent Hemodialysis Network (FHN)

Daily Trial Protocol

VERSION 2.3.1: JULY 2, 2008

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Executive Summary

The prevalence of end-stage renal disease (ESRD) is increasing, the cost of renal replacement therapy is high, and the disease and treatment are associated with significant mortality and loss in patient quality of life. Recent physiologic and observational studies have suggested improvements with more frequent hemodialysis (HD) regimens (daily or nocturnal HD).

Because no randomized trials of daily dialysis have been conducted, the first calendar year of the trial 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 in-center daily HD improves physiological, health-related quality of life (HRQL) and functional outcomes, as compared with in-center conventional HD. The target sample size for this multi-center, randomized controlled trial is 250 subjects. Finally, this trial will evaluate costs and estimate cost-effectiveness of in-center daily HD.

Using broad inclusion criteria, subjects will be recruited from dialysis units affiliated with Clinical Centers in the United States and Canada and treated and followed for 1 year. Daily HD will be delivered for 1.5 – 2.75 hours, 6 days per week, while conventional HD will be delivered for at least 2.5 hours (typically 3 to 4 hours), 3 days per week. In the daily HD group dialysis prescriptions will target an eKt/V_n of 0.9 at each of the 6 weekly dialysis sessions. In the conventional HD group subjects will remain on their usual dialysis prescriptions subject to a minimum prescribed eKt/V of 1.1. Based on simulation studies the projected median weekly standard Kt/V is 3.82 in the daily HD arm and 2.46 in the conventional HD arm. The projected median weekly treatment time is 14.2 hours in the daily-HD arm and 10.5 hours in the conventional HD arm. Because the intervention, by necessity, is unblinded, efforts will be made to control bias. These include the use of objective outcomes such as left ventricular (LV) mass, blinding the assessment of subjective outcomes, and efforts to standardize the use of co-interventions in both arms of the study.

The study has two co-primary outcomes: 1) a composite of mortality with the change over 12 months in LV mass by magnetic resonance imaging, and 2) a composite of mortality with the change over 12 months in the SF-36 RAND physical health composite (PHC). Because the hypothesized benefits of daily HD therapy encompass multiple conceptually distinct dimensions, main secondary outcomes have been designated for each of seven outcome domains. These are 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 function (change in the Trail Making 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.

In addition, potential risks of in-center daily HD, including vascular access complications will be assessed, as well as subjects adherence to and acceptance of the therapy. The incremental cost of delivery of daily HD over conventional HD will be estimated, and cost-effectiveness and cost-utility ratios of the two therapies will be compared.

1. Background and Rationale

1.1 Scope of the Problem

End-stage renal disease (ESRD) is a major health problem in the United States and Canada. Over the last decade, the prevalence has increased by approximately 6% annually [Canadian Organ Replacement Registry 2002 Preliminary Report, 2003;USRDS, 2000;Schaubel, 1998;Schaubel, 1999], and by the year 2010, an estimated 650,000 Americans will require dialysis and kidney transplantation, with direct Medicare costs of potentially well over the current estimate of 28 billion dollars annually [Xue, 2001]. Despite treatment, ESRD patients have significantly impaired quality of life compared with the general population [USRDS, 1997;Merkus, 1997;Valderrabano, 2001] and the 20% annual mortality rate for ESRD patients in North America has not changed in more than a decade [Canadian Organ Replacement Registry 2002 Preliminary Report, 2003]. In-center hemodialysis (HD) remains the major treatment modality for ESRD, and improvements in its delivery are desperately needed.

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 [Hakim, 1994;Held, 1996;Parker, III, 1994]. It was thus hypothesized that increasing doses beyond current standards may result in decreased mortality. This hypothesis was recently tested in the Hemodialysis (HEMO) Study [Eknoyan, 2002]. Over 1800 subjects on conventional, 3 times weekly HD 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 differences in dose between the dose arms were obtained by a combination of a longer session length and greater dialyzer clearance in the high dose group. There were no significant differences between the two dose groups in mortality, hospitalizations, or other secondary endpoints.

One theory explaining the negative results of the HEMO trial is based on dialysis kinetics. The rate of urea and other small toxic solute removal with HD is proportional to the concentration of solute (Figure 1a) [Depner, 1998]. Consequently, most solute removal occurs at the start of HD, with decreasing removal rates as the HD session proceeds (Figure 1b) [Depner, 1994]. During the last hour of a 4.5 hour HD session, relatively little solute is removed in comparison to the first 3 hours. Thus, increasing dialysis dose by increasing dialysis session length on conventional HD results in diminishing increments of total small solute removal. In addition, once the HD 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 after HD (rebound effect).

Moreover, the long interdialytic interval results in large "peaks and valleys" in blood solute concentrations. Some have proposed that large time-averaged deviations contribute to adverse outcomes on dialysis (sometimes referred to as the "unphysiology" hypothesis) [Kjellstrand, 2001].

Similarly, the relatively limited range of session length during conventional HD (e.g., an increase from 3 to 4 hours) does not yield substantial increases in removal of toxic "middle" molecules [Pierratos, 2001a], such as β_2-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 [DeSoi, 1993]. In addition, rebound and the time-averaged deviation are even more pronounced for molecules like phosphate, which have low diffusibility, than for highly diffusible small solutes, such as urea [Heaf, 1994].

Finally, increasing conventional HD session length does not appear to ameliorate the problem of extracellular fluid accumulation during the long interdialytic period, a major contributing factor in the development of hypertension and cardiovascular risk [Jaeger, 1999].

It is for these same physiological reasons that daily HD may be preferable to conventional HD even if total weekly dialysis time were not increased. With daily dialysis, one is dialyzing against the steepest portion of the solute concentration curve for the majority of time during each session. Daily HD would be predicted to have higher efficiency than conventional HD, resulting in greater weekly small solute, middle molecule, and phosphate removal [Pierratos, 2001b;Depner, 2001;Goldfarb-Rumyantzev, 2002]. With daily dialysis the interdialytic rise in urea and presumably other small solutes is dissipated more frequently, predicting an overall decrease in time-averaged solute concentrations. An increased frequency of HD treatments would also be predicted to improve control of interdialytic weight gain and hypertension. Indeed, observational studies have supported these theories and suggested improvements in physiology and HRQL with more frequent HD regimens. These are detailed below.

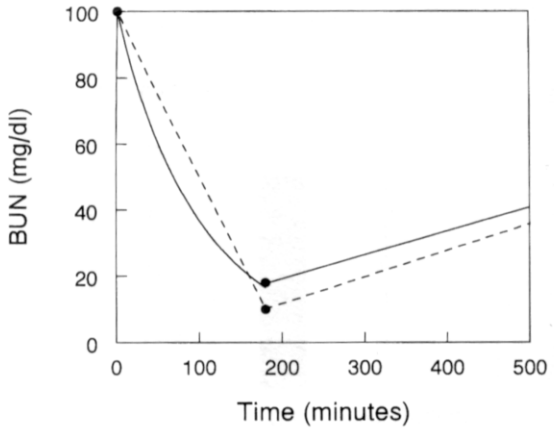


Figure 1a: First order kinetics of urea removal. The rate of urea removal is proportional to the instantaneous urea concentration, as indicated by the solid line. This results in less solute removal than a theoretical dialysis in which urea removal is constant (dotted line - zero order kinetic). Single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

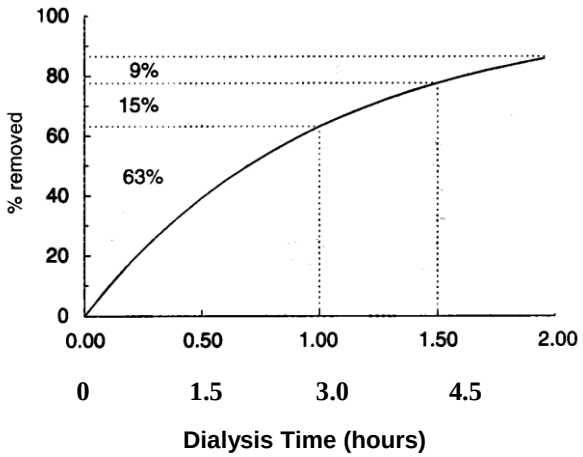


Figure 1b: Relationship between total solute removal and dialysis session time. The rate of solute removal decreases as session time increases. Percentages shown are the incremental removals associated with an increase in time between the dotted lines. (Depner TA, Kidney International, 1994)

1.3 Observational Studies Suggest Improvements in Health with Daily Hemodialysis

Daily HD was pioneered over 40 years ago by dePalma et al. [DePalma, 1968]. In the two decades that followed there were scattered reports suggesting an improvement in uremic symptoms with more frequent HD regimens [Bonomini V, 1972;Louis, 1975;Manohar, 1981;Snyder, 1975;Twardowski, 1975], but daily HD did not gain widespread acceptance due to deficiencies in dialysis technology and reimbursement issues [Twardowski, 2001]. Fostered by the promise of reducing morbidity associated with ESRD, over the last few years several centers in Canada, the United States, and Europe have started daily HD programs [Andre, 2002a;Buoncristiani, 1996;Buoncristiani, 1999;Buoncristiani, 1997b;Buoncristiani, 1997a;Fagugli, 1998;Fagugli, 2001;Galland, 2004b;Goffin, 2002;Heidenheim, 2003;Kjellstrand, 2003;Kooistra, 1998;Koshikawa, 2003;Lindsay, 2003a;Lindsay, 2003b;Lugon, 2001;Nesrallah, 2003;Piccoli, 2003;Piccoli, 2004;Pinciaroli, 1999;Quintaliani,

2000;Rao, 2003;Reynolds, 2002;Spanner, 2003;Suri, 2003;Ting, 2003;Traeger, 2004;Vos, 2001;Woods, 1999].

Observational studies have reported significant improvements in multiple physiological parameters with daily HD, as well as in health-related quality of life (HRQL) [Suri, 2006]. The number of subjects in these studies ranges from 5 to 72, with a mean follow-up of 6 to 27 months.

With daily HD, many hypertensive patients are able to achieve optimal blood pressure control, while decreasing, or completely discontinuing antihypertensive medications [Andre, 2002a;Fagugli, 1998;Fagugli, 2001;Kooistra, 1998;Koshikawa, 2003;Nesrallah, 2003;Piccoli, 2003;Ting, 2003;Traeger, 2004;Woods, 1999]. Reductions in left ventricular hypertrophy have been reported to parallel improvements in blood pressure [Buoncristiani, 1996;Fagugli, 1998;Fagugli, 2001;Pinciaroli, 1998;Traeger, 2004]. There are conflicting reports with respect to control of anemia, although some have reported decreased erythropoietin requirements in daily HD patients [Andre, 2002a;Fagugli, 1998;Klarenbach, 2002;Koshikawa, 2003;Ting, 2003;Traeger, 2004;Woods, 1999]. Many studies have also suggested that daily HD improves nutritional status; increases in appetite, protein and caloric intake, target dry weight, muscle mass, and albumin have been observed [Andre, 2002a;Fagugli, 1998;Galland, 2001b;Galland, 2001a;Galland, 2004b;Spanner, 2003;Ting, 2003;Woods, 1999].

In addition, observational studies have reported a variety of improvements in HRQL for patients on short daily HD. Patients on daily HD report a reduction in uremic and dialysis induced symptoms [Andre, 2002a;Heidenheim, 2003;Kooistra, 1998;Koshikawa, 2003;Traeger, 2004;Woods, 1999]. In addition, significant increases in mean scores of various HRQL instruments such as the SF-36, Nottingham Health Profile, and Kidney Disease Quality of Life questionnaire (KDQOL) have been observed after 6 to 12 months of daily HD [Heidenheim, 2003;Ting, 2003;Traeger, 2004].

