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# A Review of the First Year of Medicare Coverage of Erythropoietin

Robert I. Griffiths, M.S., Sc.D., Neil R. Powe, M.D., M.P.H., M.B.A.,  
Joel Greer, Ph.D., Gregory de Lissovoy, Ph.D., Gerard F. Anderson, Ph.D.,  
Paul K. Whelton, M.D., M.Sc., Alan J. Watson, M.D., and Paul W. Eggers, Ph.D.

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*Recombinant human erythropoietin (rHuEPO) is a new drug for treating anemia associated with end stage renal disease (ESRD). In a study of rHuEPO diffusion, costs, and effectiveness, we analyze ESRD program data and all claims submitted to Medicare for reimbursement of rHuEPO administered to ESRD dialysis patients. Access to rHuEPO was rapid and extensive during the first year of Medicare coverage. Dosing of rHuEPO and achieved hematocrit were lower than expected based on the results of clinical trials. rHuEPO cost Medicare \$144 million in its first year. The analysis of insurance claims data allowed effective monitoring of access, costs, and effectiveness of this new biotechnology.*

## BACKGROUND

Pharmaceutical products developed through advances in recombinant biotechnology have been reviewed by the Food and Drug Administration (FDA) and are now in use in routine clinical practice.

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Some of these products, such as monoclonal antibodies, interleukins, and colony stimulating factors, have received extensive media and clinical attention because of their potential to save lives and to improve quality of life. Yet many come with a heavy price tag and are likely to have a substantial financial impact on patients, providers, and third-party payers such as Medicare. Enthusiasm for these products may be tempered because they arrive at a time of great concern over the escalating cost of health care, a substantial component of which has been attributed to widespread use of new medical technologies, including pharmaceuticals.

## RECOMBINANT HUMAN ERYTHROPOIETIN

rHuEPO was one of the first recombinant pharmaceutical products to receive FDA approval for use in clinical practice. rHuEPO represents an important advance for the treatment of anemia (pathological deficiency of red blood cells) associated with renal disease. Normal kidneys produce erythropoietin, which acts on blood-forming organs (bone marrow) to stimulate the growth and differentiation of red blood cells, the transporters of oxygen to vital body tissues. However, in many patients with ESRD, production of erythropoietin is impaired or non-existent. rHuEPO was developed to supplement or replace production of natural erythropoietin in such patients (Watson and Spivak, 1988; Erslev,

1991). In clinical trials, rHuEPO raised and sustained hematocrit (a measure of red blood cell volume) safely and effectively in a dose-dependent fashion (Eschbach et al., 1987, 1989; Winnerls et al., 1986; Nissenson, 1991). rHuEPO also alleviated symptoms of anemia and improved quality of life of ESRD patients (Evans et al., 1990; Laupacis, 1990; Canadian Erythropoietin Study Group, 1990).

Medicare, which covers approximately 93 percent of all ESRD patients, began financial coverage for rHuEPO as soon as it received FDA approval in July 1989. Coverage at that time was \$40 per administration of less than 10,000 units (U) and \$70 per administration of greater than or equal to 10,000U. In establishing initial coverage and payment policy, Congress and HCFA attempted to balance the need for an appropriate rate of return on investment for the firms that had developed rHuEPO, reasonable payment to providers for administration, and the need for cost containment in the Medicare program (U.S. Congress, Office of Technology Assessment, 1990; U.S. Department of Health and Human Services, Office of the Inspector General, 1990).

There were a number of payer, provider, and patient concerns regarding the clinical and financial impacts of prescribing rHuEPO to anemic ESRD patients.

### **Policymakers**

The Health Care Financing Administration (HCFA) was interested in assuring that access to appropriate quantities of rHuEPO would be based on clinical need. Also, HCFA was interested in monitoring the therapeutic benefits of rHuEPO in clinical practice in order to evaluate the return on what was expected to be a considerable investment in rHuEPO. Furthermore, HCFA was concerned with the financial implications of rHuEPO, with respect to both the costs

associated with providing rHuEPO and the savings associated with any reduction in other medical services because of the therapeutic benefits of rHuEPO.

### **Providers**

Clinicians were concerned with prescribing rHuEPO based on clinical need while minimizing the risk of adverse outcomes. Dialysis facilities were concerned that rHuEPO prescription patterns provided appropriate care without imposing a financial burden.

### **Patients**

Patients were eager to receive rHuEPO with hopes that it would improve their quality of life and everyday functioning. However, they also were concerned with the potential economic burden of copayment for rHuEPO, since Medicare pays only 80 percent of allowed charges.

In order to monitor use of rHuEPO and to evaluate coverage and payment policy, HCFA required ESRD providers to collect and report 3 pieces of information on their billing claims for rHuEPO reimbursement: (1) the final dose of rHuEPO prescribed during each period (usually 1 month) of billed care; (2) the number of rHuEPO administrations during that period; and (3) the patient's hematocrit measured at the final rHuEPO administration of the period.

Hematocrit is the ratio of the volume of red blood cells to the total volume of blood and is usually reported as a percentage. Hematocrit in normal females ranges from 37 to 48 percent and from 42 to 52 percent in normal males (Jordan et al., 1992). In patients with ESRD who are not treated with transfusions or rHuEPO, hematocrits are much lower (Leaf and Cotran, 1976), typically in the range of 20 to 25 percent.

In this study, hematocrit was used as a measure of the clinical effectiveness of rHuEPO.

Collection of the information required by HCFA began concurrently with Medicare coverage of rHuEPO. This information became part of the claims history of patients and was incorporated into the ESRD Program Management and Medical Information System (PMMIS), which contains demographic and clinical information on Medicare-entitled ESRD patients.

