Cost-Effectiveness of Nutrition Therapy in the MDRD Study

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I. INTRODUCTION

For many years, the development of severe renal disease was a signal of an imminent death. The launch of hemodialysis for the management of end-stage renal disease (ESRD) in March 1960, however, noted a marked change in treatment of ESRD, and subsequently, it's mortality. Subsequent developments have included peritoneal dialysis, home hemodialysis, and renal transplantation. At present it is possible for persons developing severe renal disease to survive for long periods of time.

While the prognosis for persons with ESRD is improving, it appears that ever-larger numbers of individuals are developing ESRD. By the turn of the century, it is estimated that more than 300,000 persons will be enrolled in the federal ESRD program[1]. Of this number, about 85,000 will be new patients entering the program for the first time.

Such large projections suggest that the future economic burden of ESRD will be significant. In 1990, the total cost of care for patients with ESRD was close to $7.26 billion[1]. This figure includes payments from federal, state, and private sources, but does not include the cost of disability or Social Security Payments. The average cost per patient is now over $50,000 per year[2].

Given this forecast, increasing emphasis is being placed on identifying factors and treatment strategies that can be identified and implemented to prevent a person from developing ESRD in the first place, or to reduce the progression to ESRD. Recent studies suggest that attention to hypertension, nutrition, acidosis, severe anemia may be beneficial.

Nutritional Therapy

A large debate currently surrounds the question of the effectiveness of dietary protein restriction as a treatment for patients with moderate, or early, renal disease, and it's ability to delay the onset of ESRD. Studies in laboratory animals have shown that dietary restriction of protein slows the progression of renal disease and its ability to delay the onset of ESRD. Earlier studies in humans have likewise suggested beneficial effects of low-protein diets on renal disease. However, these studies, in general, have been limited in their experimental design[3,4,5].

The Modification of Diet in Renal Disease (MDRD) Study was a randomized clinical trial designed and implemented in 1989, in part, to determine the effects of

[1] Morbidity and mortality of dialysis. NIH Consensus Statement 1993 Nov 1-3;11(2):1-33

[2] US Renal Data System. The economic cost of ESRD, vascular access procedures, and Medicare spending for alternative modalities of treatment. Am J Kid Dis 30(Suppl. 1):S160-177, 1997.

[3] Klahr S. The Modification of Diet in Renal Disease Study. New Engl J Med 320:864-866, 1989.

[4] MDRD Study Group. The Modification of Diet in Renal Disease Study: design, methods, and results from the feasibility study. Amer J Kid Dis 20:18-33, 1992.

[5] Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G for the MDRD Study Group. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. New Engl J Med 330:877-884, 1994.

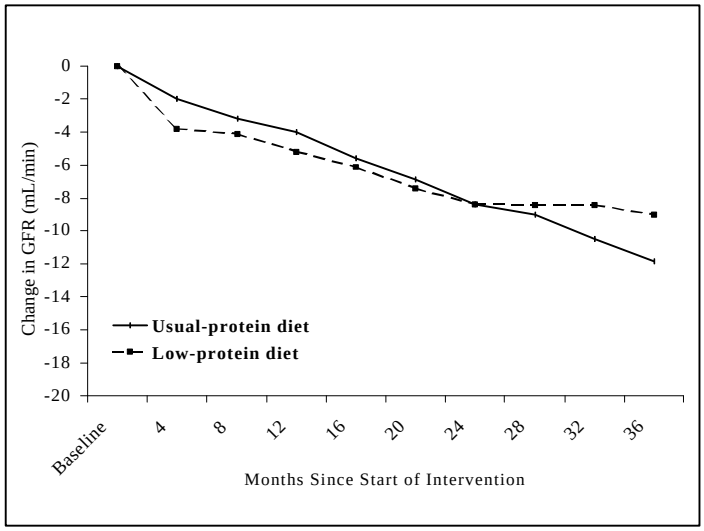
dietary protein restriction on progression of renal disease. It was comprised of two studies related to nutrition;

- one to assess the value of low protein diets (0.58 g/kg bw per day) in comparison to usual protein diets (1.3 g/kg bw day)(Study A),
- another to assess very low protein intake diets (0.29 g/kg/day) relative to low protein diets (Study B). Persons on very low protein intakes received ketoacid supplements to raise their total protein to 0.58 g/kg bw per day.

In Study A, 585 patients with moderate renal disease (baseline glomerular filtration rates (GFR) of 25 to 55 ml/min per 1.73 m^2) were randomly allocated to a low protein diet or a usual protein diet. Study B consisted of 255 patients with advanced renal disease (baseline GFR; 13 to 24 ml/min per 1.73 m^2) randomly assigned to either a low protein diet or a very low protein diet. The primary outcome measure was the rate of change in GFR[5].

Initial results of the MDRD did not show a beneficial effect of a low-protein diet on the progression of renal disease[5]. In Study A, the rate of decline of GFR from baseline to 3 years was not significantly different between the diet groups. This was attributed to a nonlinear GFR decline and a limited duration of follow-up. Those in the low-protein diet group demonstrated a faster rate of GFR decline in the first four months than did those in the usual-protein diet group. However, after four months the mean decline in GFR was slower in the low-protein group as compared to the usual-protein group (Figure 1).

Figure 1: Estimated Mean Change in GFR from Baseline in MDRD Study A Participants



The risk of renal failure or death was lower, but not significantly so, in the low-protein group compared to the usual-protein group (relative risk, 0.65; 95% CI, 0.38 to 1.19; p=0.10). The investigators concluded that a longer follow-up period might be necessary to demonstrate the beneficial effects of a low-protein diet in patients with a higher baseline GFR.

In Study B, there was a trend (p=0.07) towards a slower decline in mean GFR in the very low protein diet group versus the low-protein diet group. In patients with advanced renal disease (Study B), secondary analyses demonstrated a correlation between achieved protein intake and rate of decline in GFR[6].

More recently, a meta-analysis of five studies[7], including MDRD Study A, reported a beneficial effect of a low-protein diet on the incidence of renal failure or death (relative risk: 0.67; 95% CI: 0.50, 0.89; p=0.007). All studies had a follow-up of more than one year, and information about the number of patients who died or developed renal failure was available. The prescribed protein intake in the low-protein diet arms of these studies ranged from 0.40 to 0.60 g/kg per day. These results are consistent with those from an earlier meta-analysis by Fouque and others[8] (odds ratio: 0.54; (0.37:0.79); p<0.002).

Overall, the research findings in adults suggest that there may be a beneficial effect over the long-term from a low protein diet in preventing the progression of renal disease. Two meta-analyses also support the benefits of a low protein diet. However, dietary interventions for patients with moderate renal disease have not been widely adopted. One recent workshop[9], for example, concluded that the use of a protein-restricted diet in moderate renal disease to slow the progression of renal failure was inconclusive. This workshop recommended that patients with moderate disease receive a standard protein diet.

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[6] Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progressions of advanced renal disease in the MDRD Study. Amer J Kid Dis 27:652-663, 1996.
[7] Pedrini MT, et al. The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal disease: a meta-analysis. Ann Intern Med 124:627-632, 1996.
[8] Fouque D, et al. Controlled low protein diets in chronic renal insufficiency: meta-analysis. BMJ 304:216-220, 1992.
[9] Striker GE. Report on a workshop to develop management recommendations for the prevention of progression in chronic renal disease. Nephrol Dial Transplant 10:290-2, 1995.

The purpose of this study is to examine the possible long-term benefits of dietary intervention in moderate renal disease and to estimate it's economic efficiency. The focus of the report is on the value of low-protein diets (0.56 g/kg bw) in delaying the time to dialysis and reducing ESRD costs. The MDRD Study did not continue long enough and was not designed to demonstrate reductions in dialysis and ESRD. This study, then, represents an extension of the available information on diet and renal disease.

II. SPECIFIC AIMS

The overall goal of this study is to evaluate the cost-effectiveness of nutrition therapy in patients with moderate renal disease using information from the MDRD Study. This involves an evaluation of the costs of nutrition therapy and potential long-term benefits, and the potential savings associated with the treatment.

