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

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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 ≥ 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,[1] and in the past decade, its incidence has grown at an annual rate of 5%, with a decrease in more recent years.[1] 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

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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%.[1] Additionally, the dropout rate for PD is nearly 50% at 2 years,[2,3] and several studies have suggested that it may be inferior to HD in certain patient populations.[4,5] 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.[1] The most recent data from the US Renal Data System (USRDS) registry indicate an annual gross mortality rate of approximately 23%.[1,6] 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.[7,8]

The inherently nonphysiological nature of thrice-weekly HD treatment might be a major contributor to the observed cardiovascular morbidity and mortality.[9-12] 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.[13-21]

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,[22] and decrease in cardiovascular-related hospitalizations.[23] The effects of NHD on hemoglobin level and epoetin requirements are variable,[22] but there is consistent improvement in levels of phosphorus and calcium-phosphorus product.[24-31] Furthermore, NHD is associated with improved quality-of-life (QoL) measures[22] and sleep apnea–related parameters.[32-34] 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.[35]

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

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,[42] 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.[43] 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.[44-46] 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.[47]

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.