Recognizing that rHuEPO is a prototype for the kinds of issues arising from the use of, and coverage and payment for, new biotechnology pharmaceuticals, HCFA commissioned a study of the clinical and economic impact of rHuEPO during the first year of Medicare coverage. Data elements in the ESRD PMMIS formed the basis for our evaluation of Medicare coverage of rHuEPO during the first year of its introduction into routine clinical practice. In this article, we synthesize the key findings of this study. Selected and more detailed clinical reports are available elsewhere (Powe et al., 1991, 1992, 1993; de Lissovoy et al., 1991). This article focuses broadly on how claims data can be used in reviewing coverage and payment policy for drug therapy. We describe the patients who received rHuEPO during the first year of Medicare coverage, examine barriers to access, describe rHuEPO dosing patterns and effectiveness in routine clinical practice, and compute the cost of rHuEPO to the Medicare program. We also discuss the potential financial incentives created by Medicare coverage policy and their role in shaping provider behavior. Finally, we consider options in setting and revising optimal payment policy and make suggestions for monitoring the early use of new technologies that have substantial clinical and economic impacts on the Medicare program and its beneficiaries.

## PRINCIPAL FINDINGS

### Access

Ensuring access to life-saving dialysis care was a primary concern of patients, clinicians, and Congress in 1972, when Medicare coverage was extended to patients with ESRD who are either directly eligible or dependent upon someone who is eligible for Social Security (Rettig and Levinsky, 1991). Twenty years later, ensuring access was again a concern, but this time to rHuEPO.

We investigated access to rHuEPO by dialysis-dependent ESRD patients during the first year of Medicare coverage to determine the extent and rate of increase of use of rHuEPO by providers and to identify patient characteristics associated with receiving rHuEPO. The design of the investigation included longitudinal and cross-sectional analyses of claims data using descriptive and confirmatory analytical techniques, such as logistic regression, to identify factors associated with receiving rHuEPO. We hypothesized that females might be more likely to receive rHuEPO than males because the prevalence of anemia in ESRD may be greater among females than among males. We also hypothesized that black patients might be less likely to receive rHuEPO because a variety of studies have demonstrated that black people often receive less access to high-cost medical care.

During the first year of Medicare coverage the diffusion of rHuEPO was rapid. In July 1989, the first month that rHuEPO was covered by the Medicare program, 3.9 percent (3,658 out of a total 92,113 ESRD beneficiaries) of patients enrolled in the ESRD program, who had a claim for dialysis paid by Medicare, and had never received a transplant, received rHuEPO.

This increased to 53 percent (53,394 out of a total 100,749 ESRD beneficiaries) 11 months later. Access to rHuEPO varied markedly according to dialysis modality (hemodialysis versus peritoneal dialysis) and by site of service (in-center versus home) (Powe et al., 1992). Figure 1 illustrates the difference in monthly rHuEPO use between patients undergoing hemodialysis or peritoneal dialysis in Medicare-certified facilities, compared with their counterparts who were treated with home hemodialysis or home peritoneal dialysis.

Diffusion of rHuEPO into the in-center hemodialysis population began rapidly following HCFA coverage and FDA approval. However, the rate of increase in diffusion declined gradually toward the end of the first year. Several factors may have been responsible for this pattern of diffusion. First, Medicare elected to begin coverage for rHuEPO administered in a dialysis center (or physician's office) immediately following FDA approval. Medicare's decision to provide such coverage removed the largest financial barrier to access for in-center hemodialysis patients. Second, positive results from rHuEPO clinical trials in this population were presented at national meetings of nephrologists and appeared in the medical literature (Eschbach et al., 1987; Winnerls et al., 1986) months prior to rHuEPO's approval by the FDA. rHuEPO also had received a great deal of advertising and media attention prior to approval, suggesting that providers and patients were probably aware of its potential benefits in clinical practice. The ability to disseminate material to readily identifiable dialysis centers may have enhanced the effectiveness of advertising.

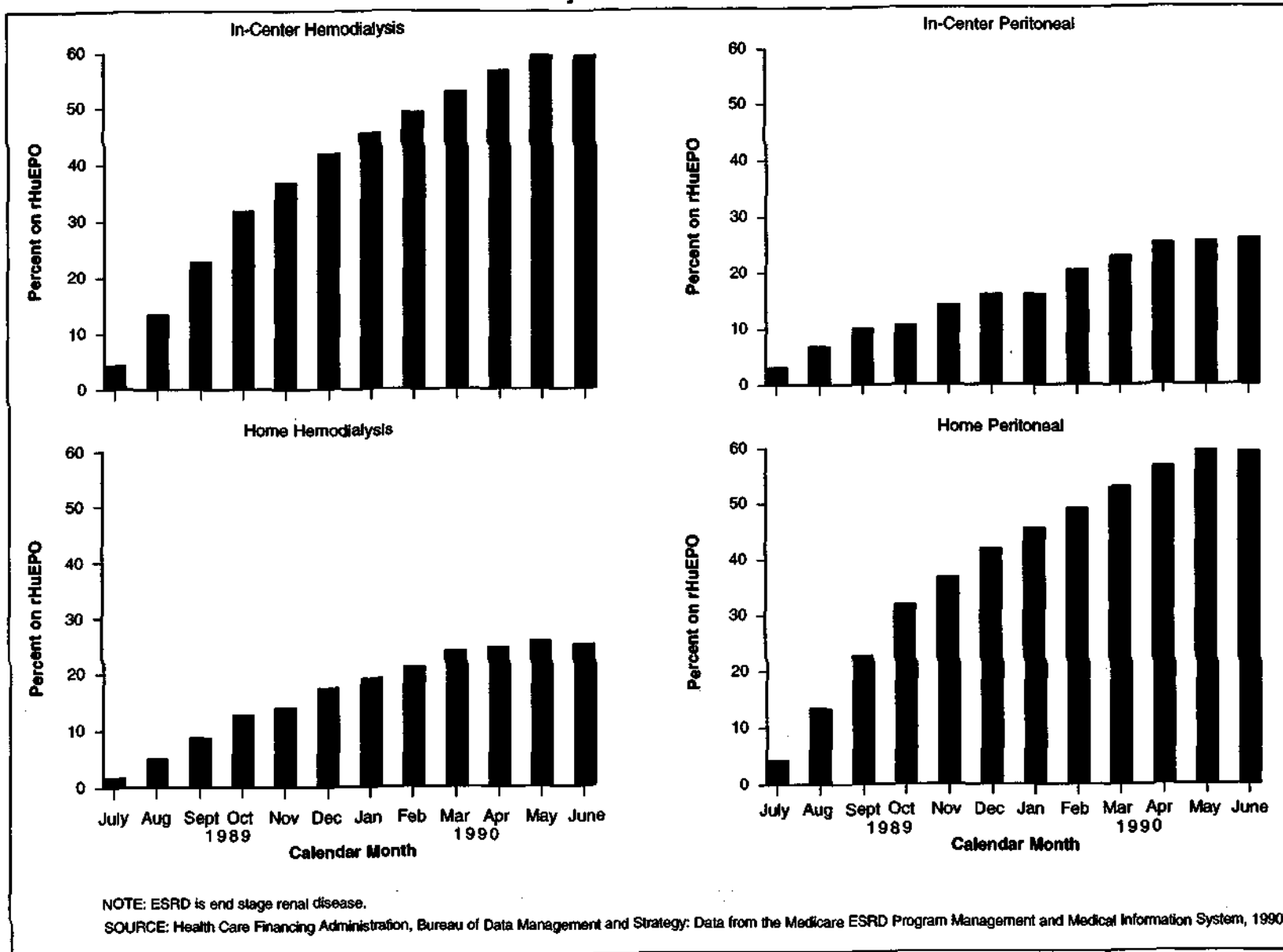
In contrast to the in-center hemodialysis population, diffusion into the home dialysis and in-center peritoneal populations was slower, and rHuEPO did not achieve a similar