The basis for this analysis lies in two areas:

(a) identifying the resource utilization, treatment and food costs associated with selected stages of renal disease, and
(b) identifying the long-term impact of nutrition intervention on the development of end-stage renal disease.

The hypothesis of this work is that a dietitian-based intervention, which establishes low dietary protein intake for patients with moderate renal disease, is cost-effective relative to the alternative strategy of a usual protein intake diet. Implicit in this hypothesis is the argument that protein restriction diets can delay the development of ESRD, and thus, the costs saved from the treatment of ESRD would outweigh the costs of additional dietitian services and the costs associated with the protein restriction diets.

III. METHODS

This investigation represents a cost-effectiveness analysis of the 585 subjects enrolled in the Study A portion of the MDRD clinical trial. Trial-related information on these subjects (n=291 on low protein diets, N=294 on usual protein diets) was collected from the Data Coordinating Centre for the MDRD trial for use in the analysis. This included survey information documented during the trial on the use of dietitian and physician services, survey information on the need for hospitalization outside of the trial, survey information on indirect costs and quality of life, laboratory information on glomerular filtration rates (GFR), and outcome information on the development of end-stage disease.

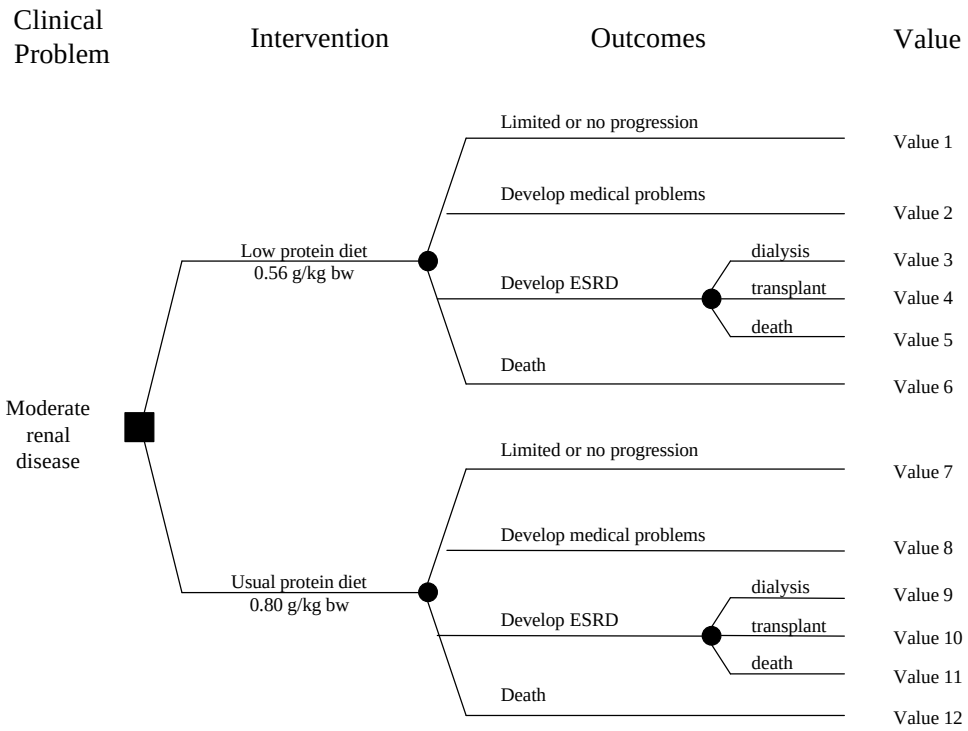
An important part of the economic analysis was our assessment of the likely long-term costs and outcomes of subjects in both diet groups. The average period of follow-up in the MDRD trial was about 2.2 years. Further, many of the study subjects did not reach the end-stages of renal disease by the end date of the trial. To estimate the impact of the nutrition intervention over a longer time frame, we developed a model, based upon several decision analysis techniques, to simulate the likely renal disease course (i.e., progression of moderate disease to ESRD) in each subject over time.

Decision analysis, as a science, represents a systematic and quantitative approach to assess the value of different decision options[10,11]. It is usually one of the first steps taken in a cost-effectiveness analysis[11]. In this report, the decision is whether a low protein diet or a usual protein diet is a better approach to the management of moderate renal disease. There are generally several possible outcomes related to each decision. To illustrate the decision options and the potential outcomes, investigators often construct a "decision tree".

Figure 2 portrays the decision tree related to our study question. In the decision tree, the clinical problem of interest is the most appropriate treatment for individuals with moderate renal disease. The decision points are whether to pursue a low protein diet intervention, or maintain the usual protein diet. The possible outcomes that one may observe with each decision include the maintenance of the current health status, defined as having renal disease not requiring dialysis, the development of medical problem that requires an individual to discontinue a low protein diet, the development of end-stage renal

[10] Weinstein MC, Fineberg HV. *Clinical Decision Analysis*. Philadelphia, WB Saunders Co., 1980.
[11] Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis*. New York, Oxford University Press, 1994.

Figure 2: Dietary Intervention and Renal Disease Decision Tree



disease, which may be treated through dialysis or transplantation, and death. Each of these endpoints will have varying costs associated with them.

As one can see from figure 2, the number of potential outcomes (n=12) is quite high. Considering this over the long-term, the process of identifying where an individual may fall at each year of follow-up can become complex. To address this, we developed a Markov process model. Markov models are often used in cost-effectiveness analyses to examine complex processes, where individuals may move from one health outcome to another over time[12].

The analysis of a Markov model is comprised of four steps[11]; identifying relevant health states, identifying a relevant length of time to test for changes in outcomes, identifying the probability of moving from one health state to another, and estimating the likely outcomes over the life of the model.

Health States in the Model

Figure 3 outlines the major health states that we have considered in the Markov model and their relationship to each other. The key health states include:

(1) The moderate renal disease health state, which includes all individuals at study entry with GFR values between 25-55 ml/min/1.73 m^2 and those in the trial who maintain a GFR value above 9.0 ml/min/1.73 m^2.

(2) The medical condition health state, which includes persons identified in the MDRD trial as having a medical stop point requiring the discontinuation of either diet intervention. After the time frame of the trial, we assumed that no individuals would reach this health state.

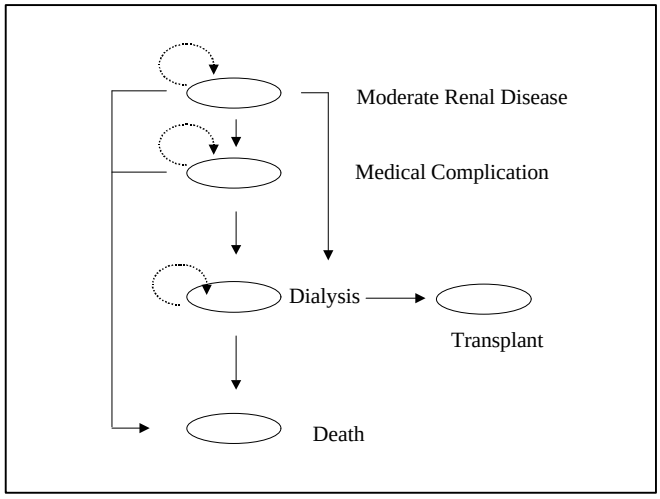
[12] Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 3:419-458, 1983.

(3) The dialysis health state, which includes individuals identified as using dialysis by the MDRD study staff, and those individuals predicted to require dialysis by the model.

(4) The renal transplantation health state, which includes persons undergoing a transplant, either identified by the MDRD study staff or predicted by the model.

(5) Death.

