

## Scope and Design of the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) Study

Bertrand L. Jaber, MD, MS,<sup>1</sup> Fredric O. Finkelstein, MD,<sup>2</sup> Joel D. Glickman, MD,<sup>3</sup> Alan R. Hull, MD,<sup>4</sup> Michael A. Kraus, MD,<sup>5</sup> John K. Leypoldt, PhD,<sup>6</sup> Jiannong Liu, PhD,<sup>7</sup> David Gilbertson, PhD,<sup>7</sup> James McCarthy, MD,<sup>8</sup> Brent W. Miller, MD,<sup>9</sup> John Moran, MB,<sup>10</sup> and Allan J. Collins, MD,<sup>11</sup> for the FREEDOM Study Group

**Background:** Conventional thrice-weekly hemodialysis (HD) has limited the ability to generate further improvements in patient quality of life, morbidity, and mortality. Daily HD (DHD) offers the promise of providing clinical and economic benefits. The objectives of the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements Study are to evaluate outcomes of DHD (6 times/wk) with the NxStage System One (NxStage Medical Inc, Lawrence, MA) device.

**Design:** Cohort study with matched control group.

**Setting & Participants:** The DHD group will include up to 500 participants at 70 clinical sites, enrolling for 3 years with a minimum of 1-year follow-up. Study candidates include adult patients (age  $\geq$  18 years) with end-stage renal disease who are considered suitable candidates for DHD with the NxStage System One device by the treating physician and who have Medicare as their primary insurance payer. The control group will consist of a matched thrice-weekly in-center HD cohort derived from the US Renal Data System database using a 10:1 ratio, totaling 5,000 patients.

**Predictor:** Treatment with DHD and "standard of care" thrice-weekly HD.

**Outcomes & Measurements:** The primary intent-to-treat analysis compares hospitalization days/patient-year between the DHD and thrice-weekly HD groups. Other outcomes recorded in both groups include non-treatment-related medical expenditures. In addition, in the DHD cohort, changes in quality-of-life measures (baseline, 4 and 12 months, and every 6 months thereafter); urea kinetics; parameters related to anemia, bone and mineral metabolism, and nutrition; vascular access interventions; and use of medications will be examined.

**Conclusions:** This study has the potential to elucidate the health and economic benefits of DHD and complement results of current clinical trials.

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**INDEX WORDS:** End-stage renal disease (ESRD); daily dialysis; hemodialysis; quality of life; cost-effectiveness.

In the United States, end-stage renal disease (ESRD) affects more than 470,000 people,<sup>1</sup> and in the past decade, its incidence has grown at an annual rate of 5%, with a decrease in more recent years.<sup>1</sup> This 0.6% of the Medicare population consumes approximately 7% of the Medicare budget. The majority of these expenses are not directly related to dialysis care. Treatment

options currently are limited to dialysis and transplantation, with the latter considered the therapy of choice for patients without contraindications.

Patients treated with long-term dialysis in the United States receive either hemodialysis (HD) or peritoneal dialysis (PD). The latter was developed approximately 25 years ago to provide patients the option of home-based therapy. PD

From <sup>1</sup>Tufts University School of Medicine, Boston, MA; <sup>2</sup>Yale University School of Medicine, New Haven, CT; <sup>3</sup>University of Pennsylvania School of Medicine, Philadelphia, PA; <sup>4</sup>Renal Management Inc, Dallas, TX; <sup>5</sup>Indiana University Medical School, Indianapolis, IN; <sup>6</sup>University of Utah, Salt Lake City, UT; <sup>7</sup>Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; <sup>8</sup>Mayo Clinic College of Medicine, Rochester, MN; <sup>9</sup>Washington University School of Medicine, St Louis, MO; <sup>10</sup>Satellite Healthcare Inc, Mountain View, CA; and <sup>11</sup>University of Minnesota, Minneapolis, MN.