1.4 Limitations of Existing Published Studies

While reported improvements in outcomes after starting daily HD 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 [Lacson, 2001;Suri, 2004;Suri, 2006].

Lack of adequate control groups: With one exception, all previous studies are pre-post case series, where changes in measurements are assessed from conventional HD to daily HD. Confounding due to time-dependent co-factors and due to period and carry-over effects influencing the results cannot be ruled out.

Selection bias: Many studies of daily HD have followed patients dialyzing at home rather than in-center. Home HD patients are a select group generally characterized by exceptional compliance, motivation and social support, and have been reported to have lower adjusted mortality compared to in-center patients [Woods, 1996]. Selection bias may account in part for reports of improved outcomes and lower rates of mortality and hospitalizations in patients on daily HD. In contrast, some centers have reported using daily HD as a salvage therapy [Ting, 2003]. 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. Non-dialysis factors precipitating the adverse conditions that led to salvage therapy may resolve spontaneously or because of increased medical attention.

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 median sample size in previous studies is 14 patients (range 5 – 42), impairing the ability to detect infrequent, yet clinically significant, potential adverse events. Possible adverse events associated with daily HD 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, fatigue and depression due to a more demanding treatment schedule.

It is unlikely that any one of these biases explain the extensive benefits reported for daily HD, however, their combined effect may be substantial. Given its promise, the potential benefits of daily HD must now be established in a rigorous experimental design. A randomized controlled trial that examines the effects of daily HD on intermediate outcomes is the next logical step

1.5 Rationale for Extending Total Weekly Treatment Time in the Daily Arm.

Some of the past observational studies of daily dialysis have investigated daily regimens in which the session lengths of individual treatments are reduced by approximately 50% from the session lengths of conventional therapy, resulting in approximately equal total weekly treatment times between the daily therapy and conventional three times per week therapy. As noted above, even with equivalent total weekly treatment time the daily therapy may be hypothesized to improve outcomes due to reduced intervals between dialysis treatments. However, daily hemodialysis with treatment times of less than 2 hours (but keeping total weekly times similar to thrice weekly HD) may not provide sufficient middle molecule clearance to effectively maximize the potential benefits from daily HD. Furthermore, the expected increased food and fluid intake of patients is projected to require increased weekly ultrafiltration [Ting, 2003;Galland, 2004b], best achieved over longer time to allow for vascular refilling. Based on these considerations, in this trial the median weekly treatment time of the daily arm will be increased by approximately 35% relative to the conventional therapy arm, thus evaluating the effects of a combination of increased dialysis frequency and a moderate increase in weekly treatment time. This is further described in Section 3.1.2.

1.6 Potential Significance of the Results

The Vanguard phase of this trial will determine the feasibility of randomizing patients and carrying out a multi-center clinical trial comparing daily HD to conventional HD. If feasibility is demonstrated, the trial will also establish the safety of daily HD, and confirm or refute the previously documented benefits of daily HD on intermediate physiological outcomes and health-related quality of life. It will also quantify the incremental cost of delivering in-center daily HD in the United States and Canada. If significant improvements are demonstrated with daily HD, and costs are not deemed prohibitive, this trial may lead to further implementation of in-center daily HD as an alternative treatment option for some patients with ESRD.

2. Objectives and Trial Design

2.1 Trial Objectives

The objectives of this study are the following:

Feasibility

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

2) To determine patient adherence with and acceptance of in-center daily HD, and to identify reasons for discontinuation from or nonadherence with the therapy.

Safety

3) To determine the safety of in-center daily HD with a particular focus on vascular access events and participant burden.

Efficacy

4) To evaluate the efficacy of in-center daily HD compared to conventional three times per week 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 (MRI), 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 in-center daily HD on nine secondary outcome domains: i) cardiovascular structure and function, ii) health-related quality of life and physical function, iii) depression/burden of illness, iv) nutrition and inflammation, v) cognitive function, vi) mineral metabolism, vii) clinical events, viii) hypertension, and ix) anemia.

Characterization of the Intervention

6) To better understand the complex therapy of in-center daily HD, by evaluating solute clearance, treatment times, volume removal, and non-dialytic factors such as differences in the frequency of medical surveillance and treatment.

Implementation

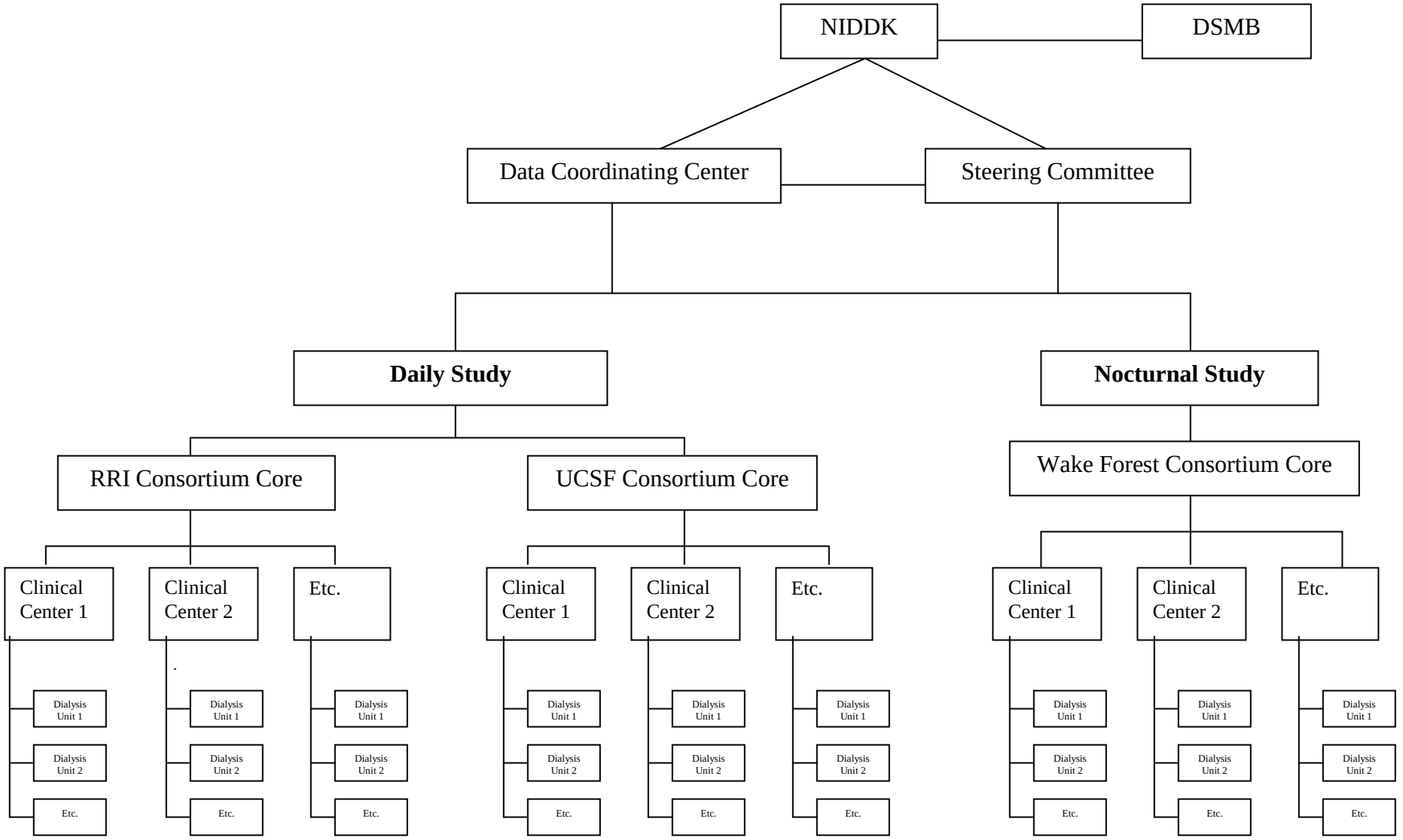
7) To determine the feasibility of implementing in-center daily HD in practice, by evaluating barriers to implementation such as the incremental cost of daily HD compared to 3 times per week conventional HD.

2.2 Overview of Study Design

This trial is a randomized controlled trial recruiting subjects from dialysis units associated with designated Clinical Centers (See Figure 2). There are about 10 Clinical Centers, but the number may vary over the course of the trial. These Clinical Centers are associated with 2 Consortium Cores at the Renal Research Institute and the University of California San Francisco. A total of 250 ESRD patients receiving in-center HD will be randomized to continue with conventional HD, 3 days per week (control group), or switch to daily HD, 6 days per week (intervention group). Because the intervention, by necessity, is unblinded, significant efforts will be made to reduce bias. These include the use of objective outcomes such as left ventricular mass index, blinding the assessment of primary subjective outcomes, and when possible, standardizing the use of co-interventions in both arms of the study. Subjects will be treated and followed for 12 months. 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) a composite of mortality with the change over 12 months in left ventricular mass. In addition, main secondary outcomes have been designated for each of seven 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 (change in serum albumin), 5) cognitive function (change in the Trail Making 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.

Figure 2

FHN ORGANIZATION



2.3 Study Timeline

This trial will be carried out in 5 phases. The first 24 months (Phase 1) will be used to finalize the study protocol, create procedures manuals, data collection forms, secure Institutional Review Board approval, program the database and train study personnel. Subject enrollment will occur over the next 32-month period

The first 12 months of the recruitment period (Phase 2) will be referred to as the "Vanguard" phase of the trial. The 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 Vanguard phase demonstrates feasibility, recruitment will continue over the remaining 20 months (Phase 3) of the 32-month accrual period. Each subject will be treated and followed for 12 months and followed for up to 2 more months for limited data collection (Phase 4). The last 5 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

The target sample size for this trial is 250 subjects, half of whom will be randomized to in-center daily HD. Subjects will be recruited from dialysis units associated with designated Clinical Centers affiliated with the two Consortium Cores. Within each of the Clinical Centers, persons receiving conventional 3 times weekly HD in the associated HD units will be potential study subjects. Currently, these dialysis units provide clinical services to > 7500 prevalent HD patients. It is estimated that approximately 50% of prevalent HD patients will be eligible for enrollment, based on inclusion and exclusion criteria. Resource and logistical constraints (e.g., available stations) may limit the numbers of subjects for whom the protocol can be implemented concurrently at a given site. Local efforts will be concentrated on those dialysis units and referring nephrology programs with large numbers of patients and adequate physical space. Under this staggered enrollment strategy, fewer than 50% of the total number of randomized subjects will be in the trial at any given time, thus easing the time required to implement the protocol for personnel conducting the study.

The progress of recruitment into this trial and into the companion nocturnal dialysis trial will be reviewed by the Data Safety and Monitoring Board (DSMB) at the conclusion of the one year Vanguard phase. Depending on the progress of the two trials, their target sample sizes may be modified.

Subjects will be recruited principally from the practices of nephrologists affiliated with the Daily Trial. These nephrologists include study investigators and numerous collaborators with admitting privileges at study-affiliated dialysis units. In order to facilitate recruitment, a variety of efforts will be undertaken to enhance knowledge and awareness of the study in local communities. All such efforts must be approved by the Institutional Review Boards (IRB) of the Clinical Centers as well as local IRBs where applicable. The efforts may include, but are not limited to, the use of a study website, study brochures, and letters to potential referring physicians. Clinical Center group information sessions may also be made available before and during the study, to answer questions from potential study subjects. Special efforts will be undertaken to encourage recruitment and retention of women, persons of racial and ethnic minorities, and persons otherwise disadvantaged due to poverty or physical disability. No HD patient will be excluded from the study on the basis of gender, race, ethnicity, sexual orientation, or other characteristics not below noted specifically in 2.5.2. Potential study subjects will be identified by physician investigators, dialysis unit medical directors and collaborating physicians. 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)

and the policies of their own institutions. Dialysis unit personnel will not be asked to participate in subject recruitment.

