TASK FORCE ON

Daily Dialysis

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Sponsors:
The National Institute of Diabetes and Digestive and Kidney Diseases
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Executive Summary

Introduction

Most hemodialysis (HD) patients in the United States undergo dialysis three times a week for 3½ to 4 hours per session. This regimen has been the **modal type of hemodialysis** ever since **end-stage renal disease (ESRD)** was added to the Medicare program. Medicare payment policy, also known as the **composite rate**, is premised on thrice-weekly dialysis.

In the past several years, hemodialysis on a daily basis has been tested at a few centers. **Two forms of daily dialysis** are currently in use: (1) **long nocturnal dialysis**, typically provided at home, and (2) **short dialysis**, usually performed in a dialysis center during the day. Although described as "daily," treatment frequencies vary between five and seven times per week. Preliminary information from these recent experiences has generally been very positive, and consequently, daily dialysis is considered by many in the renal community to be a promising alternative to current thrice-weekly dialysis.

However, the evidence for the benefits of daily dialysis is based on studies of very few patients and sites. Because daily dialysis presents the possibility of a greatly increased weekly dose of dialysis over current prescriptions, a clinical trial, including examination of cost and payment issues, offers the possibility of determining the value of this therapy.

In April 2001, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) and the Health Care Financing Administration (HCFA) sponsored a meeting to explore the issue of daily dialysis. The **goals** of this meeting were to

- Review the current knowledge base concerning daily hemodialysis
- Examine the scientific basis for more frequent hemodialysis
- Discuss the practical aspects of implementing daily hemodialysis
- Identify the essential features of a randomized clinical trial of daily hemodialysis

In her opening statements, Josephine Briggs, M.D., director of the Division of Kidney, Urologic and Hematologic Diseases, NIDDK, told participants that the meeting was neither a scientific symposium nor a public policy forum but, rather, an effort to define NIH research agenda on intensive dialysis. Research planning was the focus of the meeting, she said.

Jeffrey Kang, M.D., director of HCFA's Office of Clinical Standards and Quality, explained HCFA's policy of evidence-based coverage decisions in his opening remarks. "When HCFA was reorganized, a deliberate policy decision was made to allow science to drive coverage decisions," he noted. "In the past three years, HCFA has attempted to make evidence-based coverage decisions. What the science says (not how much it costs) will determine what Medicare covers."

Dr. Kang encouraged participants not to be concerned with coverage but to concentrate on the clinical and scientific questions to be answered such as "who can benefit, what's the right disease, and what's the right method?" The answers to those questions will drive the coverage decision, he said.

Presenters offered key observations on daily dialysis and explained the concepts involved. **Equipoise**, or the need to have ethically equivalent choices, was a central concern. Sessions of the meeting covered the following topics:

- **Mechanisms of Efficacy, Solute Kinetics**
- **Background on Daily Dialysis, Current Results, Experience**
- **Trial Design Issues**
- **Economic Issues**

At the end of the meeting, presenters and participants gathered in small groups to discuss the various topics and to make **recommendations**.

Mechanisms of Dialysis Efficacy, Solute Kinetics

The **definition of dialysis efficiency** is the ratio of patient outcome to the weekly dialysis dose, according to Thomas Depner, M.D., professor of medicine in the Division of Nephrology at the University of California Davis Medical Center. Dr. Depner, who spoke on solute removal in more frequent dialysis schedules, said that the **basic assumptions about daily dialysis** are as follows:

- Dialysis works by reducing the concentration of dialyzable toxic solutes in the patient
- Mean toxin concentrations best reflect toxicity
- Continuous dialysis is more efficient than intermittent dialysis

Dr. Depner recommended future research, including techniques for measuring clearance of uremic toxins in high frequency dialysis. Urea is a poor surrogate for more toxic compounds that accumulate but diffuse more slowly among body compartments, he said. A cumulative toxic effect of these compounds in concert with their limited diffusion within the patient may explain the markedly enhanced efficiency of continuous dialysis and provide a rationale for increasing the frequency of intermittent hemodialysis.

Session chair, Nathan Levin, M.D., medical and research director of the Renal Research Institute, Albert Einstein College of Medicine, spoke about the relative risk of mortality (RRM) being higher in small people undergoing dialysis and provided a potential kinetic explanation for

volume-dependent outcomes. The inverse relationship of relative risk of mortality (RRM) to urea distribution volume (V) is hypothesized to result from a solute with concentration-dependent toxicity generated independent of V. This hypothesis was modeled and shown to result in relative concentration profiles that closely mimic V-dependent RRM profiles, he said. The model simulations also predict greater benefit of daily dialysis for small patients; a trial of daily dialysis should include a significant number of individuals at both ends of the spectrum of body volume.