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Address correspondence to Bertrand L. Jaber, MD, MS, Caritas St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA 02135. E-mail: [bertrand.jaber@caritaschristi.org](mailto:bertrand.jaber@caritaschristi.org)

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therapy grew rapidly in its first 15 years, peaking at a utilization rate of approximately 15% more than a decade ago. However, since that time, there has been a progressive decrease in the use of PD, with the latest figures indicating a utilization rate of 7.6%.<sup>1</sup> Additionally, the dropout rate for PD is nearly 50% at 2 years,<sup>2,3</sup> and several studies have suggested that it may be inferior to HD in certain patient populations.<sup>4,5</sup> Although this progressive decrease in PD use has been the subject of much study and discussion, factors responsible for this erosion have not been fully characterized. Thus, the majority of patients with ESRD receive in-center HD, with only 0.4% on HD therapy in the home environment.<sup>1</sup> The most recent data from the US Renal Data System (USRDS) registry indicate an annual gross mortality rate of approximately 23%.<sup>1,6</sup> Unfortunately, results of the 2 largest randomized controlled trials of in-center thrice-weekly HD and PD provide compelling evidence that conventional dialysis therapies provided at the present time are limited in their ability to further improve clinical outcomes.<sup>7,8</sup>

The inherently nonphysiological nature of thrice-weekly HD treatment might be a major contributor to the observed cardiovascular morbidity and mortality.<sup>9-12</sup> Daily HD (DHD) typically is administered 6 times/wk and includes short daily HD (SDHD) and nocturnal HD (NHD). The recent literature is replete with studies reporting the numerous benefits of daily dialysis therapies.<sup>13-21</sup>

Unfortunately, most published work is for NHD, deriving primarily from uncontrolled studies. NHD has been associated with a decrease in blood pressure, decrease in antihypertensive medications, improvement in left ventricular mass,<sup>22</sup> and decrease in cardiovascular-related hospitalizations.<sup>23</sup> The effects of NHD on hemoglobin level and epoetin requirements are variable,<sup>22</sup> but there is consistent improvement in levels of phosphorus and calcium-phosphorus product.<sup>24-31</sup> Furthermore, NHD is associated with improved quality-of-life (QoL) measures<sup>22</sup> and sleep apnea-related parameters.<sup>32-34</sup> In a recently published small randomized controlled trial, compared with thrice-weekly HD, NHD (6 times/wk) markedly improved left ventricular mass, decreased the need for antihypertensive medications, and improved QoL measures.<sup>35</sup>

Similar benefits derived from fewer observational studies have been reported for SDHD, including a favorable effect on blood pressure, left ventricular mass,<sup>26,36,37</sup> anemia and nutritional parameters,<sup>10,38,39</sup> and QoL measures.<sup>26</sup> The effect of SDHD on mineral metabolism has been less impressive,<sup>27,40</sup> although more recent studies show some benefit.<sup>37,41</sup>

In summary, most previously published studies of NHD and SDHD are observational in nature and consequently have significant limitations, including patient selection biases in terms of younger age, better adherence to therapy, more reliable vascular access,<sup>42</sup> strong social and family support, fewer comorbid conditions, and possibly some other nonmeasurable factors.

Despite the growing evidence for efficacy, daily HD has not gained widespread acceptance in the United States because of deficiencies in dialysis technology and reimbursement issues.<sup>43</sup> Despite the increase in frequency and required supplies, daily dialysis might reduce the global costs of patient care, with estimates that SDHD delivered at home might confer the greatest cost savings.<sup>44-46</sup> Interest in the observed clinical benefits and potential economic benefits of daily HD led the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Medicare & Medicaid Services (CMS) in 2003 to award 4 cooperative agreement grants to conduct clinical trials of more frequent HD. This has resulted in the design of 2 randomized controlled trials comparing thrice-weekly HD with either in-center SDHD or home NHD, which are under way. Results are expected in 2009.<sup>47</sup>

In the United States, use of daily home HD recently has been growing, with more dialysis programs offering daily dialysis to patients who are expected to benefit from more frequent therapy. A significant barrier to self-care and patient empowerment is the complexity of dialysis equipment and technical issues related to maintenance of water quality, particularly in the home setting. There is a clear need to reduce the size and enhance the simplicity and portability of dialysis equipment, each of which would render the delivery of therapy more user friendly. The NxStage System One (NSO; NxStage Medical Inc, Lawrence, MA) device is a multifunctional cycler designed to deliver HD with high-purity dialysate and meets the mentioned requirements.