level of use by the end of the first 12 months of HCFA coverage. In most months, the proportion of in-center hemodialysis patients who received rHuEPO was more than double the proportion of in-center peritoneal, home hemodialysis, or home peritoneal dialysis patients. Almost 60 percent of in-center hemodialysis patients were receiving rHuEPO by June 1990 compared with less than 30 percent of those being treated with any of the other major dialysis modalities. We considered the possibility that demographic or clinical differences between patients receiving different types of dialysis at different sites might have been responsible for these observed differences. However, multiple logistic regression analysis, adjusting for patient clinical and demographic characteristics, showed similar patterns (Powe et al., 1992).

One explanation for the observed difference between access to rHuEPO in home and in-center dialysis patients is that, until July 1, 1991, Medicare did not pay for rHuEPO that was self-administered (U.S. Congress, Office of Technology Assessment, 1990). Unlike other types of home health services, receiving dialysis at home does not entail regular visits to the home by health care providers who could administer rHuEPO. Therefore, during this period, home dialysis patients faced a trade-off between fewer visits, a convenience of home dialysis, versus visiting a treatment facility more often to receive rHuEPO and having Medicare pay for rHuEPO. Peritoneal dialysis usually entails greater participation by the patient (e.g., in the processes of initiating and monitoring the process of dialysis, and of exchanging the dialysate), in contrast to in-center hemodialysis where dialysis is performed by health care professionals. Therefore, patients receiving peritoneal dialysis may be healthier than those receiving hemodialysis in-center and have less need for rHuEPO.

Figure 1

Percent of ESRD Patients Receiving Recombinant Human Erythropoietin (rHuEPO), by Dialysis Modality and Site of Service: July 1989 – June 1990



A smaller proportion of males than females received rHuEPO in each month during the study period (Figure 2). Because females in the general population have lower hematocrits than males (Jordan et al., 1992), the prevalence of anemia in ESRD patients may be higher in females than in males. (There are no definitive studies, to the best of our knowledge, however, that confirm or refute this opinion.) Overall, in unadjusted analysis, a slightly smaller proportion of black patients than white patients received rHuEPO in each

month of the study period (Figure 3). This difference became progressively smaller during later months and had virtually disappeared by the end of the study period. However, once the data were compared adjusting for dialysis modality, the differences between treatment rates in black patients and white patients became more pronounced. The proportion of black patients on in-center hemodialysis who received rHuEPO was approximately 8 percent lower, on average, than the corresponding proportion of white patients on

**Figure 2**  
**Percent of ESRD Patients Receiving Recombinant Human Erythropoietin (rHuEPO), by Gender:**  
**July 1989 – July 1990**