Frank Gotch, M.D., associate professor of medicine at the University of California, San Francisco, discussed measurement of a standard Kt/V for urea, including definitions of dialysis dose; mathematical definitions of equivalence between continuous and intermittent doses of dialysis; clinical evaluation of pkK, stdK, and EKR; and the generalized solution and clinical use of the standard Kt/V model.

Daily Hemodialysis: Background, Current Results, Experience

Panelists in this session, chaired by Michael Klag, M.D., M.P.H., interim chair of the Department of Medicine at Johns Hopkins Medical Institutions, considered the following important issues in daily dialysis:

- Nutrition
- Bone density
- Hematocrit and blood pressure
- Quality of life
- Morbidity and mortality

Nutrition. In a review of 14 studies in the literature from 1969 to 2001, Robert Lockridge, Jr., M.D., a clinical nephrologist with Lynchburg Nephrology Physicians, P.L.L.C., and colleagues reported that all subjects (248 patients followed for 3 months to 4 years) showed improvement in one or more nutritional parameters, measured as albumin, normalized protein catabolic rate (nPCR), and increased protein and calorie intake. These observations support the theory that daily hemodialysis will result in reduced mortality rates for ESRD patients, Lockridge said. He further suggested that older and sicker patients would benefit more significantly from nutritional improvements.

Bone density. Andreas Pierratos, M.D., primary investigator of the Nocturnal Hemodialysis Project at Humber River Regional Hospital (Toronto, Canada), reported that nocturnal hemodialysis was effective in phosphate removal because of the long duration and high frequency of dialysis. According to Pierratos, nocturnal hemodialysis offers normalization of serum phosphate on an *ad lib* diet without phosphate binders. Indeed, phosphate may have to be added to the dialysate in such procedures, he said. In addition, high doses of dialysate calcium are necessary to maintain bone density in patients. Increasing the dialysate calcium easily suppresses parathyroid hormone, and extraosseus tumoral calcifications are diminished. Pierratos

concluded that short daily hemodialysis improves phosphate removal and may allow decreased use of phosphate binders, but the long-term effects of this method on bone disease are unknown.

Hematocrit and blood pressure. Reports from several countries and spanning several decades are remarkably similar in their findings on the effect of daily dialysis on hematocrit and blood pressure, according to George Ting, M.D., clinical professor of medicine at Stanford University and medical director of El Camino Dialysis Services at El Camino Hospital. Those reports find that increased frequency of dialysis either maintains or improves hematocrit with significantly less erythropoietin dosage, and blood pressure is either improved or unchanged with significantly fewer blood pressure medications.

Quality of life. To many people, the quality of life is more important than life itself, noted Carl Kjellstrand, M.D., Ph.D., clinical professor of medicine at Loyola University and vice president of AKSYS LTD. Kjellstrand said that in the United States, one fourth of all dialysis patients' lives end because they choose to stop dialysis. "Annoying and crippling symptoms during and between dialysis improve quickly when patients change from regular to daily hemodialysis," he said. "Long-term quality-of-life changes take several months to emerge, but even when the objective change is not statistically significant, more than 90 percent of patients choose to remain on daily hemodialysis."

Morbidity and mortality. Fritz Port, M.D., of the Kidney Epidemiology and Cost Center at the University of Michigan, reviewed the morbidity and mortality of 72 patients from Europe and North America who switched from standard hemodialysis to short daily (six times weekly) hemodialysis. The review indicated that daily compared to standard was associated with lower morbidity (improved blood pressure, fewer nutrition problems, and a lower incidence of anemia). Dr. Port noted that this promising innovation deserves a randomized clinical trial or at least a prospective data collection or observational study.

Daily Hemodialysis Trial Design Issues

Panelists led by session chair Robert Wolfe, M.D., professor of biostatistics at the Kidney Epidemiology and Cost Center of the University of Michigan, discussed trial design issues such as the readiness of daily dialysis for a clinical trial; the design of the London (Ontario) daily /nocturnal hemodialysis study; options for a daily dialysis trial design; clinical trial issues such as outcome, sample size, and randomization; and HCFA's Medicare demonstration waiver authority.