Figure 3: Health States in the Markov Simulation Model



The primary focus of our analysis was on the transition from moderate renal disease to the initiation of dialysis. This may be a simplistic model in the sense that we assumed that individuals would maintain their respective diet interventions until the point of requiring dialysis, or until they had developed a significant medical condition necessitating the discontinuation of the intervention. Several individuals in the MDRD trial attained a health state termed as "GFR stop point." These individuals had significant declines in renal function from their baseline values and most were discontinued from the study. We did not include this endpoint as a significant health state, because it is not a relevant health state in most clinical practice settings. GFR is a measure that is commonly done in renal disease research studies, but not a measure that is done very frequently in the clinical setting.

Interval Cycles in the Model

We evaluated the likelihood of moving from one health state to another in 4 month intervals for a total of five years (15 cycles). This interval period was chosen because glomerular filtration rate data were collected on a 4-monthly basis in the MDRD study. A cycle based upon a 12 month interval would neglect much of the renal function data, and possibly lead to a less reliable model.

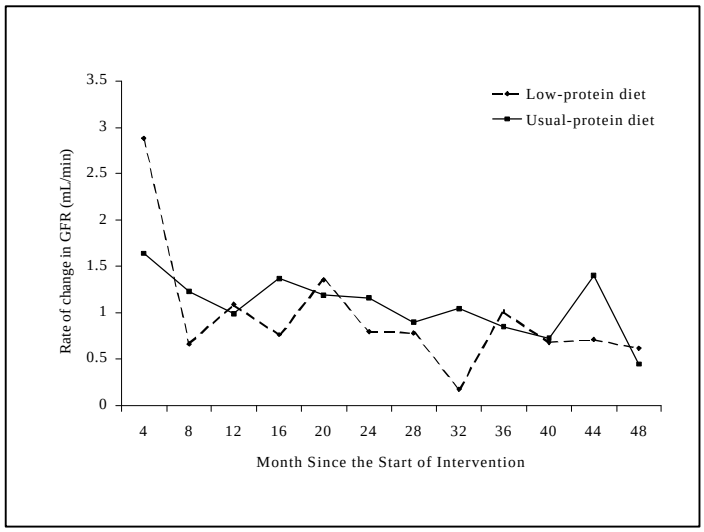
Transition Probabilities between Health States

Information on the probability of moving from one health state to another was obtained from several sources. We estimated the risk for progression of renal disease by evaluating the rate of change in GFR from one 4-month interval to the next using information available from the MDRD study. We examined the degree of change through several steps. First, we assumed that each individual started into the model with the GFR level identified for them at the baseline examination of the MDRD study. For the few individuals with missing baseline data, we assumed that they began with a GFR value of 40 ml/min/1.73 m^2. This was the mid-point value of the participants in Study A of the trial.

Second, all existing GFR data from the MDRD study were applied to the model for each 4-month cycle in which the subject was enrolled in the trial. The rate of change in GFR for these cycles, thus, represents the actual values observed in the study. Third, for the intervals in which the subject was not in the MDRD study (i.e. most of years 3, 4 and 5), we assumed that their expected rate of decline in GFR from one interval to the next would be similar to that identified from other participants in the trial.

Figure 4 portrays the rate of decline in GFR observed from the study participants at each 4-month interval. Data on the decline in GFR were available from more than 100 participants through 40 months of follow-up. After this point, we assumed that rate of decline would remain constant for each diet group, and would reflect the average of the values observed at months 36, 40 and 44 of follow-up. For participants on a low protein diet, this resulted in an average decline in GFR of 0.67 ml/min/1.73 $m^2 \pm 4.0$ for each cycle. For individuals on the usual protein diet, the subsequent average decline in GFR was 0.85 ml/min/1.73 $m^2 \pm 3.5$ for each interval.

Figure 4: Average Rate of Change in GFR (from Previous Value) by Diet Group



Another major component of our analysis was the point in time at which an individual initiated dialysis. This was evaluated in the model through two means. One, we assumed that the information on the initiation of dialysis identified by the MDRD staff was reliable and accurate. Dialysis data was identified for several individuals in the study, and this was applied directly to the model. All individuals in the trial (up to the point in time of the last assessment of GFR) who were not identified as starting dialysis were assumed to have not reached this health state.

Two, individuals reaching a GFR value of less than 9.0 ml/min/1.73 m^2 at any cycle (after the point of their MDRD study data) were assumed to initiate dialysis in that cycle. This decision rule was based upon the average GFR value for all participants in Study A and Study B who went on dialysis; 9.28 ml/min/1.73 m^2.

Secondary health states in the model include renal transplantation, death, and medical complications. We included the transplant health state in the model because existing data demonstrates that costs are much lower for persons in ESRD with a functioning transplant than for those on dialysis. Data on study subjects who underwent a transplant during the time of the MDRD study were included in the model at appropriate time intervals. Further, we assumed that a proportion of patients on dialysis would receive a transplant over time. Using data from the US Renal Data System, we noted the chance of receiving a transplant for the dialysis cohort as 6.2% per year.

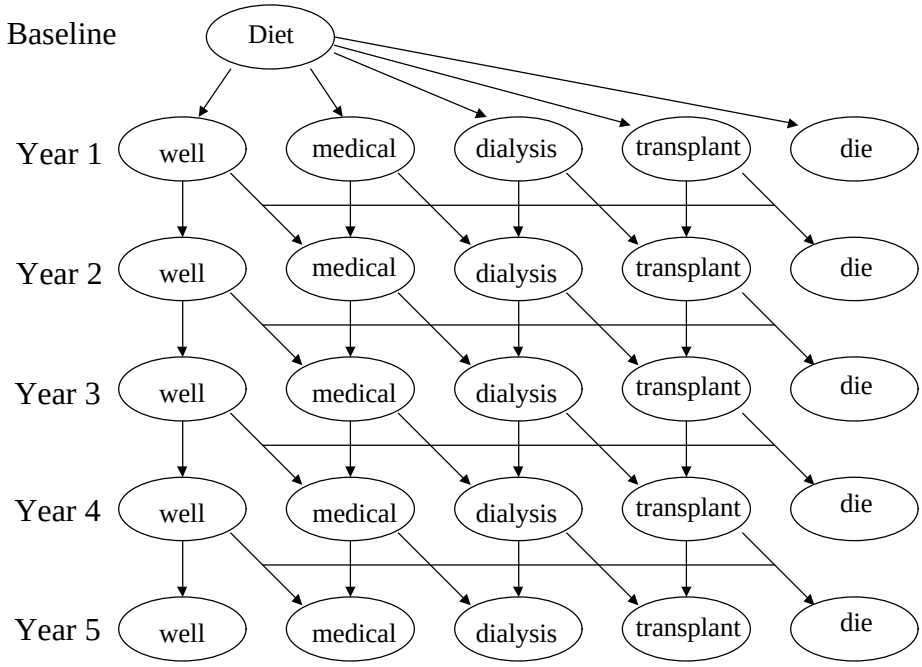
We included mortality as a health state in the model, since several studies have identified a greater risk of dying for persons in ESRD. We identified data on the annual risk of dying from the US Vital Statistics System for the general population, and the US Renal Data System for the population receiving dialysis. We used three types of mortality probabilities (Appendix Table A1.). Persons with moderate renal disease were assumed to have a mortality risk similar to the general population. Persons on dialysis in the model were assumed to have a mortality risk similar to the overall dialysis population in the United States, adjusted for race, gender, and primary cause of ESRD. Those individuals with a transplant were assumed to have a risk similar to the ESRD population with a transplant.

A medical condition health state was included in the model to include the information of individuals in the MDRD study who were identified as having medical problems severe enough to discontinue the dietary interventions. All individuals reaching this health state were identified from the MDRD study, and were assumed to adopt a usual protein diet thereafter. Further, we assumed that they would be seen in a medical environment on a bi-monthly basis, rather than a monthly basis. The transition probabilities assigned to individuals in this health state were similar to those for the other individuals in the study.

Estimating Outcomes over Time

To describe and compare the expected costs and benefits of the dietary interventions over the full 5 years, the Markov process model was simulated on a computer with Monte Carlo sampling techniques using the @Risk software program. The simulation was continued until 5000 iterations were completed. One iteration represents one estimate of the expected outcomes for the cohort of 585 Study A subjects followed for five years. Figure 5 illustrates the basic process of the model. The simulation begins by identifying which dietary group the individual belongs to and the baseline GFR value. Next, estimation is made of the number of persons expected in each of the five health states at each 4-month interval. This estimation is based upon the transition probabilities described above.