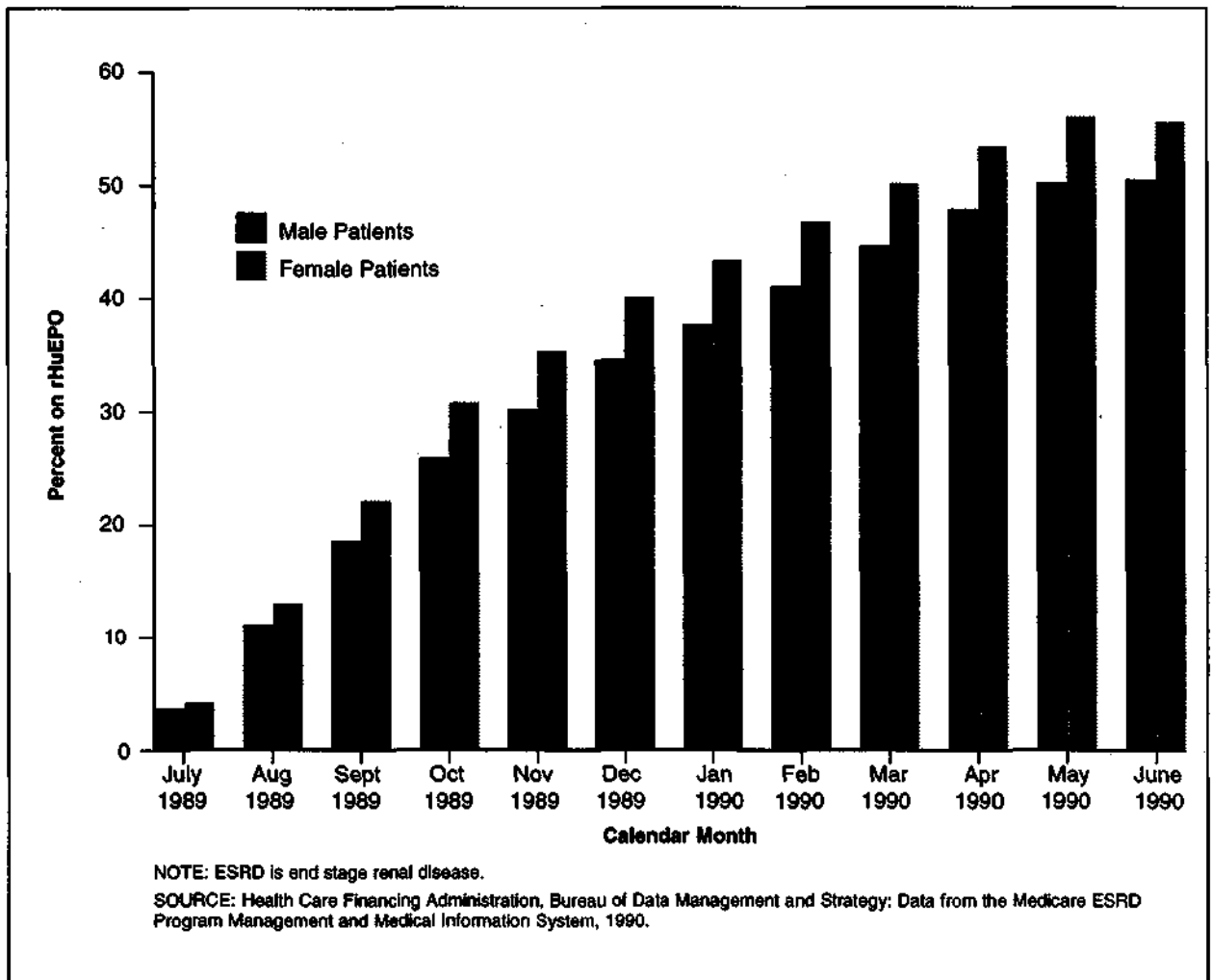
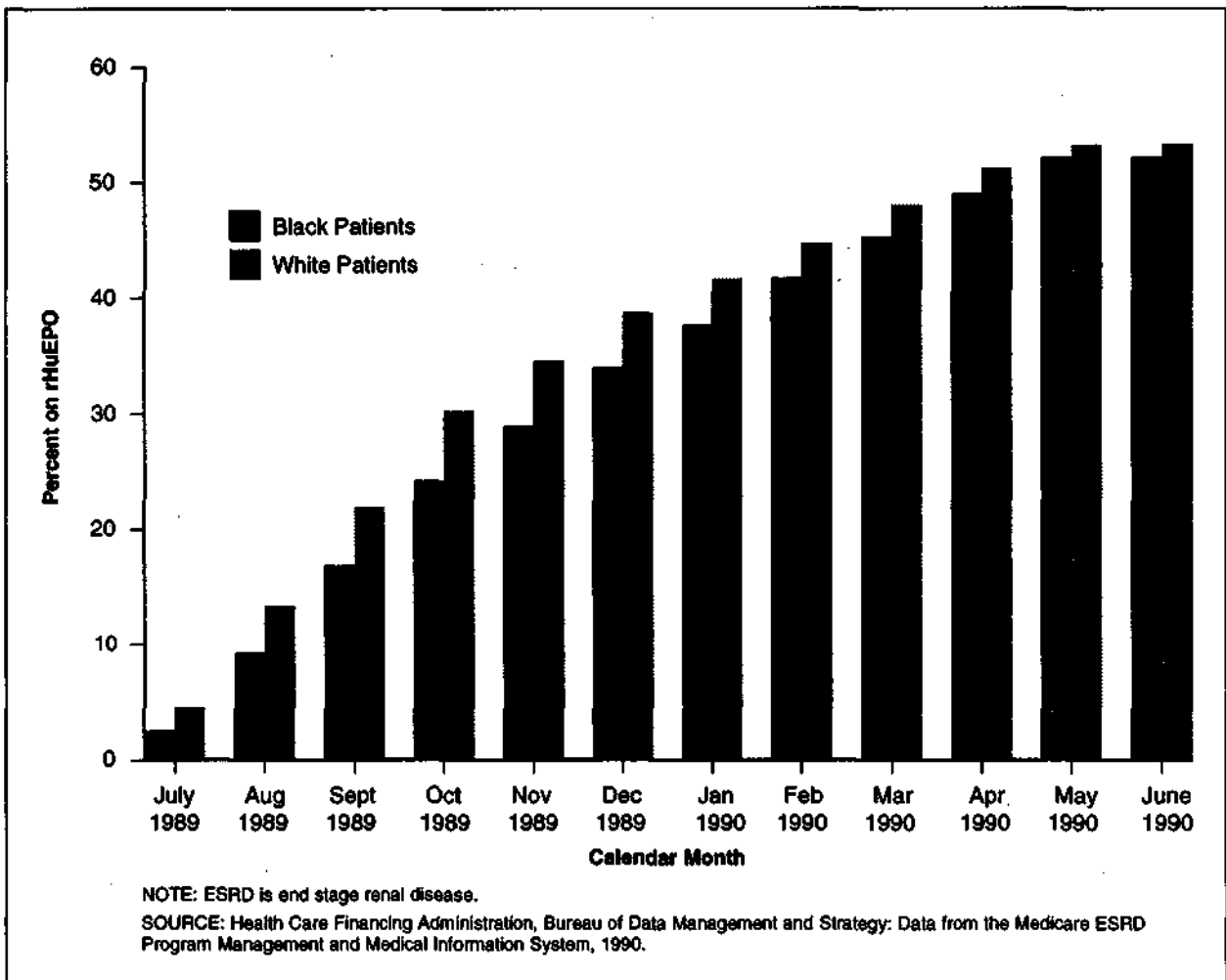