Is daily dialysis ready for a clinical trial? A clinical trial on daily dialysis is needed to determine whether it increases life expectancy. According to William Owen, Jr., M.D., director of the Duke University Institute of Renal Outcomes Research and Health Policy, conventional hemodialysis costs may be higher than previously reported, and daily dialysis costs are higher than conventional hemodialysis costs. However, daily hemodialysis may become economically

attractive if new technologies reduce treatment costs and clinical trials show increased life expectancy.

The London (Ontario) daily/nocturnal hemodialysis study. The London study is the first attempt to obtain randomized data on daily/nocturnal hemodialysis. It commenced in November 1998 and will be complete at the end of 2001. Robert Lindsay, M.D., professor of medicine at the London (Ontario) Health Sciences Centre and the University of Western Ontario, discussed the Canadian daily/nocturnal dialysis study, a three-year prospective, observational study of 20 patients, with 10 patients receiving short daily hemodialysis and the other 10 patients receiving nocturnal hemodialysis. All treatments are provided in the home environment, and patients will be followed for 18 months (follow-up is currently ongoing). Dr. Lindsay focused on patient recruitment and study design.

Options for daily dialysis trial design. Glenn Chertow, M.D., director of clinical services, division of nephrology, at the University of California, San Francisco, discussed novel dialytic options, including intermittent hemodialysis, extended time; daily hemodialysis, short time; daily hemodialysis, conventional time; and daily hemodialysis, extended time (nocturnal or daily). He also discussed limitations of observational data, blinding and randomization, subject characteristics, outcomes, sample size, and timing.

Outcomes and sample size. Design criteria for a randomized trial should include valid and compelling primary outcome measures and adequate statistical power to determine if interventions improve the primary outcome, said Thomas Greene, Ph.D., an associate staff biostatistician in the Department of Biostatistics and Epidemiology of the Cleveland Clinic Foundation. Systematic biases in design should be avoided, and results of such a trial should be generalizable to a large proportion of the dialysis population. Dr. Greene provided specific information about the number of subjects (N) needed for a two-arm design with equal allocation to the two arms, assuming a two-sided alpha level of 5 percent, three years of uniform accrual plus two years of further follow-up, and a loss-to-follow-up rate of 4 percent per year. At an event rate of 10 percent per year in the control group and a one-year event probability of 9.5 percent, an N of 1,622 would be needed to detect a treatment effect of 30 percent; an N of 3,892 (an increase of 125 percent) would be required to detect a treatment effect of 20 percent. Event rates of approximately 10 percent may be realistic for mortality, assuming that randomized subjects will have better health status than the general dialysis population; although smaller sample requirements would be less, if a high-risk population were enrolled.

HCFA Medicare demonstration waiver authority. Steven Clauser, Ph.D., director of HCFA's Quality Measurement and Health Assessment Group, provided an overview of the HCFA Medicare demonstration waiver authority, including a discussion of how HCFA Medicare demonstrations contribute to the development of Medicare policy. He also discussed the strengths and limitations of experimenting with innovative benefit models and payment policies.

In the question and answer session, substantial debate ensued regarding the feasibility of randomization**.** Several participants noted that randomization for a home protocol was particularly problematic. The pros and cons of using mortality as the main outcome measure were also discussed intensely. While participants acknowledged the subjective nature of quality-

of-life measures; nevertheless, they stressed the importance of improving the patient's sense of well-being.

Dialysis Industry Roundtable

Although industry generally supported a move to daily hemodialysis and, more specifically, the clinical trial and data collection that would precede and support general acceptance of the use of daily dialysis, panelists enumerated considerable operational problems, which will need to be addressed on a company-by-company basis.

The Industry Roundtable Panel, chaired by Michael Blagg, M.D., executive director emeritus of Northwest Kidney Centers and professor emeritus at the University of Washington, discussed the definition of "daily" dialysis; how the dose should be measured; what outcomes should be assessed; future applications and reimbursement; the percentage of the ESRD population that will likely take advantage of this therapy; and what the federal government's position will be if the therapy proves to be a significant improvement in patient care but can only be provided at additional net cost.

Panelists also discussed some of the implementation issues, including setting up and organizing in-center daily hemodialysis, training for nocturnal hemodialysis, the ongoing nursing shortage, availability of training facilities, installing and monitoring water treatment systems, monitoring safety for home (unattended) hemodialysis, and cost and reimbursement. A question-and-answer session followed this roundtable presentation.