Figure 5: Simplified Flow Chart of Simulation Model



An individual can only be in one health state at each interval, and their risk for progressing to another health state is dependent upon their current health. For simplicity, the chance for undergoing a transplant or dying was modeled on a yearly basis, rather than a 4-monthly basis.

Each health state has a cost associated with treatment and food costs assigned to it, as well as a quality of life estimate. If the model determines that the person has died, then they are not assigned any additional costs. We did not, for example, include the indirect costs of foregone earnings in the model. If the model determines that a dialysis patient has undergone a transplant, then all subsequent intervals are assigned costs associated with a transplant. At the end of the simulation, the costs and quality of life data are summed over the intervals to determine the total costs and benefits. The results presented below outline the average outcome expected after 5000 simulations

Cost-Effectiveness Analysis

The results from the decision analysis model formed the basis of the cost-effectiveness analysis. Each of the 5000 simulations ran produced an estimate of the number of persons expected in each health state over time. Cost and quality of life measures were assigned to each state. As part of this exercise, we also obtained a simulated estimate of the average total costs and the likely outcomes expected by summing the 4-month estimates. These data were then compared for each diet group in an incremental analysis. The incremental analysis examined the difference in costs between the low protein and usual protein diet groups relative to the difference in outcomes. The ratio of the incremental costs to the incremental benefits produces an estimate of the cost of using one intervention in preference to another[11].

Perspective

A common question in cost-effectiveness analyses is the issue of "to who is the intervention cost-effective". In general, it is possible to consider an economic evaluation

from a number of perspectives, including that of society, health care payers, patients, and the government. We adopted a societal perspective since it usually includes more costs and benefits than other perspectives. Also, there was a great deal of information in the MDRD Study to consider costs encountered by the study subjects.

The societal perspective considers direct and indirect costs associated with the disease and intervention under study. In our evaluation, we examined the direct medical costs related to the intervention, including outpatient visits, dietitian services, laboratory tests, and subsequent inpatient admissions. We also included direct, non-medical costs, such as the costs of travel to the medical appointments, associated childcare costs, and lost wages. As a low-protein diet may require the purchase of different foods than a usual-protein diet, we examined the food costs associated with each intervention. Dialysis and transplant costs were obtained to consider the impact of these long-term outcomes.

While our approach was that of a societal perspective, some cost components were not included in the final model. We identified the direct, non-medical, costs associated with moderate renal disease, but could not locate similar information for subjects in ESRD. The indirect costs related to lost productivity due to disability and premature death also were not included. Information on the employment characteristics of the study subjects was available, but incorporating it would have increased the complexity of the model to a considerable extent.

Time Horizon of the Analysis

We selected a five-year time horizon for the cost-effectiveness analysis. This time frame served two purposes. One, it allowed for a significant quantity of costs and outcomes to be recorded. Two, it was a length of time in which questions regarding the compliance and safety of dietary intervention could be minimized. Compliance to a low-protein diet has proven to be a difficult task in the past. Our evaluation of the MDRD data found differences in adherence to diet by the intensity of the intervention. Subjects in the low-protein diet group were non-compliant at a greater rate than those individuals in the usual-protein diet group (64% vs. 44%). Thus, we know that non-compliance is an issue of concern in the short-term. The degree to which compliance may be a factor over the long-term is not clear.

The level of safety related to a protein-restricted diet is also of concern. Protein-calorie malnutrition is a potential side effect of the protein-restriction diet. Analyses of the MDRD data[13] found that protein and energy intakes were lower in low-protein and very-low-protein diet groups. However, over the course of the study, lower achieved protein intake appeared to be safe. After controlling for baseline nutritional status and energy intake, lower achieved protein intake was not correlated with higher rates of death, hospitalization, or with decline in most indicators of nutritional status. It appears that low- and very-low-protein diets are safe for 2 to 3 years in patients with moderate to advanced renal disease, but given the decline in some of the nutritional status indices, patients' nutritional status and protein and energy intake should be closely monitored.

Discount Rate

We report all costs in 1993 dollars. Since costs in future years after the initiation of an intervention have less value than the first year costs[14], we discounted both costs and outcomes at 3% per year.

Calculating Costs

The interest of this analysis was to identify and describe the costs associated with each health state included in the decision model. To estimate costs, we examined the resources used in the treatment of moderate and end-stage renal disease for the low-protein and usual-protein diet groups. Unit cost estimates identified from the literature were then applied to these resource figures. Some figures were adjusted to 1993 dollars using the medical care components of the CPI as the adjudicator.

Treatment Costs

Costs for the low-protein and usual-protein dietary interventions were determined primarily from data on the actual resources used in the MDRD Study, excluding research costs. Several items were the same for both diet

[13] Kopple JD, Levey AS, Greene T, et al. Effect of dietary protein restriction on nutritional status in the MDRD Study. Kidney Intl 52:778-791, 1997.

[14] Krahn MK, Gafni A. Discounting in the economic evaluation of health care interventions. Med Care 31:403-418, 1993.

groups. These included the monthly use of physician and dietitian services during an outpatient visit, the monthly collection of 24-hour urine value to determine dietary adherence, and the bimonthly ascertainment of serum creatinine and serum albumin. Measures of GFR by iothalamate clearance were completed every 4 months during the trial. This assessment, though, is not likely to be done in a typical clinical setting. Thus, we excluded the assessment of GFR by iothalamate from our analysis.

Table 1 lists the specific resources included in our analyses, their unit costs in 1993 dollars, and the sources of the cost data. Physician, dietitian, and hospitalization costs each reflect expenses associated with governmental and non-governmental salaries/hospitals. Physician costs reflect the median nephrologist salary, plus fringe benefits and incentive bonuses. Dietitian costs reflect the salaries reported from a 1993 survey of the American Dietetic Association membership.

Annual dietitian and physician salaries were broken down in to hourly rates and multiplied by the average time spent with patients on the respective interventions. This information (the average amount of time per physician visit and per dietitian visit) was drawn from MDRD data. The time data were averaged over four month intervals.

Food Costs

To examine food costs, we located the 3-day food record reports of 60 randomly selected trial participants. Of the 60 records examined, 20 were identified from the baseline period (10 Study A subjects, 10 Study B subjects), and 40 were identified from the 12 month visit (20 Study A subjects, 20 Study B subjects). Further, of the participants in Study A, five records from each of the following groups were selected:

- adherent to diet moderate in protein and phosphorus
- non-adherent to diet in moderate in protein and phosphorus
- adherent to a low protein and phosphorus diet
- non-adherent to a low protein and phosphorus diet

This design allowed us to examine changes in foods consumed related to the dietary intervention, and the differences between low and usual protein diets, as well as differences between the records of compliant and non-compliant subjects.

We abstracted the food records into a dietary cost software program (Nutritionist IV, version 3.0). Food costs contained in this program reflect 1991 food prices from the Pacific Northwest Grocery Association. For items on the food records that were not included in the program, we imputed food costs by selecting a food similar in nutrient content and food group from the software database. Values for low protein food products used in the trial in Study B were assigned using the costs recorded on study invoices. Vitamin and supplement costs for subjects in Study B were obtained from the manufacturer and the Red Book[15].

Our analysis found no large difference in the average daily food costs between the treatment groups in the trial, other than a higher cost for the very low protein diets supplemented with ketoacids. This was due to the high cost of the ketoacid supplements. These supplements are not currently available to consumers. Thus, since this treatment option is not a viable policy issue, we did not include Study B participants in the analysis.

Dialysis Costs

The resources used in the management of dialysis were the bulk of the costs identified in this analysis. We examined the guidelines for nutritional care during dialysis. We obtained information on the costs related to dialysis from the US Renal Data System. We assumed that the cost of dietitian services would be included in this figure. Cost data from the 1996 Annual Data Report reflect 1994 prices. This figure was adjusted to 1993 dollars using the medical care component of the CPI, and dividing by the ESRD point prevalence for 1993.