The Food and Drug Administration (FDA) has cleared this dialysis system for marketing in the home setting. The proposed postmarketing observational study plans to examine whether DHD decreases hospitalization and nontreatment health care costs compared with thrice-weekly in-center HD, while improving QoL and other dialysis adequacy measures. This research project is unique because it provides prospective longitudinal follow-up of a large cohort of patients converted to DHD therapy with an ability to compare with a matched cohort from the USRDS database. This study will help address the question of whether daily dialysis is economically attractive through the use of new technologies that decrease treatment costs and hospitalization rates, with the longer term goal of increasing life expectancy.

## METHODS AND DISCUSSION

### Study Design

This is a multicenter prospective cohort study of DHD that will involve up to 70 clinical sites, enrolling up to 500 participants. The study will be open to enrollment for approximately 3 years, with a planned minimum 1-year follow-up period. The study population consists of patients with ESRD who are considered suitable candidates for DHD (6 times/wk) with the NSO device and have Medicare as the primary payer. Participants will be followed up according to the dialysis center's standard of care, and clinical and laboratory data will be recorded on study case report forms (CRFs). As part of the study, participants will be asked to complete a series of QoL surveys at the time of enrollment (baseline), at 4 and 12 months, and every 6 months thereafter as long as they remain in the study. The study will also include a matched cohort of patients on thrice-weekly in-center HD therapy that will be randomly chosen from the USRDS database by using a 10:1 ratio.

### Study Objectives

The long-term goal of the study is to characterize the clinical benefits and cost-effectiveness of DHD using the NSO device by pursuing the following specific objectives.

### Primary Objective

The primary objective is to compare all-cause hospitalizations (reported in days/patient-year) of patients converting to DHD using the NSO device with conventional thrice-weekly in-center dialysis using a matched cohort from the USRDS database.

### Secondary Objectives

Secondary objectives are to: (1) examine the economic impact of DHD by comparing total nontreatment expenditures (per patient-year) of patients treated with DHD using the NSO device with conventional thrice-weekly in-center dialysis using a matched cohort from the USRDS database, and (2) compare changes in QoL measures, urea kinetic modeling, anemia, and bone and mineral metabolism and nutritional parameters, as well as vascular interventions and medication use, in study participants before and after conversion to the NSO device.

### Study Protocol

#### Eligibility Criteria

**Inclusion Criteria.** Candidates must meet all of the following criteria to be eligible for enrollment into the study: (1) diagnosis of ESRD requiring dialysis, (2) Medicare as primary payer (excluding Medicare health maintenance organization [HMO]), (3) age of 18 years or older, (4) candidacy for DHD (defined by a prescription of  $\geq 6$  treatments/wk with the NSO device), and (5) the ability to understand and willingness to sign an informed consent statement and a Health Insurance Portability and Accountability Act of 1996 compliant authorization statement.

**Exclusion Criteria.** Candidates meeting any of the following criteria will not be eligible to enroll in the study: (1) current use of the NSO device, (2) previous enrollment in the study, (3) current enrollment in an investigational drug or device trial that might impact on the outcome measures planned in the study, and (4) likelihood of not surviving the training period (ie, the first 4 to 6 weeks).

After initial screening, candidates meeting all inclusion criteria and none of the exclusion criteria will be enrolled in the study after providing informed consent. Study approval is obtained from a local or a central institutional review board. This

**Table 1. FREEDOM Study Schedule of Data Procurement**

Type of Measurement	Baseline Frequency	Follow-up Frequency
Demographic information	Once	—
ESRD treatment history	Once	—
Detailed comorbidity assessment	Once	Months 4, 12, and every 6 mo thereafter
Vascular access type, history, and events	Once	Throughout study period
Dialysis prescription	Once	Monthly
Timed urine collection	Once	—
Routine laboratory data*	Last 3 measurements	Monthly
PTH and iron indices†	Last 3 measurements	Every 3 mo
Medications	Once	Months 4, 12, and every 6 mo thereafter
Quality-of-life assessment‡	Once	Months 4, 12, and every 6 mo thereafter
Hospitalization	—	Throughout study period

Abbreviations: ESRD, end-stage renal disease; PTH, parathyroid hormone.