Figure 3

Percent of ESRD Patients Receiving Recombinant Human Erythropoietin (rHuEPO), by Race:  
July 1989 – July 1990



in-center hemodialysis who received rHuEPO; the proportion of black patients on home peritoneal dialysis was, on average, 3 percent lower. Multivariate logistic regression analysis of rHuEPO use in June 1990 suggested that black patients were significantly less likely (odds ratio 0.88; 95-percent confidence interval 0.86 - 0.91) than white patients to receive rHuEPO treatment (Powe et al., 1992)

Of considerable concern in monitoring payment policy is the possibility that non-clinical factors affected prescribing of rHuEPO. Although the black and white

discrepancy in access to rHuEPO identified in multivariate analysis could be due to a lower prevalence of anemia among black people, it may be the case that black people find medical care less accessible. Therefore, there is cause for concern that the differences in access to rHuEPO between black patients and white patients that we observed may not reflect actual need for the drug. Perhaps fewer black patients receive rHuEPO because black people are less likely to obtain coinsurance to cover the 20 percent patient copayment associated with all Medicare Part B services. The burden of

the Part B copayment associated with receiving rHuEPO is likely to be considerable. For instance, during the first year of coverage by Medicare the patient was responsible for \$8 (20 percent of \$40) of the cost of each administration. If the patient were to receive 3 administrations of rHuEPO per week the cost of rHuEPO to the patient or to his or her coinsurance would be \$24 per week or \$1,248 per year.

The rate and extent of rHuEPO diffusion also varied according to patient age. Although patients 65 years of age or over were among those least likely to receive rHuEPO in July 1989, they were the most likely to receive rHuEPO in June 1990. There were marked differences in treatment rates of rHuEPO according to the underlying cause of renal failure. Figure 4 shows the rate and extent of diffusion in patients with 4 causes of ESRD: (1) multiple myeloma, (2) polycystic kidney disease, and the 2 most common causes of kidney failure, (3) diabetes mellitus, and (4) hypertension. Figure 5 illustrates the rate and extent of rHuEPO diffusion in 4 networks that were representative of the diverse patterns of diffusion by ESRD region (States were grouped by ESRD network). The regional differences in rHuEPO treatment patterns were also observed in multivariate logistic regression which adjusted for other patient clinical and demographic characteristics. Although we do not fully understand the causes of these substantial geographic differences, and it is unlikely that the ESRD networks had a direct impact on rHuEPO treatment decisions, differences in the characteristics of patients in different networks may have been large enough to produce variability in rHuEPO treatment rates. One possible explanation is that patient ability to meet Medicare copayment for rHuEPO is both a determinant of access to rHuEPO and a

factor that varies by region or State. Medicare reimbursement alone may be insufficient to cover the provider's cost of administering rHuEPO. The provider's decision to administer rHuEPO or the patient's decision to receive rHuEPO may be based, in part, on the patient's ability to pay the copayment. This may vary by State because of variability in State government programs that may finance care for indigent ESRD patients.

rHuEPO diffusion into the ESRD population during the first year of Medicare coverage appears to have occurred rapidly. Although our data do not permit determination of the relative role that clinical and non-clinical factors played in diffusion, the results suggest that both shaped diffusion of rHuEPO during the first year of Medicare coverage. For instance, patients with polycystic kidney disease as an underlying cause of renal failure received rHuEPO least often. This is consistent with clinical expectations because polycystic kidneys often continue to produce natural erythropoietin. Further diffusion of rHuEPO is likely to depend on a number of factors: the continued willingness of physicians to substitute rHuEPO for other therapies, such as transfusions or androgens, which are already effective in alleviating anemia but have significant side effects; the ability to overcome socioeconomic barriers to access; and the actual prevalence of anemia in the incident ESRD population.

### **Dosing**

The intensity of drug therapy can influence both effectiveness and costs, outcomes of extreme interest to policymakers. It can also influence providers' financial status depending on the structure of payment policy. As a result of experience with rHuEPO in clinical trials (Eschbach et al.,



Figure 4

Percent of ESRD Patients Receiving Recombinant Human Erythropoietin (rHuEPO), by Underlying Cause of Renal Failure: July 1989 – June 1990