Transplant Costs

Several studies in the literature note lower costs associated with functioning transplant patients when compared to persons on dialysis. We obtained information on transplant costs from the US Renal Data System. For the years 1991-95, the average payment per person related to transplants was $16,000[16]. This cost reflects the

[15] *1993 Drug Topics Red Book*. Montvale, NJ, Medical Economics Data.

[16] US Renal Data System. The Economic Cost of ESRD, Vascular Access, Procedures, and Medicare Spending for Alternative Modalities of Treatment. Amer J Kid Dis 30(2) (Suppl. 1) S160-177, 1997.

Table 1: Unit costs and data sources for direct health care resources used in analyses.

Item	Description	Unit Cost (1993 dollars)	Data Source
Physician visit	nephrologist salary, 1993	$73.44/hour ($152,752/year)	Hospital & Healthcare Compensation Service: *1994 Physician Salary Survey Report*.[17]
Dietitian visit	median income, clinical nutrition	$15.44.hour ($32,116/year)	The American Dietetic Association, 1993 membership database[18]
Hospitalization (DRG 316 - renal failure)	average total charge per discharge, 1993, all U.S. hospitals	$11,649/hospitalization	HCIA Inc. and Ernst & Young: *1995 The DRG Handbook: Comparative Clinical and Financial Standards*[19].
Serum creatinine	1994 price, adjusted to 1993 dollars using medical care component of CPI[20]	$6.79/test	Rodby, et al., 1996
Chem 18 lab test	1994 price, adjusted to 1993 dollars using medical care component of CPI	$15.34/test	Rodby, et al., 1996[21]
24-hour urine	1994 price, adjusted to 1993 dollars using medical care component of CPI	$7.02/test	Rodby et al., 1996
Dialysis		$48,717/year	USRDS 1996 Annual Data Report[22] Executive Summary.
Transplant		$16,000/year	US Renal Data System[23] 1991-1995

[17] 1994 Physician Salary Survey Report. Hospital and Health Care Compensation Service & John R. Zabka Associates, Inc. February 1994.
[18] Bryk JA, Soto TK. Report on the 1993 membership database of the American Dietetic Association. J Amer Diet Assoc 94:1433-1438, 1994.
[19] The DRG Handbook 1995; Comparative Clinical and Financial Standards. HCIA Inc. and Ernst & Young, 1996.
[20] US Bureau of Labor Statistics. CPI Detailed Report, January 1996.
[21] Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. Diabetes Care 19:1051-1061, 1996.
[22] United States Renal Data System. 1996 Annual Data Report; Executive Summary. Am J Kidney Dis 28 (suppl 2):S12-S20, 1996.
[23] US Renal Data System. The Economic Cost of ESRD, Vascular Access, Procedures, and Medicare Spending for Alternative Modalities of Treatment. Amer J Kid Dis 30(2) (Suppl. 1) S160-177, 1997.

Medicare payments for persons with a transplant in the ESRD program. The figure does not include costs of organ procurement.

Calculating Outcomes

We examined several outcomes in the decision model. The primary measure analyzed was the difference between diet groups in the incidence of dialysis and the time from baseline to the development of dialysis. As a summary measure, we also considered the number of ESRD free years, defined as the number of years that a subject was living without being on dialysis or a transplant.

Secondarily, we examined the impact of the intervention on mortality outcomes. We identified the number of deaths expected in each diet group and charted the likely survival curves. Two summary measures related to mortality were also investigated; life years gained and quality adjusted life years gained. Quality adjusted life years (QALYs) consider the impact of quality of life in any observed changes in length of life.

We calculated QALY scores from data on quality of life collected in the MDRD Study. As part of the trial, the Quality of Well-Being Scale was solicited from participants on an annual basis. This index assesses health-related quality of life and translates it into a scale between 0 and 1; with 1 being equal to perfect health and 0 being equivalent to death. We used the results from the Quality of Well-Being surveys for our calculation of QALYs. Table QOL shows the average mean scores for participants in the MDRD at various points in time. The scores identified at the end of the trial were used in our analysis. Not expectedly, quality of life scores were lower amongst patients on dialysis. Also of note were the higher scores in those who underwent a transplant.

Table 2. Mean Total Quality of Well Being Scores by Level of Renal Disease

	Baseline	Year 1	Year 2	End of Trial
Moderate Disease	0.75	0.75	0.74	0.75
Dialysis	0.72	0.69	0.69	0.67
Transplant	0.72	0.77	0.64	0.72

IV. Results

Resource Utilization and Costs Associated with Renal Disease Health States

We examined the manner in which individuals would be treated at each health state included in the decision model to identify associated resources and costs. Many of the resources associated with the low-protein and usual-protein interventions were dictated by the protocol of the MDRD Study. For the other health states, we gathered information on expected treatments and use of dietary services from the literature, primarily the United States Renal Data System and the current recommendations of the ADA.

Resources Related to the Dietary Interventions

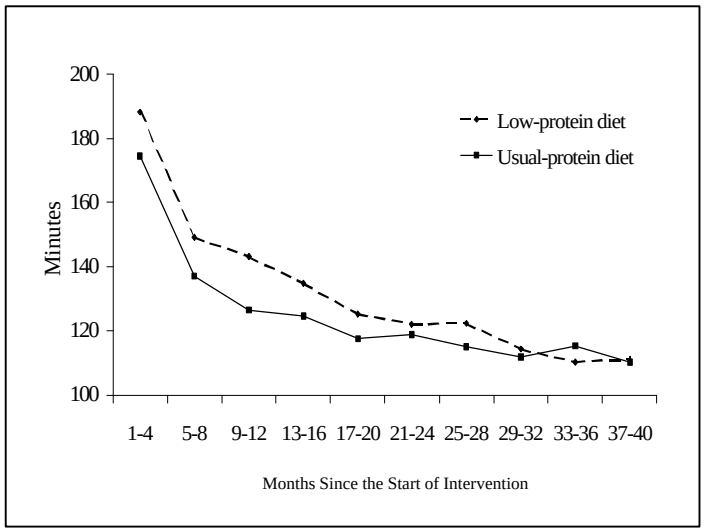
Our examination of costs focused on the medical and dietitian resources used by the participants in the trial, excluding research costs, non-medical direct costs, and the food costs associated with the diets prescribed in the trial. We requested and obtained data from the MDRD data coordinating center to examine these items. Data on the use of resources within the framework of the trial protocol were very complete. For visits occurring outside of the study protocol, the data related to hospital admissions were the most reliable and complete.

By the design of the study protocol, participants in the trial had monthly visits for the medical management of renal disease. Dietitian and physician services were used at each visit. As part of the trial, the dietitians at each clinical center recorded the amount of time spent in clinical and related administrative activities for each patient. At the end of each visit, the time recorded for each activity (e.g., preparation, counseling, charting) was totaled. This data was then used to derive the mean amount of time required per patient, per visit, in four-month time intervals, from baseline until the end of the study. Physician time requirements were also recorded and summed, and similar mean time estimates were calculated.

We found a distinct difference in the use of dietitian services by dietary intervention, particularly for the initiation of treatment. Over the first four time intervals, the

amount of dietitian time required by the two diet groups differed at statistically significant levels (Figure 6), with the low-protein diet group requiring more dietitian time. After this point in time (16 months post baseline), there was little difference in the use of dietitian services by diet group. Analysis of the time by physicians with the study participants showed no difference between the diet groups for each time interval examined.

Figure 6: Dietitian Services in the MDRD Study; Time Related to Dietary Interventions



We also examined the use of health care services outside of the study protocol by the participants. The strongest data available were those for the use of inpatient hospital admissions. Comparison of the frequency of hospital admissions after baseline found no difference between the diet groups (low-protein group: mean of 1.85 admissions post baseline; usual-protein group: mean of 1.88 admissions post baseline).