\*Routine laboratory data include serum potassium, calcium, phosphorus, alkaline phosphatase, albumin, creatinine, blood urea nitrogen, sodium, bicarbonate, hematocrit, hemoglobin, and urea kinetic modeling parameters (eg, Kt/V).

†Iron indices consist of ferritin and transferrin saturation rate.

‡Quality-of-life questionnaires include the 36-Item Short Form version 2 Health Survey, Beck Depression Inventory-II, International Restless Legs Syndrome Study Group Rating Scale, Medical Outcomes Study Sleep Index, and special study questions.

study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov) and has the identification number NCT00288613.

#### Data Collection

Study participant data collection is listed in [Table 1](#).

**Baseline Data Collection.** In brief, baseline data are collected before initiating treatment/training with the NSO device and include demographic information, ESRD treatment history, comorbid conditions (using the CMS Medical Evidence Report [Form 2728]), current vascular access type and history, current dialysis prescription and medications (oral and intravenous), and 3-month recordings of laboratory data. A 24-hour timed urine collection is also obtained to assess residual urinary volume.

The following QoL questionnaires are administered: (1) the 36-Item Short Form version 2 Health Survey (SF-36),<sup>48,49</sup> (2) Beck Depression Inventory-II (BDI-II),<sup>50-52</sup> (3) International Restless Legs Syndrome Study Group Rating Scale (version 2.2),<sup>53,54</sup> (4) Sleep Index of the Medical Outcomes Study,<sup>55,56</sup> and (5) special study questions ([Table 2](#)). A trained and qualified staff member administers these questionnaires. The site principal investigator will be immediately notified if the BDI-II score is higher than 10.

**Monthly Data Collection.** Monthly data are recorded at the time of the study participant's scheduled monthly clinic visit and include monthly routine laboratory data ([Table 3](#)), changes

**Table 2. FREEDOM Study Quality-of-Life Surveys**

36-Item Short Form version 2 Health Survey<sup>48,49</sup>

Beck Depression Inventory-II<sup>50-52</sup>

International Restless Legs Syndrome Study Group Rating Scale<sup>53,54</sup>

Medical Outcomes Study Sleep Index<sup>55,56</sup>

Special quality-of-life study questions

How long does it take you to recover from a dialysis session and resume your normal usual activities?

If you were given a choice of changing back to the previous dialysis regimen you were receiving before converting to daily hemodialysis, how likely would you be to change?

How satisfied are you with your degree of physical intimacy during the last 4 weeks?

Considering all aspects of your life, physical, emotional, spiritual, social, and financial, how would you rate your overall quality of life?

What was your employment status during the last 4 weeks?

If you were employed since the last time you took this survey, in the last 4 weeks, have you been working the same number of hours? Working fewer hours per week? Working more hours per week?

What is the one thing that has changed the most for you since starting daily dialysis?

**Table 3. Algorithm Used for the Dynamic Matching Procedure**

Step 1	Order study participant in the treatment group based on enrollment date
Step 2	For the first unmatched study participant, find all patients on conventional in-center thrice-weekly hemodialysis therapy in the USRDS database who match the study participant at the time of enrollment in steps 3 and 4
Step 3	Determine the values for all 8 matching variables based on study participant's enrollment date
Step 4	Find the matched group from the USRDS database for the study participant using the matching variables If it is not possible to match every characteristic for each study participant to a minimum of 10 patients from the USRDS database, characteristics will be systematically removed from the list to match to, beginning with the least important, until a group of at least 10 patients are identified
Step 5	Randomly choose 10 patients from the matched group if there are >10 matched patients
Step 6	Repeat steps 2, 3, 4, and 5 for unmatched participants based on the order given in step 1 until all study participants are matched

Abbreviation: USRDS, US Renal Data System.

to the dialysis prescription, vascular access events (if any), and urea kinetic modeling parameters. Guidelines for obtaining the postdialysis blood urea nitrogen value to calculate single-pool Kt/V conform to the published Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.<sup>57</sup> The proposed guideline for dosing HD delivered 6 times/wk is a single-pool Kt/V of approximately 0.50/treatment,<sup>58,59</sup> which will be adjusted as deemed appropriate by the clinician.

**Quarterly Data Collection.** Transferrin saturation rate, ferritin, and parathyroid hormone values are collected quarterly according to the dialysis center's standard of care.