The Industry Roundtable panel included Michael Lazarus, FMC; Phil Zager, DCI; Ray Hakim, RCG; Ingrid Ledebo, Gambro; Charles McAllister, Davita; William Clark, Baxter; Carl Kjellstrand, AKSYS; and Peter Crooks, Kaiser Permanente.

Economic Issues of Daily Dialysis

Economic implications of daily dialysis. Research suggests that daily hemodialysis improves clinical outcomes and patient quality of life when compared with conventional hemodialysis. However, little is known about the economic impact of daily schedules, noted Penny Mohr, M.A., senior research director of the Project Hope Center for Health Affairs in Bethesda, Maryland. Mohr and her colleagues constructed an economic model and concluded that

- Daily hemodialysis may reduce total health care costs.
- Larger, well-controlled studies of daily versus conventional hemodialysis are needed to make this determination with certainty.
- Work productivity and other indirect costs should also be considered.

Assessing costs across dialysis therapies. Cost is relative, subject to societal perspective, said Phillip Held, Ph.D., president of the University Renal Research and Education Association; therefore, cost should be evaluated over a patient's lifetime. Incomplete data may result if data is not evaluated at some point before a patient dies. Outcomes that should be considered in cost evaluation, according to Dr. Held, include

- Mortality
- Morbidity
- Vascular access
- Quality of life

Likely problems include the difficulty of random assignment and costs not being recognized fully.

Measuring costs in clinical trials. Joel Greer, Ph.D., an economist with HCFA, discussed how to measure costs in clinical trials, including

- Collecting cost data and estimating costs
- Costs of interventions,
- Costs of intervention plus other medical costs
- Computing cost-effectiveness

Most new technologies are not cost saving, but money is saved elsewhere in the health care system, he said. Dr. Greer also discussed designing a clinical trial to facilitate a cost-effective analysis.

Composite rate payment issues. "The current composite rate payment system is outdated and in need of revision," said Lana Price, director of HCFA's Division of Chronic Care Management. "HCFA has no current authority under the law to update or revise the rate payment schedule. However, recent legislation requires HCFA to report to Congress with recommendations for a fully bundled payment system and a mechanism for updating the payment amounts." Regarding a clinical trial, HCFA will pay for the added costs associated with daily dialysis for patients participating in the trial, Price said, but to assess the appropriate payment levels for this modality, HCFA will need to obtain detailed cost data from facilities participating in a proposed clinical trial. For in-home dialysis, cost information must differentiate between training the patient and the actual delivery of dialysis.

Recommendations

Participants met in four breakout sessions to discuss the following: (1) trial design—short daily hemodialysis; (2) trial design—nocturnal hemodialysis; (3) economic issues—payment and

outcomes; and (4) epidemiological monitoring. The four groups offered the following recommendations:

(1) Trial Design—Short Daily Hemodialysis Sessions

- The **general research question** should be: What is the effect of treatment with daily in-center hemodialysis on patient mortality and morbidity, compared with the current standard, thrice-weekly dialysis?

- **Variation in duration** of the trial intervention was suggested by some members of the group; others suggested **variation in delivered clearance**.

- The study should be designed as a **randomized, parallel-arm clinical trial**. The proposed intervention is dialysis six days per week, to be compared with the current standard of three days per week.

- A large, simple trial with ancillary studies is preferable to a smaller trial with extensive data collection.

- **Randomization** is feasible and should be done, according to most participants; however, it is feasible only if patients in the study have had no previous experience with daily dialysis.

- **Being willing to participate is the first eligibility criterion for the clinical trial**. High-risk patients, for whom death is not imminent, would provide the best study group.

- If the intervention turns out to be efficacious, provisions should be instituted to assure that patients in the standard-of-care arm (the control group) will have first access to daily dialysis after the trial is completed. A "**compassionate use protocol**" should also make daily dialysis available for any patient for whom it is considered medically indicated.

- The funding should contribute to helping patients with **transportation costs**.

- The **primary outcome** of the study should be **mortality**, but a composite outcome should be considered if required for statistical power. A variety of secondary outcomes were suggested, including quality-of-life measures.

- **In-center dialysis** rather than at-home dialysis is preferred, because of feasibility and speed of implementation.

- The results of the **HEMO study** and other studies should be used to inform the design of the trial.

- Duration of the trial should be at least one year.

- These recommendations should be updated, based on the recommendations of the nocturnal dialysis breakout group (for example, comparing equivalent doses).