Direct non-medical costs can be important considerations in the use of health care services by patients. We examined the travel costs, lost wages, and childcare costs associated with clinic visits for each of the dietary intervention groups. Study participants filled out a questionnaire on these costs every 12 months during the trial. Our analyses found that these non-medical costs were remarkably similar for the low-protein and usual-protein diet groups (Table 3).

Table 3. Average direct, non-medical, costs related to medical visits for maintenance of medical and dietary regimen in moderate renal disease

	Low-protein Diet			Usual-protein Diet		
	1 year visit	2 year visit	3 year visit	1 year visit	2 year visit	3 year visit
Round trip travel	$26	$22	$13	$31	$22	$17
Child care	$ <1	$ <1	$ <1	$ <1	$ <1	$ <1
Foregone wages	$10	$7	$3	$16	$12	$13

Table 4 highlights the food costs we identified for the Study A participants. For both dietary interventions, food costs during the study were higher than those observed prior to the initiation of the intervention. Subjects on low protein diets had higher average daily food costs than those on usual protein diets. Food costs at Year 1 of the trial were used in the model for both diet groups.

Table 4. Average Food Costs for Subjects with Moderate Renal Disease by Diet Group

	Low-Protein Diet	Usual-Protein Diet
Baseline	$3.752	$3.752
One Year After Baseline	$4.655	$4.198

The Impact of Non-adherence to Diet

Non-compliance to diet was the primary side effect related to dietary intervention in the MDRD Study. Overall, subjects in the low-protein diet group were more often non-adherent to their diet prescriptions than those subjects in the usual-protein diet group (64% vs. 44%). We examined if differences existed in the use of resources between compliant and non-compliant subjects with respect to dietitian and physician services, and food costs.

To conduct this analysis, we obtained data from the MDRD data center for participants who were compliant and

non-compliant to diet regimens. To assess dietary adherence, ranges for estimated protein intake were established for both diet groups. Participants were defined as adherers if their estimated protein intake was within this predefined range, and if their food records showed that they were adhering to the prescribed eating pattern[24].

Dietitian and physician time fields were analyzed to examine if the amount of time spend with patients in each dietary assignment group differed by dietary adherence. In both the low-protein and the usual-protein groups, there was no difference between the adherers and non-adherers in the amount of dietitian time required at each visit. Similar results were found for physician time requirements. Food costs were slightly higher for persons identified as consistent non-adherers to their diets. However, as this difference was not statistically large, we assumed that the impact of non-adherence on food costs would be minimal. Thus, non-adherence to diet was not included as a factor in our cost analysis.

Resources Related to Medical Complications & Dialysis

Subjects developing medical complications during the MDRD trial were treated differently in our decision model. Based upon medical guidelines, we assumed that these individuals would see a medical team for the medical management of their renal disease on a bimonthly basis. We also assumed, conservatively, that they would be placed on a usual-protein diet.

For patients with ESRD requiring dialysis, treatments differ by the modality of therapy (e.g. hemodialysis, peritoneal dialysis), but generally involve a host of health care resources, including laboratory tests, nursing care, supplies, clinic services, physician services, and nutrition services. The Health Care Financing Administration and the US Renal Data System both maintain information on the quantity of health care resources used in ESRD.

With initiation of dialysis, the dietary prescription for individuals usually changes. We had no food record data for study participants on dialysis during the trial. However, the average protein intake of participants on the usual-protein diet was approximately equal to the recommended protein intake for dialysis patients[25]. We did not include the value of food costs in the dialysis health state, because the cost of food was negligible relative to the cost of dialysis treatment. Similarly, we assumed that the cost of health services related to a dietitian's services would be included in the overall cost figure for dialysis published by HCFA.

Annual Costs of Dietary Interventions

Table 5 summarizes the costs associated with each diet group by the stage of renal disease. For patients with moderate renal disease, we estimate that the annual cost of treatment and maintenance of a low-protein diet would be higher than that for a usual-protein diet. However, the difference was relatively small; on the order of $200 per year. We assumed that there would be little difference in cost between the dietary treatments for subjects who reached ESRD.

Table 5: Average Annual Costs by Renal Disease Health State

	Low-Protein Diet	Usual-Protein Diet
Moderate Renal Disease		
Dietitian Time	$ 408	$ 386
Physician Time	$ 259	$ 261
Laboratory Costs	$ 217	$ 217
Food Costs	$ 1700	$ 1532
TOTAL	**$ 2584**	**$ 2396**
Medical Complications	$ 2041	$ 2030
End-Stage Renal Disease		
Dialysis	$ 48,717	$ 48,717
Transplant	$ 16,000	$ 16,000

[24] Milas NC, et al. Factors associated with adherence to the dietary protein intervention in the MDRD Study. J Amer Diet Assoc 95:1295-1300, 1995.

[25] Suggested Guidelines for Nutrition Care of Renal Patients, 2nd Edition. Wilkens, Schiro (Eds). American Dietetic Association, Chicago, IL, 1992.

Long-Term Impact of Nutrition Intervention on the Development of ESRD

Renal disease endpoints in the MDRD trial

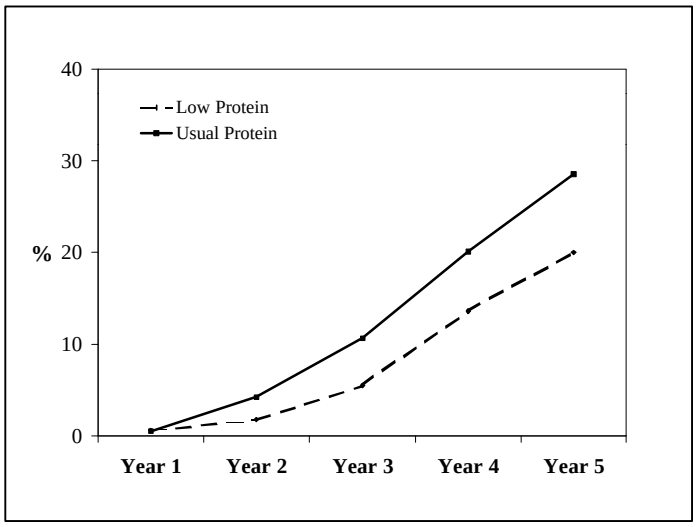
In the model, we sought to identify the relative progression of renal disease in the study participants by treatment arm, and then relate this to the use of health services. Several renal disease data points were identified in the MDRD Study during the time of the trial. We obtained study data on the frequency of these outcomes. During the time of the trial, 43 patients in Study A progressed from moderate to end-stage renal disease requiring dialysis or transplant. Overall, 37 participants went on dialysis, at a time span averaging of 2.75 years from baseline. Of the 37 going on dialysis, 25 were in the usual-protein diet group and 12 were in the low-protein diet group. Seven participants had a renal transplant.

These data show a pattern of greater progression to end-stage disease in the patients on the usual protein diets. However, there are two points of concern. One, the results of the trial found that this difference in dialysis between dietary groups was not statistically significant. Two, the meaning of this from a cost-effectiveness point of view will depend upon the time difference in which it takes for end-stage disease to develop. In economic terms, a shorter period of time for a participant to develop end-stage disease is meaningful, as the high costs of dialysis and transplantation may offset the greater costs seen for intervention with a low-protein diet. To examine this issue, we extended this analysis by analyzing the Markov process model to consider the number of renal disease endpoints over 5 years.

Development of ESRD over 5 years

After running the simulation for 5000 iterations, the analysis indicates that low-protein diets reduce the incidence of dialysis and subsequent mortality. After five years of intervention, the expected cumulative incidence of dialysis for subjects on low-protein diets was 20% compared to 29% for the subjects on usual-protein diets (Figure 7). The incidence of dialysis was actually higher for the low-protein group in Year 1, but switched thereafter with increasing dialysis cases being observed at each year for the usual-protein group.

Figure 7. Estimated Cumulative Incidence (%) of Dialysis by Diet Group over Time



The average time to dialysis (from baseline) in the low-protein diet group was 3.43 years. In the usual-protein group it was 3.22 years. The estimated expected difference in the time to requiring dialysis between the groups was 0.202 years, or 74 days.