**Additional Data Collection.** At months 4 and 12 and every 6 months thereafter until study termination, medication use and newly diagnosed comorbid condition(s) (if any) are recorded. In addition, all the mentioned QoL surveys are readministered (Table 3).

**Hospitalization Days and Medical Cost.** Number of hospitalization days and medical cost are calculated based on Medicare claims. The Medicare allowable cost without dialysis expenditure will be used for the cost analysis.

#### **Optional Participation in the International Quotidian Dialysis Registry**

Each site is invited to participate in the International Quotidian Dialysis Registry. This international registry was created in response to the recommendation of a Task Force on Daily Dialysis assembled by the National Institute of Diabetes and Digestive and Kidney Diseases and CMS and is designed to collect data describing treatments, characteristics, and outcomes of patients treated with DHD worldwide.<sup>60</sup>

In brief, if the site agrees to participate, informed consent is obtained to allow the study sponsor to share the deidentified data collected during this study with the International Quotidian Dialysis Registry. No additional data are collected for the purpose of this registry.

#### **Safety Monitoring**

The NSO is a 510(k) cleared device. Therefore, all product performance, safety, reliability, durability, appearance, and/or quality and general complaints are processed by the study sponsor's Customer Event Reporting and Complaint Process and the FDA Medical Device Reporting mechanism for manufacturers (in accordance with FDA regulation CFR 820.198 and 21 CFR 803).

#### **Selection of Investigators**

Licensed nephrologists credentialed to care for patients with ESRD will be considered eligible to serve as investigators in the study. The eligible investigator must have trained and cared for a minimum of 5 patients using the NSO device before site selection and will follow the approved study protocol.

#### **Statistical Analysis Plan**

##### **Study Hypotheses**

The study is designed to test the primary hypothesis that patients receiving DHD with the NSO device have lower hospitalization rates in terms of total hospital days/patient-year compared with a matched cohort receiving in-center thrice-weekly HD. The secondary hypotheses to be tested are that patients receiving DHD with the NSO device: (1) have lower nontreatment

costs compared with a matched cohort receiving in-center thrice-weekly HD, and (2) benefit from improvements in QoL measures; parameters related to anemia, bone and mineral metabolism, and nutrition; and from a decrease in the number of vascular access interventions and medication use.

#### **Sample Size Calculation**

In 2003, the average number of hospital days/patient-year in prevalent dialysis patients was approximately 14.4.<sup>61</sup> Based on a simulation performed using the USRDS data set, a sample size of 500 patients receiving DHD with the NSO device and a 10:1 ratio of matched patients from the USRDS database totaling 5,000 will be used for the study. This sample size will allow detection of at least a 20% decrease in hospital days/patient-year in the DHD group at the level of 0.05 for type I error and 80% power. The sample size simulation accounted for a dropout rate of approximately 30% because of loss to follow-up, change in modality, and death using observed rates in the USRDS data set. Multiple dialysis facilities will participate in the study, but each site will be allowed to enroll only up to 10% of the total study enrollment goal to control for potential biases that might arise.

#### **Database Merger**

On agreement of the USRDS Project Officers and a representative from the CMS, the USRDS will use Health Insurance Claim number, name, demographic data (date of birth, sex, and race), primary cause of kidney failure, date of dialysis therapy initiation, and Medicare provider number to merge study participant CRF data with the CMS ESRD database. Of note, all study participants must have provided signed consent forms informing them that their Health Insurance Claim number will be used to match their CRF information with health care information from the CMS database. The CMS database is composed of data obtained from CMS ESRD Medical Evidence Report (Form 2728), ESRD Death Notification Form (Form 2746), Medicare Part A Institutional Claims (inpatient, outpatient, skilled nursing, home health, and hospice), and Medicare Part B Physician (inpatient and outpatient) and Supplier Claims. Of note, baseline comorbid conditions will be defined using the Medical Evidence Re-

port and CMS claims data captured up to 6 months before study enrollment date by using a previously described method.<sup>62</sup> The merged database will include all morbidity and mortality events of patients with Medicare as the primary payer that occurred after enrollment. In brief, patient baseline information will come from the ESRD Medicare Evidence form and Medicare claims. Hospitalization admission dates, hospital days, and medical expenditures will be procured from the Medicare claims data. The data sets will be merged twice, once for the interim analysis and once for the final analysis.