2.5 Study Population

Any individual who meets the inclusion and exclusion criteria will be eligible for enrollment, regardless of gender, race, ethnicity, or national origin.

2.5.1 Inclusion Criteria

1) Patients with end stage renal disease requiring chronic renal replacement therapy
2) Age $\geq$ 13 years
3) Achieved mean eKt/V of $\geq$ 1.0 on at least two baseline sessions
4) Weight $\geq$ 30 kg

2.5.2 Exclusion Criteria

1) Residual renal urea clearance > 3 mL/min per 35 L
2) Expectation that native kidneys will recover
3) Vascular access being used for HD is a non-tunneled catheter
4) Inability to come for in-center 6 days a week, including inability to arrange adequate transportation
5) History of poor adherence to thrice weekly HD
6) Medical conditions that would prevent the subject 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) Requires HD > 3 times per week due to medical co-morbidity (such as, but not limited to: systemic oxalosis or requiring total parenteral nutrition). Occasional ultrafiltration on a fourth day per week is not an exclusion criterion.
9) Currently on daily or nocturnal HD, or less than 3 months since the subject discontinued daily or nocturnal HD
10) Scheduled for living donor kidney transplant, change to peritoneal dialysis, home HD, or plans to relocate to another center within the next 14 months
11) Expected geographic unavailability at a participating HD unit for > 2 consecutive weeks or > 4 weeks total during the next 14 months (excluding unavailability due to hospitalizations) (frequent HD subjects who leave for vacation may resort back to conventional HD during these time periods)
12) Less than 3 months since the patient returned to HD after acute rejection resulting in allograft failure
13) Currently in acute or chronic care hospital
14) Life expectancy < 6 months

15) A medical history that might limit the subject'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 actively planning to become pregnant in the next 12 months

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

2.6 Screening Evaluation

The purposes of the screening evaluation are to identify potential study subjects for trial enrollment, to provide potential study subjects with information regarding the study, to obtain written informed consent for participation and randomization. The length of the screening evaluation will generally be 2-12weeks.

A trained study coordinator for each study site will consult with physician investigators and collaborators to determine whether patients who have recently developed ESRD, or who are scheduled to begin HD within the next several weeks, will be appropriate candidate subjects for the study. For existing patients at study facilities, the physician investigators, collaborators and study coordinators may review on-site medical records to determine potential trial eligibility. The physician investigator, collaborator or study coordinator will approach patients deemed eligible and will provide patients with verbal and written information regarding the study. Other resource materials, including study brochures will be provided to potential candidates. If the patient is agreeable, written informed consent to conduct a detailed baseline assessment and undergo randomization will be obtained and the patient will be asked to sign an Institutional Review Board - approved consent form, along with a form allowing for the use of personal health information. A written informed consent will be obtained for the storage of blood for future biochemical testing.

2.7 Baseline Evaluation

The purposes of the baseline evaluation are to provide subjects with further information regarding the study, collect detailed data on eligibility and exclusion criteria (including practical issues such as transportation), and document baseline characteristics and clinical information to allow stratification and assessment of important baseline prognostic variables, as well as enable pre- and post-study comparisons of specific outcomes between treatment groups. *[2014 FHN Archive Note: FHN Executive Committee dropped prognostic covariates from the analyses.]* In addition, some of the characteristics assessed will enable observational comparisons with the Nocturnal Study being conducted in parallel with this trial. The length of the baseline evaluation period will be three to fifteen weeks.

Baseline Visits will be labeled as B1 visits. The baseline assessment will include two kinetic modeling sessions, separated by at least one week (see Section 3) and labeled as the B1 and B2 visits. Key biochemical tests, including predialysis serum albumin and pre- and post-dialysis serum urea nitrogen, creatinine, and phosphorus will be obtained from local laboratories for both baseline kinetic

modeling sessions. Derived kinetic modeling parameters and the pre-dialysis albumin and phosphorus concentrations will be averaged to determine the actual assigned baseline value. A timed urine collection (minimum 18 hours) will be obtained during the interdialytic interval preceding a dialysis session, preferably midweek for subjects producing urine prior to a baseline kinetic modeling session for evaluation of the residual renal function exclusion criterion. During the baseline period, participants will also be asked to travel to and from the HD unit for 6 consecutive days (i.e., on 3 HD days and on 3 intervening non-HD days), to determine if they are able to arrange and tolerate daily travel should they be randomized to the frequent arm of the trial. On the days subjects travel to and from the dialysis unit but do not receive dialysis (before randomization), they will not be required to stay at the dialysis unit for an extended period.

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

Once the baseline evaluation is completed, subjects will be re-evaluated by the study coordinator for eligibility to undergo randomization. If the patient is deemed eligible, the study coordinator will review the implications of randomization with the patient, and confirm the subject's desire to undergo randomization. For subjects choosing not to be randomized, or deemed ineligible for randomization at any time during the baseline period, a baseline dropout form will record the reason for dropout.

All baseline case report forms, including valid results for each of the primary and main secondary endpoints must be entered into the database in order for a subject to be randomized.

2.8 Randomization of Trial Participants

Once the baseline evaluation is completed and eligibility is verified, consenting subjects will be randomly allocated in a 1:1 allocation to conventional or daily HD. 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 diabetes 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 all baseline period studies have been completed, the forms corresponding to these studies have been received by the Data Coordinating Center, and the forms have been checked to be sure the patient meets eligibility requirements, the Principal Investigator or the study coordinator shall access the interactive randomization program. The program will verify through a defined set of questions that the participant is eligible and 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 subject starts the study treatment regimen or not, how long the patient continues on the

study treatment regimen, and how well the patient adheres to the study treatment regimen (see Section 7). These efforts should continue until termination of the Follow-up Period.

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 one of two HD regimens:

i) *Conventional hemodialysis* of 3 sessions per week. Subjects may remain on their usual dialysis prescription subject to a minimum eKt/V of 1.1 per session and a minimum treatment time of $\geq$ 2.5 hours per session;

ii) *Daily hemodialysis* of 6 sessions per week, to maintain a target eKt/$(V_n)^*$ of 0.90 per session, and a treatment time of 1.5 hours to 2.75 hours.**

*V_n = "normalized V" = $3.271 \times V^{(2/3)}$

**If a patient is unable to achieve the target eKt/(V_n) of 0.90 within 2.75 hours, the patient's target eKt/(V_n) will be reduced to that which can be achieved within a treatment time of 2.75 hours. If necessary, the maximum treatment time may be exceeded in order to maintain an ultrafiltration rate of <1.0 L per hour, or upon the discretion of the treating nephrologist for clinical reasons.

Although the dose target for the daily HD arm is expressed in terms of urea clearance, by varying both treatment frequency and total weekly treatment time the design is intended to achieve a large separation in the clearance of a wide range of solutes and in volume stability (see Table 3 below). In particular, the projected separation in total weekly treatment time (median 14.2 hours for the daily HD group vs. 10.5 hours for the conventional HD group) will result in a separation between dose groups in clearance of middle-molecular weight solutes in addition of small molecular weight solutes such as urea. The study design is not intended to determine the effects of each specific component of the daily HD treatment regimen, but rather is based on the pragmatic objective of determining whether the combination of factors associated with the daily HD regimen can improve outcomes. If subjects in the daily HD arm develop an unwillingness or inability to follow the 6x/week treatment regimen specified by the protocol, efforts will be made to adopt a reduced treatment regimen which approximates the intended 6x/week regimen as closely as possible (see Table 7 of Section 3.1.6).

3.1.2 Rationale for Choosing Target Doses

a) Conventional HD Group

HD dosing is traditionally 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 HD [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]. In order to assure adherence to current national standards, a minimum eKt/V of 1.10 will be required in the conventional HD group. However, consistent with its designation as a conventional therapy arm, the dialysis prescriptions in the conventional HD group will be otherwise unspecified (subject to a minimum treatment time of 2.5 hrs).

Table 3: Summary of the Dose Treatment Regimens

Parameter	Conventional HD (CHD)	Daily HD (DHD)	% Difference in Medians (DHD vs. CHD)
Sessions per week	3	6	100%
Target prescription	Unspecified: eKt/V $\geq$ 1.10	eKt/(V_n) = 0.90	-
Hours per session	$\geq$ 2.5 (median = 3.50)	1.50 to 2.75 (median = 2.36)	-33%
Maximum interdialysis interval (median, hours)	68.5	45.6	-33%
Average interdialysis interval (median, hours)	52.5	25.6	-51%
Hours per week (median, 5^{th} – 95^{th} percentile)	10.5 (9.0 – 13.1)	14.2 (11.5 – 16.5)	+35%
eKt/V urea per treatment (median, 5^{th} – 95^{th} percentile)	1.39 (1.12 – 1.75)	0.92 (0.74 – 1.05)	-34%
Weekly stdKt/V urea (median, 5^{th} – 95^{th} percentile)	2.46 (2.16 – 2.80)	3.82 (3.32 – 4.17)	+55%
Weekly eKR β_2-microglobulin (ml/min per 35 L total urea volume) (median, 5^{th} – 95^{th} percentile)	4.80 (3.77 – 6.21)	5.43 (4.26 – 6.85)	+13%
Standardized phosphorus removal (mg/day) (median, 5^{th} – 95^{th} percentile)	299 (254 – 374)	415 (338 – 497)	+39%

eKt/V = equilibrated Kt/V, stdKt/V = standard weekly Kt/V, eKR = continuous equivalent renal clearance

Medians, 5^{th}, and 95^{th} percentiles based on simulations assuming distributions of patient characteristics and baseline dialysis prescriptions from the Renal Research Institute Database, n=3285.

b) Daily HD Group

i) Rationale for Factoring Kt by V_n

The rationale for factoring Kt by V_n rather than V involves pragmatic and physiological considerations. From a pragmatic perspective, factoring Kt by $3.271V^{(2/3)}$ rather than V reduces the effect of large V's on calculation of Kt/V, resulting in moderately higher eKt/V's for smaller patients

and moderately lower eKt/V's for larger patients (Table 4). In addition, empiric data from 3285 patients associated with the Renal Research Institute (RRI) suggests that this adjustment corresponds to current practice patterns at these dialysis units (Table 5). The final row of Table 5 indicates that mean eKt/(V_n) is approximately constant for different values of V, whereas mean eKt/V declines as V increases.

Table 4: **Achieved eKt/V for Different V's when eKt/(V_n) = 0.90**

Patient Weight (kg) (assuming weight = V/0.6)	**Patient V (L)**	**eKt/(V_n)**	**eKt/V**
42	25	0.90	1.01
50	30	0.90	0.95
58	35	0.90	0.90
67	40	0.90	0.86
75	45	0.90	0.83
83	50	0.90	0.80

Table 5: Relationship of Treatment Time, eKt/V, and eKt/(V_n) to Patient Volume (V)*

Patient V (L)	Treatment Time (min)	eKt/V	eKt/(V_n)
< 27.5	189	1.51	1.35
27.5 – 32.5	202	1.43	1.36
32.5 – 37.5	212	1.35	1.34
37.5 – 42.5	224	1.29	1.35
> 42.5	240	1.21	1.34

*N=3285 from RRI database

From a physiologic perspective, factoring Kt by V raised to a power less than 1 is justified by the argument that toxin generation may be more directly related to body surface area rather than to volume. Native renal clearance is traditionally standardized to body surface area rather than volume of body water. The exponent of 2/3 is suggested by the physical relationship that the surface area of a 3-dimensional body is approximately proportional to volume raised to the 2/3 power.

ii) *Rationale for Choosing Target eKt/*(V_n) *= 0.90*

The target *eKt/*(V_n) of 0.90 was determined as providing the maximum separation that could be achieved between the daily HD and the conventional HD treatment groups for a wide range of parameters related to solute clearance, treatment time, and volume while only modestly increasing total weekly treatment time in the daily arm.