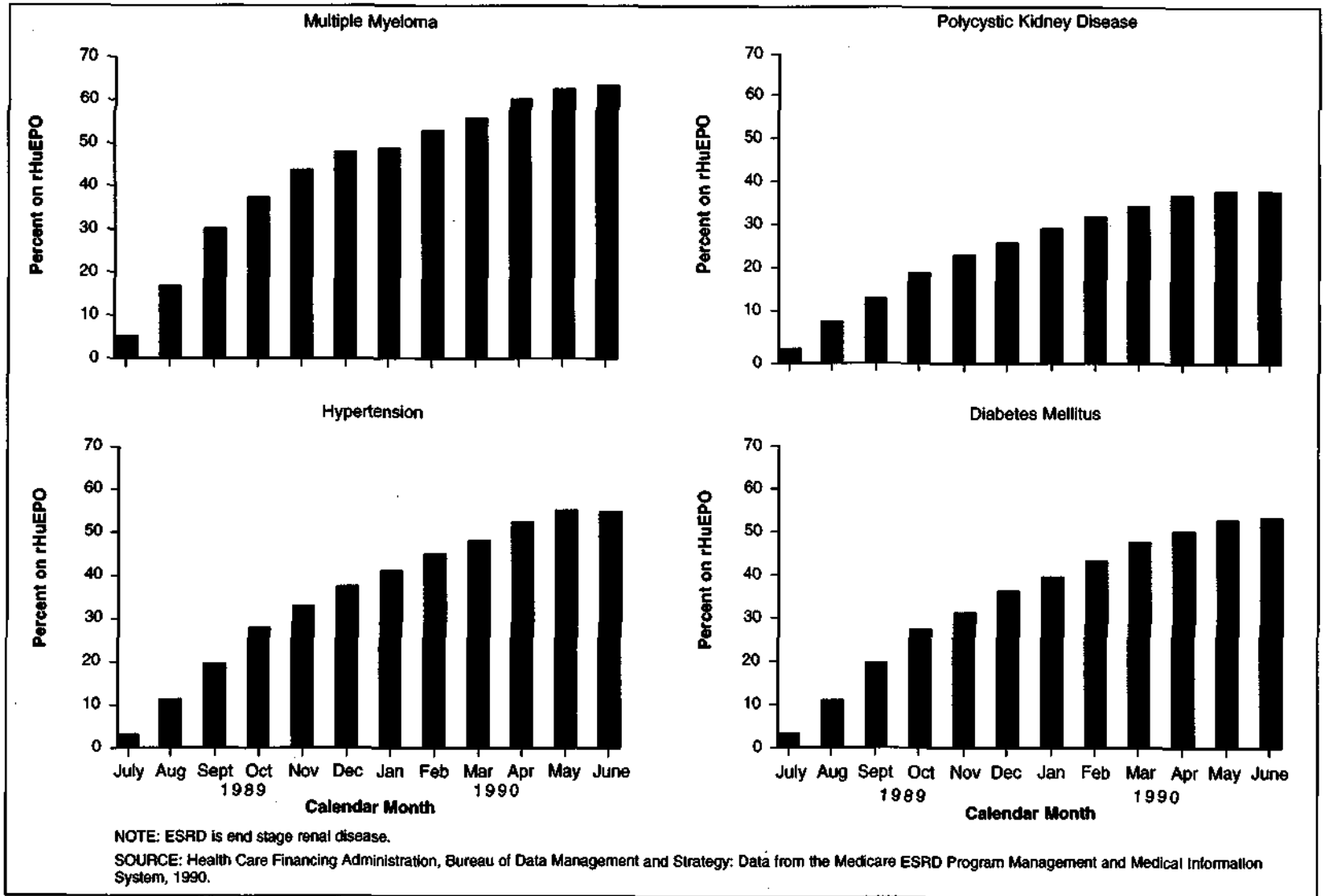
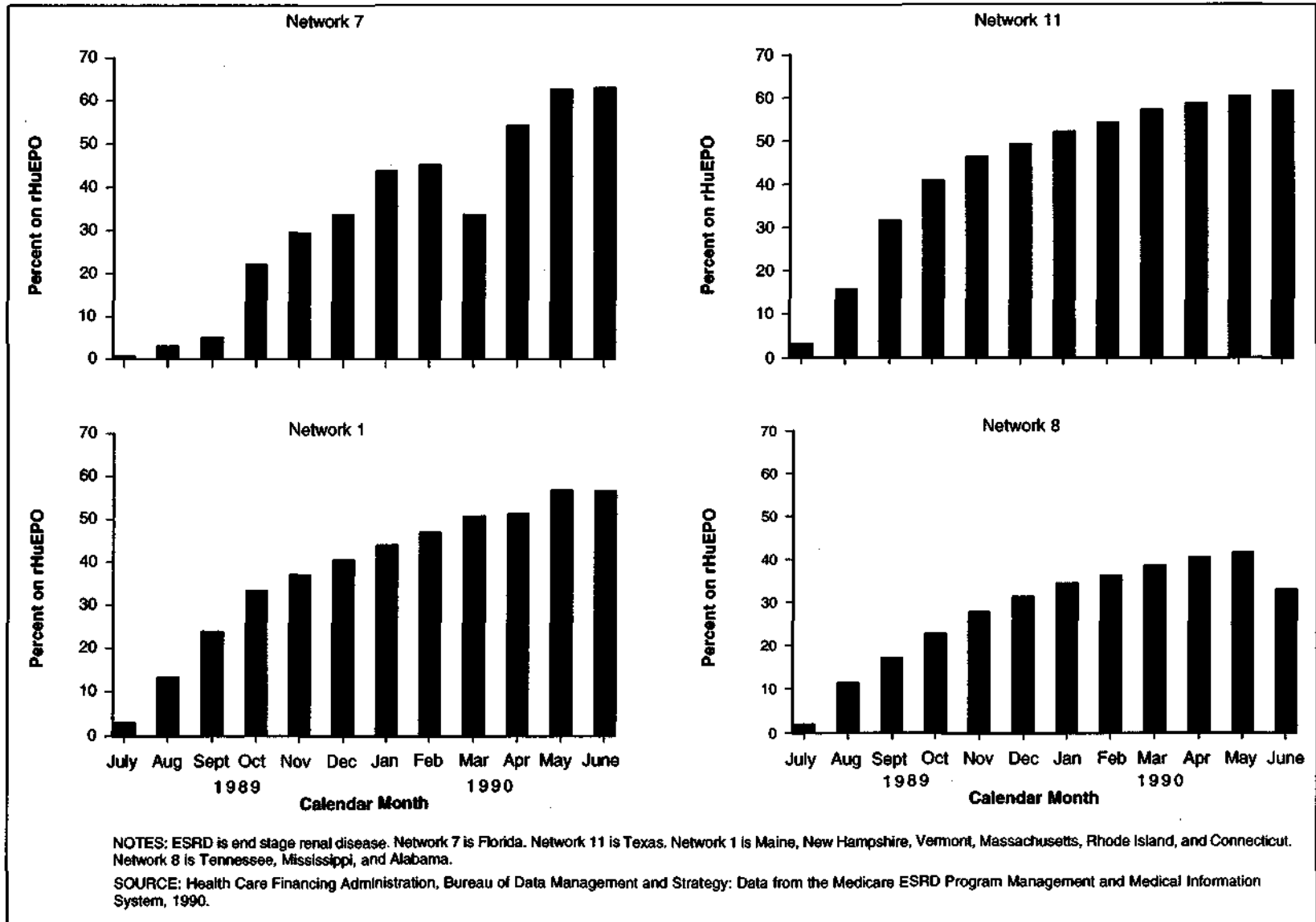