#### **Matching Procedure**

The matched cohort for this study is a random sample of thrice-weekly HD patients identified in the USRDS database. In brief, each study participant will be matched at the enrollment date for 8 variables. Listed in order of descending importance, the matching variables include age ( $\pm 5$  years), sex, race (African American, and non-African American), primary cause of kidney failure (diabetes mellitus, hypertension, and glomerulonephritis/cystic kidney disease versus other), dialysis vintage ( $<1$ , 1 to 5, and  $> 5$  years), baseline comorbid conditions (derived from the Medical Evidence Form and 6-month claims before the enrollment date, including congestive heart failure, atherosclerotic heart disease, other cardiac disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, and cancer), hospital days in the 6 months before study enrollment (0, 1 to 3, 4 to 7, and  $>7$  days), and geographic region (including census division, and rural versus urban setting). A 10:1 dynamic matching procedure will be performed using a predefined algorithm listed in [Table 3](#). The matching procedure will be performed in 2 phases. The first phase will be completed at the time of the interim analysis, when 10 USRDS patients will be matched to each study participant enrolled at that time. This same matched cohort will be carried through for the final analysis. The second phase will be completed at the time of the final analysis and will entail matching only for participants enrolled in the study after the initial match was performed.

### **Study Completion and Early Termination**

**Daily Dialysis Treatment Group.** Study completion is defined as completing a minimum of 12 months of DHD therapy using the NSO device. Early study termination is defined as discontinuing daily dialysis before completing the first 12 months of observation for one of the following reasons: dialysis modality change (defined by a switch to PD or in-center thrice-weekly HD therapy or discontinuation of the NSO device for >6 weeks); kidney transplantation; relocation to another dialysis center; nonadherence to the prescribed therapy; investigator's judgment; participant or investigator request that the participant be withdrawn from the study; the investigator or study sponsor for any reason closes the study or stops the participant's participation in the study; change to HMO, Medicare as the secondary payer, or non-Medicare; loss to follow-up in the ESRD database; or death.

**Thrice-Weekly In-Center Dialysis Control Group.** In the control group, study completion is defined as completing a minimum of 12 months of conventional thrice-weekly in-center HD treatment from the time the study participant to which the control patient has been matched is enrolled in the study. Early study termination is defined as discontinuing thrice-weekly in-center HD before completing the first 12 months of observation because of dialysis modality change (defined by a switch to PD or more frequent HD); kidney transplantation; change to HMO, Medicare as the secondary payer, or non-Medicare; loss to follow-up in the ESRD database; or death. Of note, switch of dialysis modality for longer than 6 consecutive weeks would qualify as a modality change.

### **Analytical Approaches**

**Primary End Point.** The primary analysis will be an intent-to-treat analysis comparing hospitalization days/patient-year between the daily and thrice-weekly HD groups. The intent-to-treat population is defined as all enrolled study participants and the corresponding matched USRDS cohort. For this analysis, follow-up time will begin to accrue from the enrollment date to death, payer status change, loss to follow-up, or end of study, whichever comes first.

The following secondary analyses comparing hospitalization days between the 2 groups will

also be performed: (1) "conditional" intent-to-treat analysis in which the conditional intent-to-treat population is defined as all enrolled study participants who have completed 2 months of DHD from the enrollment date and the corresponding matched USRDS cohort; this 2-month grace period was chosen because it encompasses the initial daily dialysis training period, and follow-up time will be similar to that of the mentioned analysis; (2) a per-protocol analysis restricted to all enrolled study participants who have completed 12 months of DHD from the enrollment date and their corresponding matched USRDS cohort; for this analysis, follow-up time will begin to accrue from the enrollment date and through 12 months of DHD to death, payer status change, loss to follow-up, or end of study, whichever comes first; and (3) optional conditional per-protocol analysis in which the population is the same as defined for the per-protocol analysis, but follow-up time would begin to accrue after participants complete 2 months of daily therapy and through 12 months of daily therapy.