3.1.3 Calculation of eKt/V and eKt/(V_n)

Single pool Kt/V will be calculated by applying the 2-BUN algorithm [Depner, 1989] to the predialysis and post-dialysis ureas collected according to current K/DOQI standards. For the Conventional HD group, the modification of the method of the Tattersall rate equation developed in the HEMO Study [Daugirdas, 2004] will be used to estimate eKt/V from spKt/V according to the formula:

$$eKt/V = spKt/V \times (T/(T+30.7)) \qquad \text{(EQ 1)}$$

where T denotes treatment time in minutes. Additional calculations based on equation 1 will be used to obtain an estimate of the actual (2-pool) V from the single pool V derived from the 2-BUN method. To minimize the risk that errors in modelled V would affect the dialysis dose, when determining dialysis prescriptions in the daily HD group eKt/(V_n) will be computed as [eKt/V] × 3.271^{-1} × $[Vant]^{(1/3)}$, where Vant is the anthropometric volume estimated using the Watson formula. Details are provided in the Manual of Operations.

3.1.4 Data Collection, Determining the Initial Prescription, and Monitoring of Dose

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

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 membrane type
Reuse number
Interruption status (was total interruption time >15 min?)
Intradialysis 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)

* In addition to data collection from the kinetic modeling session itself, start and end times, pre and post HD weights, predialysis blood pressures, and intradialytic hypotensive episodes leading to treatment interruptions will also be obtained from the dialysis run sheet for all HD sessions during the week preceding the kinetic modeling session once during baseline and monthly during follow-up.

a) Baseline Kinetic Modelling Sessions

Two kinetic modelling sessions, designated B1 and B2, will be conducted during the baseline evaluation phase of the trial. The two sessions will be spaced at least one week but no more than six weeks apart.

If the coefficient of variation of the estimates of urea distribution volume (V) from the two baseline kinetic modeling sessions (B1 and B2) differs by 20% or more, a third baseline kinetic modeling session (labeled B3) will be required. The median of all baseline urea volume estimates will be used to determine the initial post-randomization dialysis prescription.

In order to prevent randomization of patients who are unable to achieve an eKt/V close to the minimum level of 1.10 in the conventional HD arm, subjects must achieve a mean eKt/V of at least 1.00 on the final two baseline kinetic modeling sessions in order to be randomized. If the mean eKt/V for the final two of the baseline kinetic modeling indicated above is less than 1.00, then an additional kinetic modeling session may be scheduled, and the mean eKt/V recomputed from the last two baseline sessions. This process may be repeated up to 4 times, and the minimum eKt/V requirement will be met if at any of these tries the average eKt/V for the final two assessments exceeds 1.00. The baseline minimum threshold of 1.00 is set 0.10 eKt/V units below the minimum eKt/V of 1.10 in the conventional HD arm, to take into account the random variation that can be expected from the average eKt/V over two modeling sessions.

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

i) Conventional HD Group

Subjects randomized to the Conventional HD group may follow any dialysis prescription provided their prescribed eKt/V is at least 1.10 and treatment time is at least 2.5 hours. Modeling data will be obtained monthly. The prescribed eKt/V will be computed centrally based on the subject's current running median V over the preceding 4 months, and the subject's current blood flow, dialysate flow, dialyzer type and ultrafiltration rate. If the prescribed eKt/V falls below 1.10, the Data Coordinating Center will e-mail a warning to the study coordinator at the patient's Clinical Center that includes the patient's study ID number and the patient's prescribed eKt/V, and provide alternative prescription options for a prescribed eKt/V of at least 1.10.

ii) Daily HD Group

At randomization, the Data Coordinating Center will send an array of dialysis prescription options for a target eKt/(V_n) of 0.90 in which the treatment times are between 1.5 and 2.75 hours. Subsequently, 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 eKt/(V_n) to a value less than 0.75. Failure to implement the revised prescriptions will be regarded as non-adherence to the protocol. This procedure is designed to assure that the running median achieved eKt/(V_n) does not fall more than 0.15 eKt/(V_n) units below that 0.90 target throughout follow-up.

The Data Coordinating Center will also send a revised prescription if the running median V changes by an amount that leads to an increase in the prescribed eKt/(V_n) to a value greater than 1.05. In this case, reductions in dialysis dose in accordance with the revised prescription will be at the discretion of the treating nephrologist.

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, and phosphate kinetics. Phosphate clearance will be calculated by the method of Gotch. [Gotch, 2003] Pre- and post-dialysis blood samples will be obtained according to current National Kidney Foundation K/DOQI Hemodialysis Adequacy guidelines [NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy: update 2000, 2001].

3.1.5 Residual Renal Function

Residual renal function will be measured prior to a modeling session during baseline and during follow-up at Month 4 and Month 12 for all subjects who produce urine. Timed urine collections of at

least 18 hours will be obtained during the interdialytic interval preceding a dialysis session, preferably midweek. Aliquots will be shipped to the local laboratory of the dialysis unit for measurement of urea, creatinine, and phosphorus. 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 80 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 80 ml, then the patient will be considered to be anuric.

For determination of eligibility, the baseline residual renal clearance measurement will be expressed per 35 L of anthropometric volume (Watson formula)[Watson, 1980] to adjust for body size. The anthropometric volume will be used rather than modeled volume because accurate estimation of modeled volume requires averaging over several kinetic modeling sessions, which will not be possible at the first baseline assessment.

3.1.6 Non-adherence and Deviations from the Protocol

If during follow-up subjects randomized to 6x/week therapy are unwilling or unable to continue to follow their 6x/week dialysis prescriptions stipulated by the protocol, efforts will be made to approximate the target 6x/week prescription as closely as possible with a revised prescription with either reduced total weekly treatment time or with a reduced frequency of dialysis sessions. The hierarchy of alternative options outlined in Table 7 below will be followed for patients unwilling or unable to adhere to the protocol 6x/week regimen.

In the event of a deviation from the 6x/week schedule specified by the protocol, the Clinical Center's personnel will consult with the study subject in an effort to adopt the highest option in the above table. If one of Options 1-4 is adopted, the Clinical Center's staff will periodically discuss the treatment options with the patient to determine if the patient is willing or able to return to a higher Option number, or ideally to return to the full 6x/week regimen specified by the protocol. Missed treatments will be monitored closely to ensure the safety of trial participants (Section 3.2).

3.2 Duration of Treatment and Follow-up

Each subject will be treated in his or her respective group for 12 months, or until death, a treatment stop-point is met, or loss to follow-up (see Section 7.3). The complete data collection procedures of the protocol will continue for the full 12 month follow-up period except for those subjects who die or are lost to follow-up. For subjects who relocate to a non-study dialysis unit, all attempts will be made to collect vital status, the primary and main secondary outcomes (see Section 5.1.2), and other centrally administered quality of life questionnaires at the 12-month assessment. When possible, the complete data collection procedures designated in the protocol will be maintained for subjects who switch to home 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. 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 daily HD 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.

Table 7: Stepped Options for Modifying 6x/Week Daily HD Regimen

Option Number	Description of Option
1	Maintain 6x/week treatment schedule, but reduce treatment time to the projected total weekly treatment time or an amount acceptable to the patient, subject to: a) minimum session length ≥ 1.5 hours, b) total weekly treatment time ≥ total weekly treatment time the patient would have had if assigned to the conventional HD group.
2	Adopt a 5x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the patient such that the projected weekly stdKt/Vurea approximates the patient's target stdKt/V_{urea} as closely as possible.
3	Adopt a 5x/week treatment schedule, without increasing the time per treatment, so long as a) minimum session length $\underline{\geq}$ 1.5 hours, and b) total weekly treatment time $\underline{\geq}$ total weekly treatment time the patient would have had if assigned to the conventional HD group.
4	Adopt a 4x/week treatment schedule, but increase treatment time to the maximum amount acceptable to the patient such that the projected weekly stdKt/Vurea approximates the patient's target stdKt/Vurea as closely as possible.

Patients on daily HD may perceive improvements in their HRQL which have more to do with the novelty of the therapy than to its true benefits ('honeymoon effects'). However, HRQL benefits due solely to the novelty of daily HD would not be expected to persist over 1 year. For this reason, the HRQL outcomes will be assessed at months 4 and 12. In addition, at month 12, an assessment of health expectations will be made.

Due to increased opportunity for ultrafiltration, subjects on daily HD may have lower extracellular volume (ECV) than subjects on conventional HD. 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 the method of calculation is less subject to volume effects than is echocardiography. To assess for potential hemoconcentration effects in laboratory measurements, key assays that are affected by ECV contraction will be measured at 1 month after randomization before true effects of increased dialysis would be expected to have occurred.

In-center daily HD is a complex intervention, involving not only the provision of increased dialysis dose, but also the potential for significantly increased interaction with the health care team. Thus, in the setting of a positive trial result, it is possible that HRQL or physiological benefits conferred by daily HD may in part be the result of increased surveillance and care by the medical team rather than increased HD dose. This does not represent a source of bias *per se*, as any such differences in care

would represent a component of the daily HD intervention which is under investigation. However, in order to better understand the intervention, data will be collected in patients to characterize potential differences between groups in health-care team/patient interactions (See Section 3.5).

3.4 Co-Intervention Protocols Not Related to Dialysis Dose

3.4.1 The Dialysis Prescription

Specific recommendations to the treating nephrologists outlined in are stipulated regarding non-dose aspects of the dialysis prescription (see Manual of Operations). These recommendations are based on current practice guidelines, and are intended to minimize differences between treatment groups in machines, dialyzers, and dialysate water and composition.

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

These co-interventions are divided into 3 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. Interventions in this tier include immunizations, diabetes and lipid management. 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 (Table 8).

Tier 2 co-interventions include those aspects of medical care specifically related to ESRD for which there are evidence-based treatment recommendations, and that directly affect the clinical outcomes of this trial. Items in this tier include management of anemia, calcium and phosphate metabolism, and acid-base balance. Recommendations based on K/DOQI 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 (see Table 8). Local laboratory data related to items in this tier will be entered into the database on a regular basis (Table 8). For subjects who have values that fall outside the recommended ranges for three consecutive months, feedback will be provided to the Clinical Center's research coordinator and treating nephrologist via automated reports generated by the Data Coordinating Center.

Tier 3 co-interventions include those aspects of care that are directly related to dialysis care, but cannot practically be standardized between groups due to the varying frequency that patients are seen in the HD unit in the 2 arms of the trial. Such aspects of care thus will be regarded as components of the treatment interventions. Items in this tier include management of blood pressure, frequency of ideal weight monitoring and prescription changes, frequency of vascular access monitoring, and frequency of visits by health-care professionals. General recommendations regarding these aspects of care will be made, but their implementation will not be monitored as for Tier 2. However, detailed data collection for items in this tier will be performed in order to better characterize the non-dialytic aspects of the intervention of daily HD (see Section 3.5).

See Table 8 and the Manual of Operations for additional details regarding recommendations for each of the 3 tiers.