The benefits of protein-restricted diets can also be expressed in terms of the number of years than an individual spends living without being in the ESRD health state. Subjects on low-protein diets spent more time, on average, on treatment and less time on dialysis (4.3 years free of ESRD vs. 4.07 years). This translates to an average of 84 extra days free of ESRD.

As ESRD is associated with a marked increase in mortality risk, we next examined the potential influence of dietary intervention on length of life and quality of life. Overall, we observed that the risk for death was higher in the usual-protein diet group. After five years, the model estimates that 11% of the usual-protein diet cohort would have died compared to 6.5% of the low-protein diet cohort (Figure 8). Averaged across each intervention group, a subject undergoing a low-protein diet intervention would be expected to have 4.59 life years over the 5-year model. A subject on a usual-protein diet would have 4.48 life years (Table 5). The difference in life years between the groups represents an additional 40 days for the low-protein diet intervention.

Figure 8. Estimated Survival by Diet Group over Time

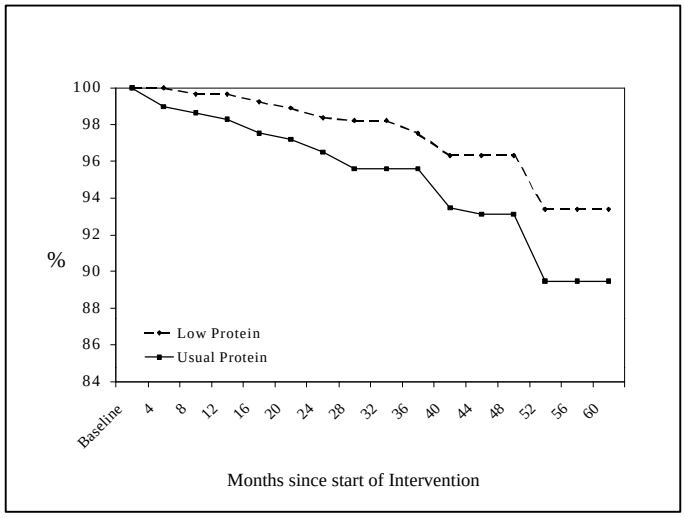


Table 5. Estimated Values per Patient over Five Years by Diet Group (discounted at 3%)

	Low Protein Diet	Usual Protein Diet	Difference
Total Costs	$ 24,252	$ 29,178	$ 4,926
Quality Adjusted Life Years	3.42	3.33	0.09
Life Years	4.59	4.48	0.11
ESRD Free Years	4.30	4.07	0.23

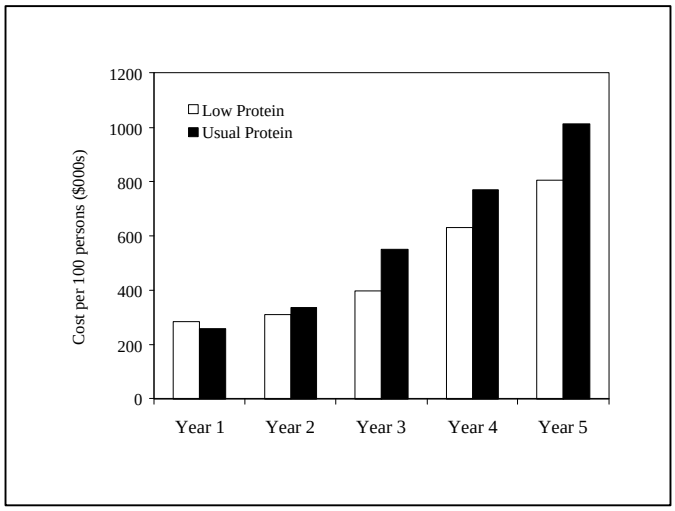
One issue that often arises in treatments that extend life is the question of the quality of life expected when life-expectancy is prolonged. Our evaluation found that subjects on a low-protein diet would also have a higher quality of life in the years that they were living (3.42 QALYs vs. 3.33 QALYs) (Table 5). The difference, though, was not extraordinarily large. This is probably due to the closeness of the preferences assigned to moderate disease and dialysis on the Quality of Well-Being Scale by the MDRD Study participants.

Cost-effectiveness

We next examined costs as an outcome measure in the decision model. Over a five year time span, the model estimates that there would be about a $5000 difference per patient between the diet groups in expected total costs (Table 5). Average costs per patient in this time would sum to $29,178 for a subject on a usual-protein diet, and $24,252 for a person on a low-protein diet.

Figure 9 portrays the expected annual costs in each year of the model. We see higher costs in Year 1 for the low-protein diet group. This is due to the slightly higher cost of treatment for these subjects and the lack of any difference in the frequency of dialysis at this point in time. As time progresses, more cases of dialysis are observed for the usual-protein diet group. After Year 2, there is a consistent pattern of higher annual costs for subjects in the usual-protein diet group.

Figure 9. Annual cost per 100 subjects over 5 years of the model by diet group (costs are $ thousands and discounted at 3%)



When expected costs were observed in relationship to expected outcomes (Table 6), we again found cost savings associated with the low-protein diet intervention. Over the five years of the model, the low-protein diet saved approximately $100,000 per quality adjusted life year gained. Moreover, 99.8% of the estimates generated by the simulation had an expected cost per QALY value of less than 0 (indicating cost savings in all but 0.2% of the simulations ran).

Table 6. Expected Values over the Five Year Model

	Undiscounted	Discounted at 3%
Cost / QALY gained	-96,929	-100,680
Cost / life year saved	-102,021	-112,245
Cost / ESRD year saved	-27,537	-27,416

In the cost-effectiveness literature, most interventions are more expensive, and an acceptable cost/QALY that one looks for is in the range of $20,000-$50,000 per QALY gained. The high costs associated with ESRD appear to influence the evaluation here to such an extent that it is possible to show cost savings for an intervention on a chronic disease.

Cost savings were also observed when different outcomes were examined. The low-protein diet intervention was estimated to save $112,000 per year of life gained, and $28,000 per year of ESRD prevented.

V. Discussion

Overall, we found that the implementation of protein restricted diets, as practiced in the MDRD Study, is associated with cost savings over a five year time frame. This comes about because the tremendous costs associated with dialysis outweigh the burdens of enhanced dietitian's services for maintenance and adherence to a low-protein diet. In this evaluation, we observed a meaningful difference in the development of the need for dialysis by treatment group, where subjects on a usual-protein diet had a higher incidence of dialysis. As mortality is markedly higher for persons on dialysis, we also found higher numbers of deaths in the usual-protein diet group.

The core of this analysis is made up of the Markov process model to estimate the likely outcomes of dietary intervention over time. Decision analysis models such as the one used in this study have several advantages. These include the explicit identification of the assumptions used in the analysis, the identification of areas where data are poor in the analysis, and the ability to combine costs and outcomes in the analysis.

There certainly are areas in our decision model where different assumptions or more accurate data could influence the results. These areas include the expected rate of decline in GFR in the future, the role of non-adherence to diet in the future, and our estimates of quality of life for dialysis patients, amongst others. We have not conducted any sensitivity analyses to examine the extent to which the results could be changed by these parameters.

One of the possible limitations of the model used here is that we modeled a simplistic path to dialysis from the point of initiation of dietary therapy. There are likely to be other paths to the dialysis state, and other approaches to modeling. For example, GFR stop points were a major part of the MDRD Study. They identified persons with significant declines in renal function. We did not include this information in our analysis, because it was, primarily, a research endpoint, and not an outcome that could be easily identified in clinical practice. However, it is possible that many of the study subjects who reached a GFR stop point may progress to ESRD faster in reality than the model predicted.

We have chosen a model based upon the actual data of the MDRD subjects and followed their disease status over time by extrapolating the MDRD GFR data. It is possible to construct other simulation models with different approaches to estimating the time to dialysis. One such approach may be to model the decline in GFR on the basis of the slope of decline over time, rather than our incremental approach.