Figure 5

Percent of ESRD Patients Receiving Recombinant Human Erythropoietin (rHuEPO), by Selected Renal Dialysis Network:  
July 1989 – June 1990



1987, 1989; Winnerls et al., 1986), initial dosing of 50 to 150U per kilogram of body weight intravenously 3 times per week was approved by the FDA. The National Kidney Foundation (1989) also recommended 150U per kilogram of body weight. Assuming that the average ESRD patient weighs between 60 kg and 80 kg, one would have expected to observe an average initial dose of between 3,000 and 12,000 U per administration. In addition to a range of expected average dose, experience from clinical trials suggested two distinct phases of dosing were likely: an initial phase of relatively large rHuEPO doses lasting approximately 3 months and designed to raise hematocrit above 30 percent; and a maintenance phase of smaller doses, administered thereafter on a chronic basis and designed to maintain the target hematocrit level once it had been attained.

We performed an analysis of rHuEPO dosing practices during the first year of Medicare coverage to compare dosing in routine clinical practice with dosing in clinical trials and dosing recommended at the time rHuEPO was approved for marketing. We also sought to identify patient characteristics associated with lower or higher doses. For example, we hypothesized that females would receive less rHuEPO than males because they generally weigh less. Unadjusted and multiple linear regression analyses were performed on cross-sectional and longitudinal claims data to test this hypothesis.

In contrast to the expected average dose, the observed average dose in the first month of rHuEPO therapy was 2,752U for 59,462 patients who began rHuEPO during any calendar month from July 1989 to June 1990. The average dose fell to 2,668U in the fourth month of rHuEPO therapy for those 40,891 patients who received rHuEPO for at least 4 months during the study period.

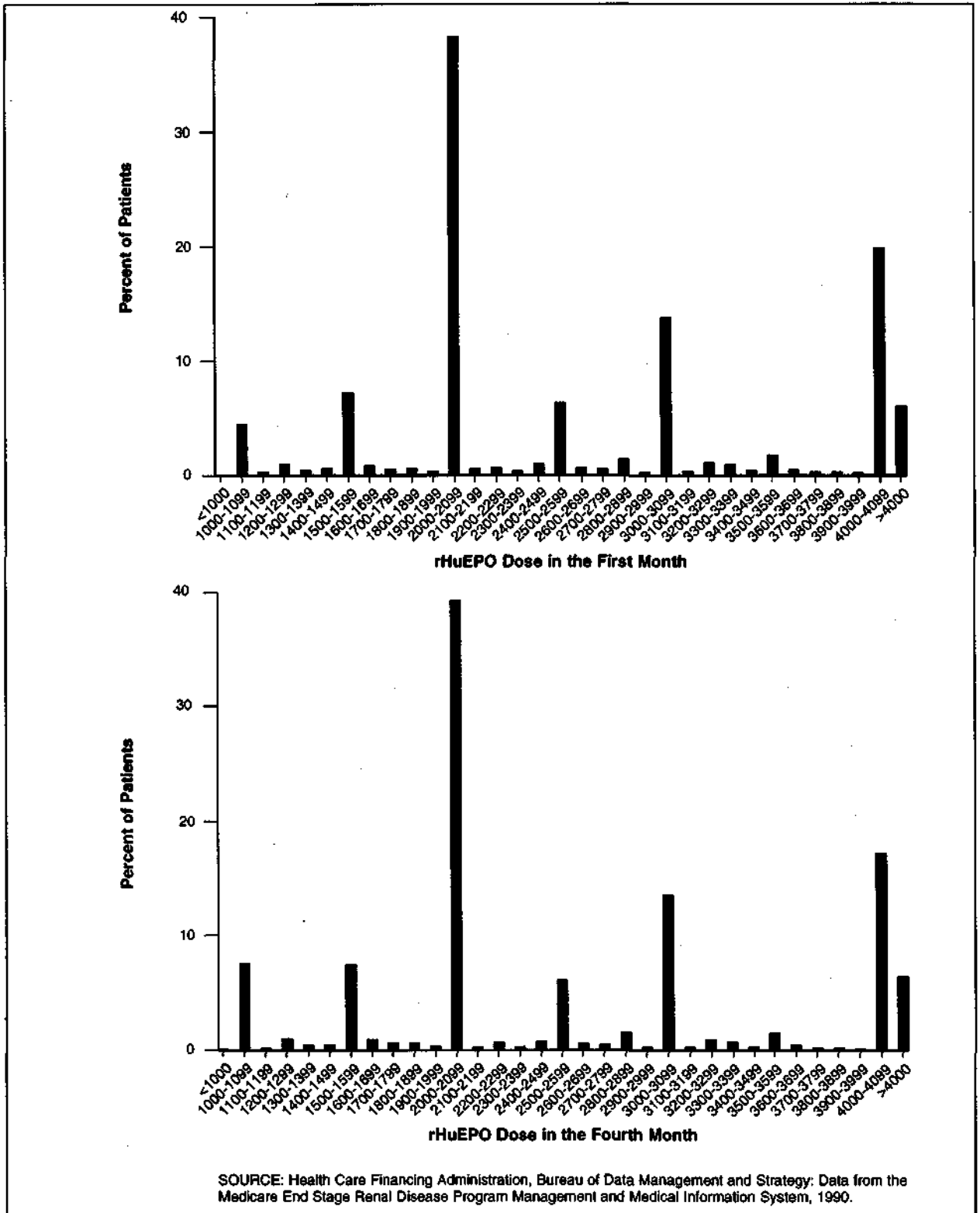
The mean dose was 3,576U in the first month and 3,243U in the fourth month of rHuEPO use for 2,619 patients who began rHuEPO therapy in July 1989, a reduction of 9.3 percent. For patients who began rHuEPO later in the study period, the mean first month dose was substantially smaller, as was the change between first and fourth month dose. Mean first and fourth month doses were significantly lower for females than for males. Figure 6 shows that although the average first month dose was 2,752U per administration, the distribution of average first month dose was distinctly bimodal, with peaks at 2,000U and 4,000U and very few doses greater than 4,000U. During this period rHuEPO was packaged in 2,000 and 4,000U vials, and it is possible that the size of the rHuEPO dose administered was based on the size of available vials in addition to being based on patient weight.