4. Vanguard Phase

4.1 Early Monitoring and Process Adjustments.

Because this is the first randomized trial of 6-times per week in-center dialysis with long-term follow-up, 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

Table 8: Co-Interventions and Standards of Care Not Related to HD Prescription

Item	Recommendations*	Data Collection**	Feedback
Tier 1			
Immunizations	Yearly Influenza Hepatitis B as per Appendix 2 Pneumovax as per Appendix 2	*None*	*None*
Diabetes Management	Target HbA1C <7.0%		
Lipid Management	Target LDL≤ 2.6 mmol/L		
Tier 2	*Targets (DOQI):*	*Regular local lab entry*	*Automated feedback by DCC* to treating nephrologist and research coordinator for patients whose monthly labs fall outside of target for 3 consecutive months, or whose iron studies are out of target for 2 consecutive quarters
Anemia Management	hemoglobin 110 – 120 g/L (11.0 – 12.0 g/dL) ferritin 100 – 800 mcg/L transferrin saturation ≥ 20%	hemoglobin ferritin transferrin saturation	
Calcium-Phosphate	phosphate <1.80 mmol/L calcium¶ 2.10 – 2.60 mmol/L	phosphate calcium	
Acid-Base Status	bicarbonate 22 – 25 mmol/L	bicarbonate	
Tier 3	*Routine monitoring frequency:*	*See Section 3.5*	*None*
Ideal weight assessment	Weekly (maximum)		
Formal vascular access monitoring	Monthly (maximum)		
Visits by health-care professionals (other than nurses)	Weekly (maximum)		

*all lab values are pre-dialysis

¶corrected calcium (for albumin)

** indicated labs collected MONTHLY, except for transferrin saturation and ferritin which should be collected at least every 4 months

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 two benchmarks: a) 100 randomized

patients within one year of the start of enrollment, and b) 80% of patients attending at least 80% of scheduled dialysis treatments within each treatment arm. 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 DSMB 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 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 that are successful and facilitate the implementation of these strategies at other centers.

At the one 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 appears as if one or the other of the trials might fall substantially short of its recruitment target.

Missed Dialyses.Trends in the rate of missed dialyses 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 for participants at that center is deemed to be unacceptable.

5. Outcomes

5.1 Outcome Measures

5.1.1 Summary of Primary and Main 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 daily HD 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 9). 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 (LVM), will serve as the 2 co-primary outcomes of the trial. The changes over 12 months in LVM and the PHC score, without the mortality component, along with the other five first priority

outcomes in their respective domains, are the main secondary endpoints. Additional secondary outcomes will also be measured within each of the designated domains; these are summarized in Table 10 in Section 5.1.3.

The two co-primary outcomes were chosen in part due to the complementary nature of the information provided by LVMi and the PHC score. LVM is an objective physiological marker of cardiovascular structure and function but is not a clinical endpoint, while the PHC score is an important clinical endpoint, but as a self-reported outcome 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 two study groups and

Table 9: 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
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 function	Change in Trail Making Test B score
Nutrition and inflammation	Change in serum albumin concentration
Mineral metabolism	Change in pre-dialysis serum phosphorus concentration
Survival and hospitalisations	Rate of non-access hospitalization or death
Hypertension	-
Anemia	-

All changes are measured over 12 months of follow-up

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 LVM and PHC score for most patients. A demonstration of positive effects on both of the co-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 outcomes, or significant effects in opposite directions for the two

outcomes, 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, 1988] to assure that the upper limit of the studywise Type I error rate for both of the co-primary outcomes is approximately 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 complex effects of multiple factors within these domains renders it difficult to adequately represent treatment effects with individual outcomes (e.g., maintenance of blood pressure control or a target hemoglobin concentration with changes in antihypertensive therapy or erythropoietin). Key outcomes to be assessed for evaluation of these domains are summarized in Table 10 and Section 5.1.3.

5.1.2 Primary Outcomes

The LVM 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 with adequate reliability 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.

Details for these outcomes are provided below.

(1) Left Ventricular Mass

LVM will be assessed by cine magnetic resonance imaging (MRI) at baseline and at 1 year after randomization. Details on the characteristics of cine-MRI are provided in Section 6.2.5.

At the time of dialysis initiation, left ventricular hyperthrophy (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;Zoccali, 2001b]. Changes in LVM have been associated with clinically relevant differences in outcomes even over a relatively short one-year period [Foley, 2000]. In a study where a 10% change in LVM was considered significant, there was a 22% reduction in all-cause mortality and a 28% reduction in cardiovascular mortality [London, 2001].

The major causes of LVH in ESRD are volume overload and elevated blood pressure. Expanded extracellular volume is caused by increased sodium and water retention, leading to hypertension, particularly among patients without significant residual renal function [Horl, 2002;Lins, 1997;London, 2003;Onesti, 1975]. Increased arterial stiffness and lack of vascular compliance in uremia that manifest as increased systolic and widened pulse pressures further exacerbate LVH

[Chaignon.M, 1981;Horl, 2002;Lins, 1997]. Development of LVH is also associated with metabolic factors (e.g., hypoalbuminemia, hyperhomocysteinemia, glycation end products, disturbed calcium-phosphate metabolism and secondary hyperparathyroidism) which may promote cardiac interstitial fibrosis and myocyte hypertrophy [Blacher, 1999;Galland, 2001c;Ganesh, 2001;Moon, 2000;Rostand, 1999;Scharer, 1999;Zoccali, 2001a;Zoccali, 2001b]. Daily HD may lead to regression in LVH due to improved volume and blood pressure control, and increased removal of uremic toxins. Indeed, several reports have indicated that regression of LVH with reductions in LVM index of up to 38g/m^2 is possible with a switch from thrice-weekly HD to daily HD [Fagugli, 2001;Traeger, 2004].

(2) Physical Health Composite Summary Score of the SF-36

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 SF-36 questionnaire will be administered by interviewers blinded to treatment allocation through a central telephone service at baseline, 4, and 12 months.

In the context of this study, health related quality of life (HRQL) is defined as the subjects' perception of how ESRD and HD influence their physical, functional, emotional and mental well-being [Gill, 1994]. The SF-36 is one of the most commonly used instruments to measure HRQL [Ware, 1992;Ware, 1993;Ware, 1994], and its eight subscales have been tested extensively for reliability, validity against mortality, and responsiveness to interventions in HD patients [Allen, 2002;Beusterien, 1996;Cagney, 2000;DeOreo, 1997;Diaz-Buxo, 2000;Edgell, 1996;Levin, 1993;Merkus, 1997;Meyer, 1994;Painter, 2000;Rettig, 1997]. The survey is well-accepted by HD patients, taking only 5 to 10 minutes to complete [Kurtin, 1992;Rettig, 1997]. In addition, norms for the general U.S. population have been reported [Ware, 2000]. Finally, the SF-36 physical function score has been shown to be responsive to clinical change for daily and nocturnal HD [Reynolds, 2002;Traeger, 2004].

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 incongruous 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. [Nortvedt, 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, 1993]. This allows the PHC to correlate with mental health, unlike the PCS.

5.1.3 Secondary Outcomes

The secondary outcomes of the study are summarized in Table 10 below.

5.1.3.1 Cardiovascular Structure and Function

Main Secondary Outcome:

The change from baseline to 1 year in the LV mass, without mortality, will serve as the main secondary outcome in this domain. The details are provided in Section 5.1.2.

Other Secondary Outcomes:

Outcomes based on the Cardiac MRI: 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 (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 12-month change in each of these parameters will be used as additional secondary outcome parameters.

Heart Rate Variability.The heart rate is naturally quite variable, and mathematical analysis of variability of beat-to-beat intervals reveals both high and low frequency components which have been linked to the degree of parasympathetic and sympathetic tone. Heart rate variability (HRV) also has a structural component, and has been shown to be markedly reduced in CHF and in LVH [Nishimura, 2004]. Reduced HRV also has been linked to diabetic autonomic neuropathy. HRV may be a surrogate outcome for mortality [Adamson, 2004;Wichterle, 2004].

Table 10: 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: **(9 domains – 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 Heart rate variability measures 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 score**
Cognitive Function	**Trail Making 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	Weekly average pre-dialysis blood pressure
	Weekly average post-dialysis blood pressure
	Weekly average pulse pressure
	Proportion of patients with weekly average predialysis systolic blood pressure <110 mmHg
	Number of prescribed antihypertensive agents
Anemia	Pre-dialysis hemoglobin
	Erythropoeitin dose
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 access failures
Iron Losses	Cumulative intravenous iron requirements (over 12 months)
	Serum ferritin and transferrin saturation
Patient Burn-out	Proportion of subjects 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 daily HD at 12 months

*gait speed, time to stand, standing balance

The method of analyzing HRV includes five basic measures: Two time domains: SDNN, SDANN (standard deviation of the NN interval), and two frequency domains: low frequency power spectrum value (LF), high frequency power spectrum value (HF), and the LF/HF ratio. Both LF and the LF/HF ratio have been linked to parasympathetic dysfunction, LVH, and increased mortality in non-ESRD patients. It is hypothesized that more frequent dialysis will improve LF/HF ratio due to improvement in the uremic milieu, whereas with standard therapy the LF/HF ratio will remain largely unchanged. The 12-month change in LF/HF ratio will be used as an additional secondary outcome parameter. Details on the measurement of HRV are provided in Section 6.2.6.

Intradialytic Hypotension: Intradialytic hypotensive episodes (IDHE) occur in approximately 20% of standard 3x/week dialysis treatments [Kyriazis, 2004]. In addition to complicating delivery of an adequate treatment and reducing patients' quality of life, repeated IDHE may cause ischemia to critical body organs, including brain, heart, intestines, and thereby contribute to an increased risk of hospitalization and death [Ishida, 1999]. IDHE has been associated with mortality in HD patients [Shoji, 2004;Tisler, 2003]. Due to a shorter interdialytic interval, daily HD results in lower ultrafiltration rates provided total daily fluid intake remains constant or minimally increased. It is thus hypothesized that daily HD will reduce the rate of IDHE, as suggested by some observational studies [Heidenheim, 2003].

Interdialytic Weight Gain: Absolute interdialytic weight gains correlate with pre-dialysis blood pressure. A decrease in interdialytic weight gain has been hypothesized to be one mechanism by which LVMi and blood pressure may improve. In previous observational studies, absolute weight gains between dialysis sessions have decreased with daily HD due to halving of the interdialytic interval, but in fact cumulative weekly gains have tended to increase [Andre, 2002b;Fagugli, 2001;Galland, 2004a;Kooistra, 1998;Nesrallah, 2003;Ting, 2003]. Thus, in this trial, both the 12-month changes in mean interdialytic weight gain between dialysis sessions, as well as in cumulative weekly weight gains will be assessed as additional secondary outcomes.

5.1.3.2 Health-related Quality of Life and Physical Function

Main Secondary Outcome:

The change from baseline to 1 year in the SF-36 PHC score, without mortality, is the main secondary outcome in this domain.

Other Secondary Outcomes:

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 convert questionnaire responses into a measure of overall health utility, which can then be used to calculate quality-adjusted life years (QALYs) in clinical trials. In the London study, the HUI showed differential responsiveness to change in nocturnal versus conventional HD patients during longitudinal follow-up [Heidenheim, 2003]. Test-retest reliability at 4 weeks was a 0.77. HUI scores will be used for quality-adjustment in the economic evaluation of this trial.

Feeling Thermometer: The feeling thermometer is a single question that asks subjects 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 [Churchhill 98], it has demonstrated responsiveness to therapy in multiple health states[Baldassarre, 2002;Schunemann, 2003]. Thus, the 12-month change in feeling thermometer score will be used as an additional secondary outcome in this trial.

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, 4 months and 12 months (B, F4, and F12).