**Secondary End Points.** Nonhospitalization secondary analyses will focus on the comparison of costs between patients receiving DHD versus the matched USRDS cohort. Patient health-related QoL, urea kinetic parameters, blood pressure parameters, anemia parameters, bone and mineral metabolism parameters, vascular access interventions, and nutritional parameters will be compared before and after treatment for the DHD group.

### **Planned Interim and Final Analyses**

In addition to the final analysis to be performed after completion of the study, interim analyses are planned. Both analyses will examine hospitalization and economic outcomes comparing the DHD group with the matched cohort, as well as the QoL surveys and laboratory measurements obtained before and after conversion to DHD therapy. The Data Coordinating Center will receive the study data set for 2007 at the end of 2008, allowing the interim analyses comparing cases with the matched cohort to be performed with follow-up through 2007. The study Data Coordinating Center will receive data for 2009 at the end of 2010, at which time the final analyses can be performed. Based on the O'Brien and Fleming<sup>63</sup> sequential testing procedure, a *P* value of 0.005 will be required to consider

**Table 4. Effect Size Estimates and Required Sample Sizes for the Proposed Interim Analyses on Quality-of-Life End Points**

Quality-of-Life End Point	Time Point (mo)	Dropout Rate (%)	Mean Change	SD of Change	Sample Size (80% power)	Supporting Reference
Physical Component Summary score	4	20	4 units	10 units	65	64, 66
	12	30	3 units	10 units	153	
Time-to-recovery-from-a-dialysis-session	4	20	150 min	150 min	23	65
	12	30	100 min	150 min	55	
Beck Depression Inventory score	4	20	6 units	10 units	30	70, 71
	12	30	8 units	10 units	25	
International Restless Legs Syndrome Study Group Rating Scale	4	20	4.5 units	9 units	43	72
	12	30	6 units	9 units	35	

the treatment effects statistically significant at the interim analysis, whereas a *P* value of 0.048 will be required to achieve statistical significance at the end of the study. Analyses will be based on the merged study CRF and USRDS database. For all analyses, 2-tailed hypothesis tests will be used.

For the interim analysis of the QoL surveys obtained before and after conversion to DHD therapy, sample size calculations have been performed to assess changes in 4 prespecified components; namely, the Physical Component Summary score of the SF-36 Health Survey,<sup>64-67</sup> the response to the time-to-recovery-from-a-dialysis-session special study question,<sup>65</sup> the BDI score,<sup>68-71</sup> and the International Restless Legs Syndrome Study Group Rating Scale<sup>72</sup> (Table 4). All sample size calculations have been performed for the 4- and 12-month time points to achieve 80% power for a 2-sided test with type I error of 0.05. All interim analyses will be performed when the prespecified number of study participants is reached at the respective study times. Additional interim analyses may be performed on individual domains of the SF-36, as well as on the special study questions listed in Table 2 (analyses not shown), and for such analyses, adjustment for multiple testing will be performed.

### Strengths and Limitations

Strengths of this large postmarketing prospective observational study of patients initiating DHD therapy are the large sample size from up to 70 sites within the United States, use of a comparative cohort of patients on in-center thrice-weekly HD therapy that is matched to several key baseline covariates, and ability to ascertain the primary outcome with precision because of the merge with the USRDS database. The end points of the study

are of utmost importance to health care providers and administrators because they address both clinical benefits and cost-effectiveness of DHD.

Some of the limitations that are worthy of mention include the observational study design, which introduces potential biases and confounders. Although the planned dynamic matching procedure attempts to minimize bias, there is likely to be residual measured and unmeasured confounding that cannot be accounted for. In addition, candidacy for DHD, which is determined by the treating physician, introduces an additional selection bias that cannot be overcome. The study also is not powered to examine such hard end points as mortality, and includes incident and prevalent patients with ESRD, which might introduce an element of time bias.

### CONCLUSION

In summary, the FREEDOM Study has the potential to be the largest prospective cohort study of DHD in the United States, aimed at addressing whether frequent HD can decrease hospitalization rates, improve QoL, and decrease nontreatment expenses. Daily HD will become economically attractive and enter mainstream practice only if new technology decreases treatment costs and more patients are empowered to consider self-care dialysis.

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Moran are former members of the Scientific Advisory Board of NxStage Medical Inc.

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