In the analysis, we assumed that the study cohort maintained their dietary intervention throughout the five year period, unless they developed a medical complication or end-stage disease. Non-adherence to diet was not considered in the model because the available evidence suggested that it added very little in terms of additional costs. The MDRD adopted a behavioural model to enhance participation and adherence. Adherence to diet may not be as strong in the general clinical population. Thus, our results could differ by varying levels of adherence to diet.

Our estimates of quality-adjusted life years were determined from MDRD Study participant responses to the Quality of Well-Being Scale. This is a widely used approach in economic evaluations. However, the estimates of quality of life attributed to dialysis and renal transplantation are based upon a small number of

individuals in these health states. Another report[26] found a lower quality of life index figure for patients in ESRD than we report here. Considering a lower figure would enhance the results reported to the advantage of low-protein diets.

There are other items that we did not include in the model which could increase the expected benefits related to low-protein diets. For example, we did not include indirect costs related to disability or premature mortality in our model. Nor did we include non-medical, direct costs because of the difficulty in identifying an estimate for patients on dialysis. Including these cost items in the model would further enhance the cost advantage observed for a low-protein diet.

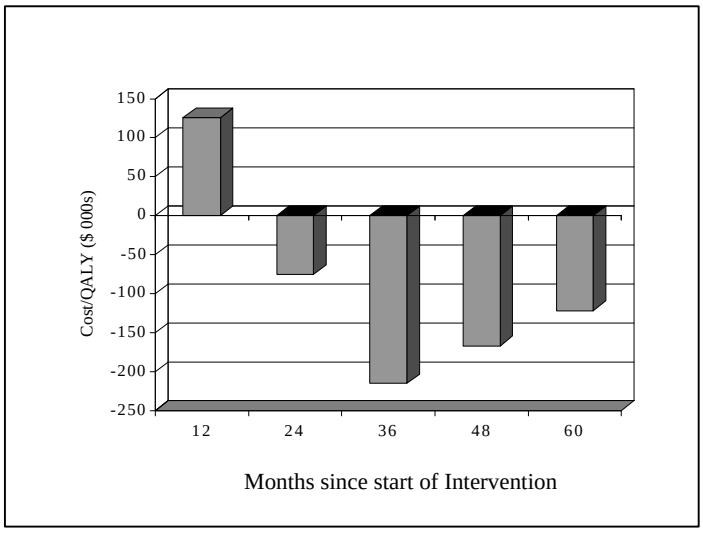
We conclude with a discussion of three concerns regarding the interpretation of this analysis. One, there will likely be some criticism of the relative value of a undertaking a cost-effectiveness study to examine the economic value of low-protein interventions, given the results of the MDRD trial. Generally, a cost-effectiveness study is used to provide information on the best means to allocate resources in a clinical area. A comparison of treatments is made in an attempt to guide future policies for resource allocation[11]. It assumes that the treatments available are effective. The results of the MDRD Study do not appear to have resolved the debate over the effectiveness of protein restricted diets. In general, arguments for changes in health policy or health financing are more persuasive when the clinical value of the treatment is not under question.

This evaluation, though, may represent a unique situation. It very likely is a situation where a treatment of marginal clinical benefit can have a dramatic cost benefit. This exists because the annual costs of patients in the ESRD program in the United States are quite large. Thus, even a small delay in the onset of end stage disease can result in significant cost savings.

Two, the MDRD Study was designed to evaluate the change in GFR over time by diet group (a short-term outcome). Secondarily, the study group examined longer-term outcomes, including the initiation of dialysis and death. Overall, they found no statistical difference between the diet groups in the time to the development of ESRD or death. However, the MDRD Study was not powered to identify differences in the development of end-stage disease with the same degree of certainty that they had for GFR. The analysis that we report here had a different focus than the MDRD Study. While we used GFR data to estimate the expected development of dialysis, the focus of our analysis was on the dialysis endpoint rather than the GFR endpoint. We report that there is likely an economically important difference between the intervention groups on the basis of the development of dialysis and the onset of death. This analysis does not supersede that undertaken by the MDRD Study.

Three, one could argue that the time span of our evaluation was too short and that the costs related to low-protein diets are just being postponed into the future beyond five years. Possibly. The analysis suggests that the cost-effectiveness of the protein-restricted diet is declining over time (Figure 10). However, after Year 1, each yearly point in time demonstrated cost savings. It is possible that low protein diets may cost more than usual protein diets over a long time frame. This would be due to the higher rate of mortality in the usual protein group and the inclusion of costs for patients on low protein diets who have survived longer. This, however, does not seem to be a justifiable reason to argue against low protein diets from a cost point of view.

Figure 10. Cost per QALY (undiscounted) by point in time over the model (Cost $ thousands)



[26] Lawrence WF, Grist TM, Brazy PC, Fryback DG. Magnetic resonance angiography in progressive renal failure. Amer J Kidney Dis 25:701-709, 1995.

VI. Appendix

1. Mortality Probabilities

Table A1. Death Rates per 1000 Person Years at Risk by Health State

Age	General Population	Dialysis Patients	Transplant Patients
20-24 years	1.09	37.7	5.2
25-29 years	1.22	55.7	7.3
30-34 years	1.62	72.3	11.3
35-39 years	2.08	84.1	15.8
40-44 years	2.73	98.3	25.1
45-49 years	3.75	113.4	32.3
50-54 years	5.71	145.0	40.0
55-59 years	8.77	171.1	51.1
60-64 years	14.01	210.7	62.2
65-69 years	20.9	261.3	
70-74 years	31.49	312.1	
75-79 years	47.21	372.8	

Sources: 1998 Annual Data Report, US Renal Data System (1996 data).
Vital Statistics, NCHS

2. Transplantation Probability

Table A2. Percent of ESRD subjects with a Transplant by Year after initiation of ESRD

Time since start of ESRD	Percent of ESRD Patients with Transplant
1 year	6.21
2 years	12.43
3 years	18.64
4 years	24.85
5 years	27.4

Sources: 1993 & 1996 Annual Data Report, Renal Data System.

The probability of first renal transplantation within two years of the initiation of dialysis was available from the 1993 Annual Data Report of the US Renal Data System, but the annual rate of transplantation was not. To estimate the risk for a transplant, we assumed that the annual probability of transplant in the first five years of ESRD was equal to one-half of the probability of transplant in the first two years. We further assumed that the total chance of having a functioning transplant would not exceed the overall rate noted for the ESRD population in the 1996 Annual Data Report Data (27.4%). The frequency of transplants as a modality of therapy did not differ significantly between the 1993 and 1996 Annual Data Reports.

Figure A1. Number of New Cases of Dialysis (Actual & Expected) by Diet by Year

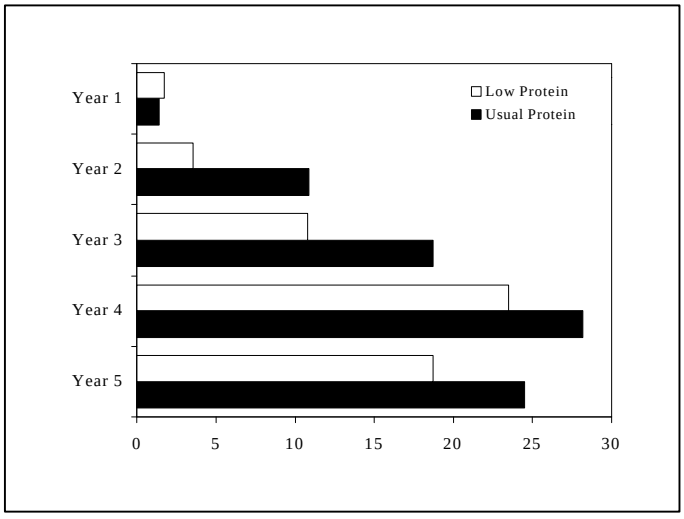


Figure A2. Number of Deaths (Actual & Expected) by Diet Group over Time