Objective Physical Function Measures: 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].

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 PHC was selected as the primary outcome for the physical function domain. However, it was recognized that the SF-36 PHC scores are subject to bias because of self-report in this non-blinded study. Thus, the 12 month change in an objective performance measures (the LEP battery score) will be used as supplementary secondary outcomes in the physical function domain.

A lower extremity performance battery (LEP) designed for use in a large epidemiological study, the Established Populations for Epidemiological Study of the Elderly (EPESE) will be employed in this study [Guralnik, 1994]. The LEP consists of three tasks that represent activities necessary to be mobile: standing balance, walking speed, and timed chair stands. The LEP combines the ability to complete these 3 activities gait 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]. 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]. The upper extremity test is also highly responsive to change [Onder, 2002]. Details on the LEP are provided in Section 6.2.2.

5.1.3.3 Depression/Burden of Illness

Main Secondary Outcome:

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

Depressive symptoms are frequently encountered in patients with ESRD [Lopes, 2004]. It is hypothesized that improved overall health, well-being and physiology with daily HD will lead to

reduced depression in HD patients. The BDI is a 21-question validated survey presented in multiple choice format, and measures the presence and degree of depression in adults. Each of the answers is scored on a 0 to 3 scale, and inventory items correspond to a specific category of depressive symptom and/or attitude. BDI results are highly correlated with psychiatrists' ratings using the Hamilton Rating Scale (0.75-0.80) [Spilker, 1990]. Based on a pooled analysis of studies in primary care, the sensitivity and specificity of the BDI in detecting moderate-severe depression are approximately 90 and 56%, respectively [Mulrow, 1995]. The BDI has been frequently used to assess depression in patients with ESRD [Craven, 1988;Kimmel, 1993;Kimmel, 1995;Kimmel, 1998;Peterson, 1991;Sacks, 1990;Shulman, 1989;Kimmel, 2000]. Moreover, high scores on the BDI are associated with mortality in this patient population [Kimmel, 2000]. Finally, the BDI has been previously used in daily HD patients [Troidle, 2003].

5.1.3.4 Cognitive Function

Cognitive function is impaired in patients with ESRD and chronic kidney disease. It is hypothesized that daily HD will lead to improved cognitive function as a result of improvements in the uremic milieu due to increased solute clearance and possibly to an improvement in sleep hygiene.

Main Secondary Outcome:

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

The Trail Making Tests (TMT) A and B test the ability to visually search, sustain attention, and perform cognitive shifting as the activity is completed. The TMTs are brief, sensitive to subtle neuropsychological impairments, can be compared with age-adjusted norms, and are useful in monitoring the progression of neuropsychological dysfunction. Test-retest reliability, construct validity, and concurrent validity have been previously documented [Reitan, 1958]. The TMT has been used in studies of ESRD and CKD and in patients following kidney transplantation [Kurella, 2004]. In addition, Trails A and B work well over a wide range of cognitive function and are less subject to floor or ceiling effects than several other widely used tests of cognitive function. In Trail B, the subject must also draw 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. Errors are not counted, but the subject is alerted to mistakes made. The subject is instructed to correct mistakes, which increases the amount of time needed to complete the task. For this trial, the 12 month change in time to complete Trail B has been selected as the main secondary outcome for evaluation of the cognitive function domain, as it assesses higher order "executive" functions.

Other Secondary Outcomes:

Modified Mini Mental Status (3MS): The 3MS is a widely used tool to determine global cognitive function. Although likely to be less sensitive to change than the Trail Making Test B, its broad use, acceptance in the cognitive function literature and the availability of age-matched, population norms makes it attractive to apply in this trial. 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;Teng, 1987]. 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 SDHD, and may mediate some of the potential benefit of SDHD on cognitive function if one exists. The 3MS requires approximately 5-10 minutes to complete, and can be completed by telephone. The main analyses will compare changes in 3MS scores from baseline to month 12.

5.1.3.5 Nutritional Status and Inflammation

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 [Centers for Medicare & Medicaid Services: 2001 Annual Report: End Stage Renal Disease Clinical Performance Measures Project, 2002;Allman, 1990;Alvestrand, 1996;Bansal, 1980;Bellizzi, 2000] and interventions that successfully treat malnutrition are uncommon. Lower serum albumin is strongly associated with increasing mortality [Leavey, 1998;Lowrie, 1990;Pifer, 2002], and decreases of as little as 10 – 15% have been shown to predict mortality [Combe, 2001;Culp, 1996]. In addition to being influenced by protein and energy nutritional status and changes in volume 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 volume status is constant [Stenvinkel, 1999b;Zimmermann, 1999]. In fact, there is substantial evidence linking hypoalbuminemia with atherosclerotic disease [Bergstrom, 1998;Stenvinkel, 1999a;Zimmermann, 1999] congestive heart failure [Bergstrom, 1998] and infectious complications [Bansal, 1980;Churchill, 1992;Mattern, 1982].

Despite the numerous advances in HD therapy in the past ten years, including higher doses of HD and better anemia control, there has been no significant change in serum albumin levels reported for HD patients [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 serum albumin [Eknoyan, 2002], and there was a decline in serum albumin levels of 0.21g/dL over 3 years in this cohort [Rocco, 2004]. Previous studies as to the effect of daily HD on serum albumin have had mixed results, with half showing positive effects [Andre, 2002a;Fagugli, 1998;Galland, 2004b;Spanner, 2003;Woods, 1999] and half reported no significant effect [Fagugli, 2001;Piccoli, 2003;Ting, 2003;Traeger, 2004;Vos, 2001]. It is hypothesized that daily HD may improve uremia by providing increased clearances, thus potentially reducing the inflammatory stimuli that lead to reductions in serum albumin. For all these reasons, serum albumin was chosen as the main nutritional and inflammatory outcome measure in this trial.

Other Secondary Outcomes:

It is recognized that potential increases between baseline and 12 months in serum albumin may be the result of reductions in extracellular volume with daily HD rather than an improvement in inflammation or nutrition. For this reason, the change between 1 and 12 months is defined as an additional secondary outcome as any increases in serum albumin solely due to reduced extracellular fluid volume would be expected to occur by 1-month post-randomization.

No nutritional parameter rivals serum albumin in terms of predictive power for outcomes such as mortality and hospitalization. However, serum albumin reflects both inflammation as well as nutrition, and it may be influenced by volume status. In addition, nutritional status extends beyond the visceral protein pool. Unfortunately, there is no ideal true nutritional marker, due to the lack of a single measure that is easily performed, reproducible, inexpensive, and able to predict hard outcomes. Most studies rely on a combination of measures to assess nutritional status. For this trial, the 12 month change in the normalized protein catabolic rate, post-dialysis body mass index, and lean body mass by single frequency bioimpedance have been chosen as additional secondary nutritional outcomes. Since poor appetite and altered body composition are observed frequently in patients with

advanced chronic kidney diseasewith evolving uremia, we hypothesize that daily HD might improve these parameters due to increased clearance of uremic toxins.

Normalized Protein Catabolic Rate (nPCR): The nPCR has been used in dialysis patients for decades as an estimate of dietary protein intake [Gotch, 1995]. The use of the nPCR assumes, however, that the patent is in neutral nitrogen balance, an assumption that is not always met in conventional HD patients. Moreover, the agreement between nPCR and true dietary protein intake has not been assessed for daily HD patients. Despite these concerns, the nPCR has been chosen as a measure of dietary protein intake in this trial because of budgetary constraints and ease of measurement of nPCR compared to dietary records, interviews by dieticians, and food frequency questionnaires.

Body Mass Index (BMI): BMI is used as a surrogate measure of total body fat in the general population. However, higher BMI has been shown to be protective in HD patients, a finding that is contrary to the general population [Cheung, 2000;Hakim, 1999;Kopple, 1997;Rocco, 2004;Sarnak, 2000]. Because of its correlation with mortality, BMI using post-dialysis weight has been chosen as an additional secondary outcome.

Phase Angle, Vector Length, and Estimates of Body Composition by Single Frequency Bioimpedance (BIA): One potential reason for the discrepant results between the general population and HD patients with respect to BMI is that the measurement of body mass index is confounded in HD patients by the presence of both muscle wasting and excess fluid weight. In one study of chronic kidney disease patients, the survival advantage for patients with high body mass index was found in only those patients with low body fat; in fact, in the low body mass index group, high body fat and low muscle mass were associated with increased mortality [Beddhu, 2003]. These data suggest that maintaining or increasing muscle mass and/or lowering body fat may be important in decreasing mortality rates in HD patients, and that measurement of lean body mass will be an important outcome in this study. Bioimpedance is one of the most accurate methods to estimate body composition [Cooper, 2002]. Single frequency BIA will be used to measure reactance and resistance, to calculate phase angle and vector length, and to estimate total body water and body cell mass. Several of these factors have been associated with mortality and morbidity in HD patients [Chertow, 1997;Ikizler, 1999;Pillon, 2004]

5.1.3.6 Mineral Metabolism

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 mortality and cardiovascular morbidity among patients on maintenance HD [Block, 1998;Block, 2004;Ganesh, 2001]. Whether or not this relationship is causal is unclear, but it is hypothesized that hyperphosphatemia may lead to cardiovascular morbidity and mortality through effects on vascular calcification [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 has also been shown that hyperphosphatemia may cause calcification via the induction of genes for bone protein formation by vascular smooth muscle cells [Jono, 2000].

The extent of arterial calcification in patients on maintenance HD 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 chronic kidney

disease 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].

The majority of previously published observational studies of daily dialysis have not shown reductions in serum phosphate (in contrast to studies of nocturnal dialysis). However, most prior studies of daily dialysis have been conducted in small samples and either did not specify a target dose or did not stipulate a substantial increase in total weekly treatment time, which is the primary treatment factor affecting solute removal. The daily HD intervention in this trial is designed to increase the standardized phosphate removal by 39% (see Section 3.1.1).

Other Secondary Outcomes:

It is possible that despite improvements in phosphate clearance with daily HD, the serum phosphate concentration may not change, but rather the phosphate binder dose to achieve the same phosphate concentration may be reduced. Thus, additional secondary outcomes will be the 12 month change in phosphate binder dose, and the composite of 12 month change in serum phosphate concentration and in phosphate binder dose.

In addition to the serum phosphorus, serum calcium, and parathyroid hormone concentrations have been associated with mortality in ESRD. As with serum phosphorous, the control of serum calcium and parathyroid hormone may also influence progression of vascular calcification [Chertow, 2004]. It is hypothesized that improved phosphorus control with daily HD may improve the control of hyperparathyroidism, obligating lower doses of vitamin D analogues, which may result in further lowering of serum phosphorus. Thus, additional secondary outcomes of mineral metabolism will be the 12-month change in predialysis serum calcium, parathyroid hormone, and vitamin D metabolite dose.

5.1.3.7 Survival and Hospitalization

Main Secondary Outcome:

The composite of non-access hospitalization and mortality represents a clinically important outcome, and has been chosen as the main secondary outcome in this domain. The sample size of 250 patients in this trial provides adequate power to detect reductions in the rate of non-access hospitalizations or death larger than approximately 40% (see Section 9.11). A large effect on nonaccess hospitalization or death of this size is considered to be plausible due to the large separation in multiple parameters between the daily and conventional HD interventions (see Table 3 of Section 3.1). However, it is recognized that a clinically important reduction in nonaccess hospitalization rate in the 20% to 35% range may not be detected by this trial.

The rate of non-access hospitalizations has been designated as a main secondary outcome rather than the rate of all hospitalizations for the following reasons.

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 nonaccess 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 nonaccess hospitalizations are distinct, potentially resulting in different effects on these 2 outcomes.