(2) Trial Design—Long Nocturnal Hemodialysis

- **Primary outcome** should be a mortality/cardiovascular (CV) composite outcome, in which overall mortality, CV hospitalizations, myocardial infarction, and cerebrovascular accidents would be judged as primary outcome events.

- **Secondary outcome** information should include, but not be limited to, causes of death and hospitalization, neuro-cognitive function, and health-related quality of life and functional status.

- The **treatment arm** of this trial should provide nightly nocturnal dialysis at least six times per week, with providers allowed to use their discretion as to whether to increase the frequency to seven times per week; location could be either at home or in-center. The control arm should consist of three times a week daily dialysis in-center.

- To reach the composite outcome suggested, with adequate statistical power, more than **1,500 patients** will be needed. To augment patient accrual, all patients, including pediatric patients, should be recruited, and patients with CV disease and major co-morbid conditions should be over-sampled.

- The trial should use both **incident and prevalent patients**, recognizing that some incident patients will become prevalent patients during their training.

- This trial should be a **randomized clinical trial**. Patients randomized to conventional therapy should be promised that, if long nocturnal dialysis proved efficacious and safe and if funding were available, they would be first in line to assume this modality once the trial ended.

- Patients, rather than dialysis units, should be randomized; randomizing dialysis units would pose substantial operational challenges.

- A **pilot or feasibility study** should be implemented because of patient recruitment and accrual issues and the steep learning curve associated with the operation of long nocturnal dialysis. The NIH leadership should focus on how patients will be recruited by investigators. Alternative recruitment strategies could be tested during the pilot or feasibility phase.

(3) Economic Issues—Payment and Outcomes

- A clinical trial should measure the **cost-effectiveness** of dialysis treatment; consideration should be given to using quality of life, as well as length of life, as a measure of treatment effectiveness.

- The societal perspective should be paramount, but the **perspectives of other stakeholders**—including dialysis providers, patients, and HCFA—must also be considered.

- **HCFA**, as the major payer, would particularly need to know the delivery costs of daily dialysis and what the **cost-impact** will be on subsequent Medicare expenditures.

- **Personnel and training** are the most significant cost items for providers. Liability is a cost that providers cannot afford to overlook, and liability costs increase with treatment frequency.

- For patients of working age, the clinical trial should capture **employment data**, but employment should not be a component of the cost-effectiveness analysis.

- Because any economic savings are likely to occur downstream, **follow-up** should be for a minimum of one year and preferably longer.

(4) Epidemiological Monitoring

- A centrally located data collection system should be implemented. It could begin as a joint U.S.–Canadian registry that would then expand to additional countries. At the conclusion of the Task Force on Daily Hemodialysis meeting, physicians currently involved in daily hemodialysis met and discussed the creation of a **North American Registry**. Dr. Robert Lindsay was appointed chairperson of the committee to establish this registry, and a subcommittee was directed to develop appropriate guidelines. The registry will be Internet-based, with the information housed in London, Ontario, under the auspices of the International Society of Hemodialysis.

- The **goals** of epidemiological monitoring should be to
  (1) Evaluate a spectrum of outcomes before and after change from standard hemodialysis to frequent hemodialysis, using patients as their own controls
  (2) Evaluate a spectrum of outcomes with frequent hemodialysis versus standard hemodialysis, using “matched” controls and statistical adjustment
  (3) Describe national trends in frequency of hemodialysis and hours of hemodialysis per week, including mortality and hospitalization, using the United States Renal Data System.

- For the prospective study using patients as their own controls, **specific data elements** to be collected include
  - -Demographics
  - -ZIP code
  - -Prior and new prescriptions for treatment
  - -Reason for new modality
  - -Laboratory data
  - -Residual renal function
  - -Medications
  - -Co-morbidity
  - -Quality of life
  - -Employment status
  - -Vascular access and history
  - -Dialysis unit characteristics
  - -Contact number/person
  - -Travel time and distance from home for patient
  - -Training status of home patient
  - -Other data needs as they occur

- **Outcomes** that should be recorded include
  - -Follow-up laboratory data at one month and six months
  - -Change of prescription for treatment and reasons
  - -Events (infection, cardiovascular, other), hospitalization
  - -Vascular access
  - -Residual renal function
  - -Quality of life
  - -Death

- A **second prospective study**—a matched controlled study—should be conducted, with patients in the same dialysis units. The same data should be collected as listed above.

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