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

Other Secondary Outcomes:

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, and

d) total hospital days over 12 months.

5.1.3.8 Hypertension

Hypertension is an important comborbidity in the hemodialysis population, and high levels of systolic blood pressure are strongly associated with total mortality, coronary events, and stroke in both the general and ESRD populations. Previous studies of daily HD have been relatively consistent with respect to findings of improved (i.e., reduced) blood pressure [Andre, 2002a;Fagugli, 1998;Fagugli, 2001;Kooistra, 1998;Koshikawa, 2003;Nesrallah, 2003;Piccoli, 2003;Ting, 2003;Traeger, 2004;Woods, 1999]. However, in this study comparing HD 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 with the use, number and dose of anti-hypertensive medication,

b) the association of lower blood pressures in dialysis patients with impaired cardiac function,

c) halving of the interdialytic interval with daily HD, resulting in change in the shape of the blood pressure levels vs. time curve, as well as potentially reduced ultrafiltration rates.

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. The 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 HD patients, which decline during dialysis treatments and increase between treatments due to fluid accumulation. 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.

Due to these complexities, we do not attempt to designate a single main secondary outcome for the hyptertention domain. Rather, the effects of the interventions will be evaluated primarily based on the following four outcomes: i) the change from baseline to 12 months in the weekly average predialysis systolic blood pressure, ii) change from 1 to 12 months in the weekly average predialysis systolic blood pressure, iii) change from baseline to 12 months in the number of antihypertensives prescribed, and iv) change from baseline to 12 months in the proportion of patients with weekly average predialysis systolic blood pressure less than 110 mm Hg. The rationale for evaluating the change in the predialysis systolic blood pressure from 1 month to 1 year is that most of the effects of the changes in the dialysis treatment schedules on volume status and on the shape of the blood pressure vs. time curve are likely to occur relatively early after randomization, and thus these factors are less likely to confound changes in blood pressure after 1 month. Assessing the proportion of patients with systolic blood pressure <110 mmHg will help to address issue (b), and the antihypertensive medication outcome will help address issue (a).

The focus on pre-dialysis systolic blood pressure as a key outcome is based on the hypothesis that more frequent HD leads to decreased fluid overload, and predialysis blood pressure is known to be influenced by volume status [Kooman, 2004]. In addition, some studies have shown that pre-dialysis systolic blood pressure is a good predictor of cardiovascular events [Tozawa, 2002] and correlates will with mean 24-hour ambulatory systolic blood pressure and left ventricular mass in HD patients [Conion, 1996].

There is also a growing body of evidence for pulse pressure as a surrogate outcome measure. 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]. Moreover, increased pulse pressure has been shown to be an independent predictor of coronary heart diseases, and of total mortality [Tozawa, 2002]. Thus, the mean change in pre-dialysis pulse pressure from baseline to 12 months, and from 1 month to 12 months will be used as additional secondary outcomes.

Details regarding the measurement of blood pressure and ascertainment of antihypertensive medications are given in Section 6.2.

5.1.3.9 Anemia

Anemia is present in the vast majority of patients with ESRD and is caused primarily by an inadequate production of endogenous erythropoietin (EPO), although recent evidence suggests an additional component of EPO resistance reflecting a state of chronic inflammation. While debate continues over the appropriate target hemoglobin, partial correction of anemia in ESRD patients has been associated with lower rates of mortality [Ma, 1999] hospitalizations [Xia, 1999], and cognitive and brain function [Pickett, 1999] in observational studies, and improved quality of life [Evans, 1990] in randomized controlled trials of EPO.

The effect of daily HD on anemia is not clear. Some observational studies have shown that daily HD improves anemia, resulting in higher hemoglobin levels at a fixed or lower EPO dose, or a stable hemoglobin, but at a lower EPO dose [Andre, 2002a;Fagugli, 1998;Klarenbach, 2002;Koshikawa, 2003;Ting, 2003;Traeger, 2004;Woods, 1999], while others have reported no significant effect [Fagugli, 2001;Piccoli, 2003;Pinciaroli, 1999;Rao, 2003;Ting, 2003;Vos, 2001;Woods, 1999]. Whether any improvements in anemia were masked by increased blood losses in these later studies is not known. In this trial, parameters related to anemia and iron use will be closely tracked, including hemoglobin, erythropoietin dose and route of administration, ferritin, transferrin saturation, and iron

utilization. The secondary outcomes related to anemia will be the 12 month change in hemoglobin, and the 12 month change in EPO dose. Outcomes related to iron status are described in Section 5.2.

5.2 Potential Risks of Daily HD

Prior observational studies of daily HD suggest overall benefit with no increased risk. However, these studies may have been inadequately powered to detect potential complications.

5.2.1 Vascular Access Complications

A theoretical risk of daily HD is that of increased vascular access failure due to twice as many access usages per week. Some studies suggest that this may be a risk for arteriovenous fistulae [Ting, 2003;Lindsay, 2003b], while others suggest that rates of access infection, stenosis and thrombosis may decrease with daily HD [Twardowski, 1999;Quintaliani, 2000;Woods, 1999;Lindsay, 2003b]. Access infections, interventions, and failures will be defined in the Manual of Operations, and will be monitored closely in both groups. Treatment groups will be compared with respect to: time to first access intervention, number of access interventions per patient year, time to first access failure, number of access failures per patient year, and number of infection related access failures per patient year.

5.2.2 Iron Losses

Patients on daily HD have been shown to have increased iron losses compared with conventional patients [Rao, 2003]. Cumulative monthly iron utilization will be compared between both groups, along with the 12 month change in transferrin saturation and in ferritin.

5.2.3 Malnutrition and Water Soluble Vitamin Deficiency

Although it is anticipated that nutritional status will improve with daily HD, the potential for malnutrition exists. There may be increased dialytic losses of amino acids due to increased clearances provided with daily HD. In addition, patients may miss more meals with daily HD, especially if their mealtimes coincide with their dialysis treatments or their travel to and from the dialysis unit. Nutritional status is being monitored as described in Section 5.1.3.5.

5.2.4 Patient Burn-Out

Patient fatigue is a potential concern with the increased frequency of treatments with daily HD, especially with in-center treatments requiring patients travel to and from the HD unit. In a review of daily HD, the median discontinuation rate for in-center daily HD ranged 0-43%, median 41%. Thus, adherence to therapy will be closely monitored in this trial. At each monthly kinetic modeling session, the number of missed treatments over the prior month will be recorded, as well as the number of shortened sessions over the prior week. The monthly trends in adherence will be compared between the study groups. In addition, the proportion of patients who require a change in dialytic modality lasting > 3 weeks (back to conventional, or to peritoneal dialysis) will be assessed along with reasons for modality change (see Section 7.3). Finally, the proportion of patients wishing to continue, or switch to, daily HD at the end of follow-up will be compared between groups.

5.3 Assessment of Treatment Burden

Compared to conventional HD, the daily HD intervention may have increased treatment burden, due to the need for patients to travel to the dialysis unit twice as often. This may be reflected by decreased adherence to the daily therapy, as discussed above.

The patient's perception of burden will also be assessed using the question, "How long does it take you to recover from a dialysis session?" which was validated in the London study [Heidenheim,

2003]. This question was successfully answered on 313 of 314 occasions, and was directly correlated with subscales evaluating fatigue, disease stress, and psychosocial stress; and was negatively correlated with the SF-36 physical and mental component summary scores (unpublished data). This question was shown to be responsive, as significant reductions in recovery time were found when patients switched from conventional to either daily or nocturnal HD [Heidenheim, 2003].

6. Data Collection

6.1 Frequency of Measurements

The frequency of measurements is summarized in Table 11 below.

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 assessment is to allow evaluation of short-term effects prior to significant attrition, while the 12-month assessment is intended to allow evaluation of longer-term effects. The cardiac cine-MRI, and Holter monitor for heart rate variability will be performed at baseline and 12 months only. Bioelectric impedance should be performed at 1 month post-randomization in addition to baseline, 4, and 12 months. The purpose of the additional 1-month assessment is to elucidate early effects of the therapy on volume status.

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 10 B). The pre and post-dialysis blood pressures, post-dialysis weight, and the presence of intradialytic hypotensive episodes will also be obtained for the kinetic modeling session. Once during baseline and monthly during follow-up, start and end times, pre- and postdialysis blood pressures, and pre- and postdialysis weights will be retrospectively obtained for the one-week interval preceding the modeling session, generally including two additional dialyses (for a total of three dialyses, including the modeling session) for conventional patients, and five additional dialyses (for a total of six dialyses, including the modeling session) in daily patients. In addition, information on the dialysis prescription (but not local laboratory measurements) will be recorded for quality control for one of the dialyses during the second week follow-up randomization.

The frequency of local laboratory measures other than those described above for basic kinetic modeling will depend on the frequency with which they are performed at the various Clinical Centers, and should follow DOQI clinical practice guidelines. Locally performed pre-dialysis hemoglobin, calcium, bicarbonate, potassium, and sodium should be recorded at baseline and at least once per month post-randomization, while ferritin, transferrin saturation, and parathyroid hormone should be recorded at baseline and at least once every 4 months. Only baseline values done within 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, except for intravenous iron, which will be recorded at baseline and then monthly thereafter. The reason anemia medications will be recorded monthly is because of the frequency with which prescriptions and doses of these medications are changed.

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

The two baseline kinetic modeling sessions are designated as the B1 and B2 visits. The follow-up visits are designated as F1 (month 1), F2 (month 2), and so on through the F12 visit. However, if assessments that are designated for a specific visit window are missed during that window, attempts should be made to perform them during the following visit window.

6.2 Details of Measurements

6.2.1 Questionnaires

Most questionnaires will be administered at baseline and at the F4 and F12 visits (Table 11 A). 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 blinded to treatment allocation through a central telephone core. Questionnaires that cannot be administered by telephone due to the need for visual cues (i.e., Feeling Thermometer, Trail Making B, and Modified Mini-Mental Status) will be administered by the local study coordinator.

6.2.2 Objective Tests of Physical Function

The Lower Extremity Battery (LEP: timed 8-foot walk, timed chair stand, and balance test) will be performed at baseline, and at the F4 and F12 visits (Table 11 A). These tests 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 these tests 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 8-foot 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.

6.2.3 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.

Table 11. Summary of Data Collection Schedule

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

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

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

B. 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 at least once every 4 months (center may optionally enter these labs at additional time points)

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

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

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

E. Events (hospitalizations, access complications, survival, and discontinuation of 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 as needed)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Central` QoL- Burden of Treatment													
Minutes to recovery question	✓				✓								✓
Modality preference question	✓				✓								✓
Characterizing the Non-dialytic aspects of the Intervention													
Time spent with health-care professionals	✓				✓								✓
Frequency of reductions to ideal weight prescriptions		✓			✓								✓
Frequency/method of vascular access monitoring PRN		✓			✓								✓
Compliance to medications question		✓			✓								✓

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

6.2.4 Medications

Study coordinators will verify that the medications correspond to the prescribed medication list prior to data collection and entry. All prescribed medications (except intravenous iron, erythropoeitin/darbopoetin, and intravenous vitamin D metabolites) will be recorded with daily doses using the WHO DRUG system at baseline and at the F4, F8, and F12 visits. For vitamin D metabolites, the frequency and total weekly dose will be recorded. For erythropoeitin/darbopoeitin, the frequency and total weekly dose, along with the cumulative dose over the last 4 weeks will be recorded. Intravenous iron use will be recorded monthly, as the cumulative dose over the prior 4 weeks. Please see Table 11 B.

6.2.5 Cardiac MRI

The cardiac Magnetic Resonance Imaging (MRI) study will be performed at baseline and at the F-12 visit (Table 11 D). 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. 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]. Moreover, 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 suspect that the relative superiorities of MRI over echocardiography are compounded in ESRD patients who not only have a high prevalence of left ventricular hypertrophy, but who also suffer from volume expansion between HD sessions [Stewart, 1999]. 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 study Clinical Centers using a standardized questionnaire. MRI scans will be performed at designated MRI centers close to each patient's study HD unit. Scans will be digitized and provided to a Central MRI reading center where they will be analyzed in a standardized way by a trained person, blinded to the patient's treatment allocation.

6.2.6 Heart Rate Variability/Holter Monitoring

Heart rate variability will be measured at baseline and at the F12 visit using 24-hour Holter measurements from KCI (Table 11 C). Holter at baseline is not required for randomization.

It is recommended, if possible, for Holter monitoring to be done on the first dialysis day following the weekend. Each 24-hour Holter analysis period will commence immediately after placement of the Holter equipment, which will take place at any point in time in the hour proceeding the start of dialysis.

Analysis will be carried out for three periods:

Period 1: the time between placement of the Holter and the end of the dialysis session,

Period 2: the time between the end of the dialysis session and starting time + 12 hours,

Period 3: the time between the end of Period 2 and starting time + 24 hours.

Each study site will download the data onto CD and send to the core lab, where data will be analyzed by a trained person blinded to the patient's treatment allocation.

6.2.7 Blood Pressure, Interdialytic Weight Gains, and Intradialytic Hypotensive Episodes

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 monthly during follow-up. In other words, these measures will be recorded for 3 sessions in the conventional arm, and at most for 6 sessions in the daily arm. Interdialytic weight gains will be calculated from the pre and post weights. See Table 11 C.

6.2.8 Bioelectric Impedance

Single frequency bioelectric impedance (BIA) assessments should be performed at baseline and at the F1, F4, and F12 visits. The baseline measure is not required for 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). BIA should not be performed on bilateral amputees or who have metallic implants such as a pacemaker.

6.2.9 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 will be 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, 4 months and 12 months. 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 Outcome Committee. 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 Daily Study hospitalizations, the Outcome Committee will be available for consultation but will not do formal reviews. After the first 12 FHN Daily 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 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. However, for subjects in the daily HD group who are not able to adhere to the 6 times per week schedule as prescribed, a series of alternative prescription options will be offered by the Kinetic Modeling Committee (see Section 3.1.6), including a temporary “holiday” from the randomized therapy. 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

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 group, not meeting eKt/V of 1.10 per session for 2 or 3 consecutive measurements; for daily and nocturnal group, not meeting a std Kt/V of 2.0 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 tests 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 Holter Core will transmit a report to the Data Coordinating Center 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 to the study center when received by the database. These findings may include, but are not limited to: arrhythmias due to ventricular tachycardias, torsades de pointes, AV blocks 2b and 3, sinus arrest / SA blocks 3, and atrial fibrillation.

e) The Central Cardiac MRI Core will transmit a report to the Data Coordinating Center 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 and is not lost to follow-up, 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, and all participants who permanently discontinue therapy will be interviewed regarding the reasons for discontinuation. 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) The subject changes from in-center hemodialysis to home hemodialysis. Where possible, recommendations will be made to continue the subject on their assigned

treatment frequency (i.e., in-center daily will change to home daily HD; in-center conventional will change to home conventional HD).

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.
e. Subject changes to home HD.

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

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

8. Economic Evaluation

8.1 Hypothesis

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

8.2. Purpose

If daily hemodialysis proves to be cost-effective, 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 (primarily 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).

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

*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 12 - 14 below.

Table 12: Costs per Dialysis of In-center Dialysis (6 or 3 Times Weekly)

Cost element	Method of assessment	Calculation of standard cost
"Dialysis Unit Shifts, Staffing, and Equipment" at each dialysis station (1)	Compiled by a subset of dialysis administrators. Collected starting eight months after the first patient has been randomized.	For shifts and staffing, cost is calculated using published salary scales. For equipment, cost is calculated using the GSA price list, with amortization period determined by consensus. Cost ***per dialysis*** will be computed.
"Costs of machines and supplies"	Collected starting eight months after the first patient has been randomized	Costs are recorded.
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.

Comments:

(1) We anticipate that larger Clinical Centers with a higher fraction of subjects on daily dialysis may be able more frequently than smaller units or units with few daily patients to assign more than the usual number of daily patients to one station, thereby increasing the number of dialyses per station per day and reducing per dialysis station costs. If daily dialysis proves advantageous, this practice is likely to evolve over time. Rather than trying to estimate the impact of this possibility during the course of this trial, we will model this issue based on observed ratio of dialysis time to clean-up/set-up time (from the time and motion study) and

stipulated unit sizes and fractions of patients on daily hemodialysis. This modeling will be used for sensitivity analyses of the per dialysis costs of station equipment.

Table 13: Other CMS Covered Medical Care

Cost element	Method of assessment	Calculation of standard cost
Injectable medicines	Recorded at multiple time points.	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 form 208 and 209 collected at Baseline, F4 and F12. Can be crosschecked with claims data from CMS.	Assignment of CMS HCPCS codes. Standard CMS payments.

Comments: 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 14: 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 Plans

a) **Intention to treat**: All analyses will be performed on an "intention to treat" basis. That is, the average costs of subjects in each arm will be determined retaining all subjects in their originally randomized arm, irrespective of the treatment that is ultimately used for that subject. If a subject is lost to the trial by death, transplantation, withdrawal of consent, or move to a non-participating center, that subject 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 sensitive parameters include rate of hospitalization, cost for a hospital stay, EPO dose and rate of EPO use, weekly nursing time within the facility, facility capacity, proportion of frequent 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 daily 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%**. See Appendix 4 for additional details.

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 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 daily 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 daily hemodialysis (compared with standard 3 times weekly 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, daily 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 short daily with nocturnal hemodialysis:** While not a primary purpose of this randomized trial, there will be interest in comparing the

outcomes of daily in-center dialysis with the outcomes of overnight nightly home hemodialysis, being studied in the companion trial performed by this Consortium Core. 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 (in-center 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 low. Specifically, formal power analyses have suggested that there will be low power to detect differences in survival and the rate of hospitalizations, unless the effects of the intervention are far more potent than we have anticipated. Hospitalizations account for 50% more costs than dialysis itself (absent dialysis-related medications); therefore modest changes in hospitalization may yield significant differences in total costs. 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 daily short hemodialysis on the patient:** Information on these aspects of the economic impact of SDHD 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 ordinal 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 1-year 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 1-year 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 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 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 surviving to 12 months. The ranks will be compared between treatment groups using the log-rank test which allows the integration of both survival time and a quantitative measure (e.g., the change in PHC score) in the same outcome.

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, 1988] will be used to assure that the upper limit of the studywise Type I error is approximately 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 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 Trail Making Test B), vi) mineral metabolism (change over 12 months in average pre-dialysis phosphorus), and vii) clinical events (rate of nonaccess 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.

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 nonaccess hospitalization or death. The main analysis for each outcome will evaluate the treatment effect on the change from baseline to 1 year. For outcomes evaluated monthly (e.g., serum albumin and pre-dialysis phosphorus), the baseline value will be averaged over two baseline assessments and the 1 year value will be averaged over the Month 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, Trail Making 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 1 year 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:

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

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 two pre-specified baseline covariates age, and diabetic status, 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 77) 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. 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.

The target sample size of 250 patients is sufficient that inferences for the fixed effect terms in these analyses will remain valid with moderate departures from normality (Verbeke 97). However, standard diagnostics will be performed and simulations conducted to address this issue, and modifications to the model will be made if necessary.

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 in (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 nonaccess 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 intra-dialytic 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 blood pressure and body weight may shift shortly after initiation of daily dialysis 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 daily intervention due to hemoconcentration) with contrasts evaluating the changes from the month 1 visit, at which time most hemoconcentration effects should have occurred. Contrasts for changes from baseline to the month 1 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 ($<$ 4 years vs. $\geq$ 4 years), presence of residual renal function (defined by > 100 mL urine volume per 24 hours).

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 depend 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. *[2014 FHN Archive Note: FHN Executive Committee dropped prognostic covariates from the analyses.]* 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. 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 non-compliance 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 from the HEMO Study database. 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 1 year assessment. Data from the HEMO Study was also used to estimate the standard deviation of the change in the PHC, average serum albumin, and average serum phosphorus 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 [Pitt, 2003].

The minimum detectable effect sizes for the co-primary PHC/Mortality and LV mass/Mortality composite endpoints were estimated under the following assumptions: a) the target sample size of 250 randomized patients is achieved, b) exponentially distributed survival, with a 12%/yr mortality rate in the control group, c) exponentially distributed transplantation, with a 4%/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) indicated in Table 15a, 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 15a. Note that 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 250 patients has 90% power to detect treatment effects ranging from 4.59 to 4.96 points for the change in SF-36 PHC score, depending on the size of the treatment effect on LVmass. Similarly, the study has 90% power to detect treatment effects ranging from 12.1 to 13.3g for the change in LV mass, depending on the size of the treatment effect on the PHC.

Table 15b 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 the table, 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 as outlined in Section 9.5. The power calculations do not take into

Table 15a

Estimated Detectable Effect Sizes for the Primary Outcomes (N = 250)

Outcome	Treatment Effect on Other Primary Outcome[1]	80% power	90% power
LVmass - Mortality	0	11.3 g	13.0 g
	2.28 g	10.9 g	12.6 g
	4.56 g	10.3 g	12.1 g
PHC - Mortality	0 units	4.28 units	4.96 units
	6 units	4.12 units	4.80 units
	12 units	3.91 units	4.59 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 LVmass-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 LVmass. The simulation results indicate the above calculations are accurate if the correlation between the change in LVmass and the change in the PHC score is between 0 and +0.5.

Table 15b

Estimated Detectable Effect Sizes for the Main Secondary Outcomes (N = 250)[1]

Outcome Variable	Assumed SD of 1 Yr Change	80% power	90% power
PHC (points)	8.310	3.31	3.83
LV mass (g)	24.00	9.6	11.1
Average Albumin (g/dL)	0.296	0.12	0.14
Average serum phosphorus (mg/dL)	1.636	0.66	0.77
Beck Depression Inventory (1 SD)[2]	-	0.40	0.46
Trail Making Test B (1 SD)[2]	-	0.40	0.46

[1] Treatment effect tested at alpha = 0.05 using a 2-sided test. The estimated minimum detectable reduction in rate of non-access hospitalization or death is 39% and 45% at 80% and 90% power, respectively.

[2] Detectable treatment effects expressed per 1 standard deviation of the changes in the Beck Depression Inventory and Trail Making Test B because pilot data on 1-year changes in these outcomes in dialysis patients is not available.

account information provided by the 4 month measurements for patients with missing data at 12 months, and in this respect are slightly conservative.

Assuming event rates in the control group of this trial are similar to those observed in the HEMO Study, that the relationship between non-access hospitalizations and death events are similar between the two trials, and that the loss-to-follow-up rates are also similar, the estimated minimum detectable reduction in rate of non-access hospitalization or death is 39% and 45% at 80% and 90% power, respectively.

10. Safety and Monitoring

10.1 Data Safety and Monitoring Board (DSMB)

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 phase in the trial's first year, the DSMB will review quarterly reports summarizing the operational conduct of the study, including analyses of recruitment, retention, 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 phase. 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 phase, 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 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 Outcomes 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 Outcome 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

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 events (interventions and failures)

iv) adherence rates

10.3 Stopping Rule

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 the frequent 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 [O'Brien, 1979].

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