In general, the average dose used in clinical practice was significantly lower than expected based on the experience in clinical trials, FDA approval, and the recommendations of the National Kidney Foundation (1989). For patients beginning rHuEPO therapy soon after FDA approval, there was a steady decline in dosing levels between the first and the fourth month of therapy and a constant dose or slightly increasing dose thereafter. Patients beginning rHuEPO therapy later in the study period experienced smaller declines. Neither of these patterns defines two distinct phases of dosing as recommended on the basis of clinical trials.

One explanation for this finding is that clinicians were concerned with the possible adverse effects associated with increasing their patient's hematocrit too rapidly, such as the occurrence of hypertension. This may have resulted in a more conservative approach to dosing designed either to

**Figure 6**

**Distribution of Recombinant Human Erythropoietin (rHuEPO) Dose in the First and Fourth Months of Patient Utilization**



minimize the risk of side-effects or to facilitate patient management. Another explanation is that clinicians may have believed they were achieving satisfactory results with relatively low doses of rHuEPO.

Evidence suggests that clinicians did take patient clinical characteristics into account when determining rHuEPO dose. For instance, clinical trials and product labelling advocated dosing based on patient weight. Although we did not have access to weight data, we observed that females received smaller doses than males, which is consistent with the fact that females generally weigh less. It is noteworthy that black patients received the same amount of rHuEPO as white patients. Therefore, although black patients were less likely to receive rHuEPO (as discussed earlier), those who obtained rHuEPO received an amount similar to white patients.

Under the Medicare coverage and reimbursement policy during the first year, economic incentives existed to minimize the rHuEPO dose and to provide rHuEPO to a large number of patients in order to maximize profit or break even. All other things being equal, the proportion of patients receiving rHuEPO in a provider's caseload and the average dose among those being treated with rHuEPO might have been expected to vary depending on the degree to which profits are important to a provider.

In an analysis of 1,968 ESRD providers, for-profit independent facilities provided the lowest mean caseload dose (2,465U) compared with for-profit hospitals (2,493U), not-for-profit independents (2,798U), not-for-profit hospitals (3,081U), and government facilities (3,112U) (de Lissovoy et al., 1991). The fact that for-profit facilities provided significantly smaller doses than either not-for-profit or government facilities suggests that they may have attempted to maximize

profit on an individual patient basis. For-profit independent facilities also provided rHuEPO to a larger proportion (47 percent [ $n = 862$ ]) of their caseload than not-for-profit and other for-profit facilities (35 percent [ $n = 118$ ]) in for-profit hospitals, 46.1 percent [ $n = 244$ ] in not-for-profit independents, 40.4 percent [ $n = 353$ ] in not-for-profit hospitals, and 26.1 percent [ $n = 51$ ] in government facilities). This is also consistent with a profit-oriented behavior which includes maximization of the number of profitable administrations of rHuEPO. The results of multivariate analyses, which adjust for variation in provider caseload characteristics, are consistent with those of the unadjusted analyses.

Our findings are consistent with the hypothesis that dialysis providers may have provided smaller than expected doses in order to break even or to make a profit. They are also consistent with the hypothesis that providers might respond differently to incentives under Medicare coverage and reimbursement policy, depending on the importance of profits. However, it is important to recognize that our findings do not prove that provider behavior was influenced by financial considerations.

Several caveats should be kept in mind when using these results to compare the behavior of for-profit and not-for-profit facilities. First, for-profit facilities face a tax liability, whereas not-for-profits do not. Therefore, for-profit facilities may provide smaller doses of rHuEPO in order to retain the same excess of revenue over expenses after taxes as their not-for-profit counterparts. Second, the extent to which the ability to collect the 20 percent copayment owed by patients varies by facility profit status is unknown. If patients in for-profit facilities have greater ability to meet the copayment obligations from their personal resources, the actual difference in excess of revenues over expenses between for-profit and

not-for-profit facilities may be greater than that implied by the observed discrepancy in dosing. Finally, these results do not necessarily indicate that rHuEPO treatment in not-for-profit or government facilities was more appropriate than in for-profits. It is possible that the lower doses observed in for-profit facilities are indicative of greater efficiency. Higher doses were not consistently associated with either a more rapid increase or higher sustained hematocrit than lower doses.

### **Effectiveness**

Clinical effectiveness is an important outcome for providers, patients, and policymakers. We performed an analysis designed to determine the effectiveness of rHuEPO in routine clinical practice as measured by the effect on patient hematocrit and to identify patient characteristics associated with variation in response to rHuEPO. Several clinical measures available on claims data were used to assess the effectiveness of rHuEPO treatment. These included the proximate indicators hematocrit and transfusion status. Unadjusted and multivariate linear regression were performed to establish the dose-response relationship in routine clinical practice and to identify factors associated with response.

In general, patient hematocrit increased steadily during the first 3 months of therapy and then stabilized. Mean hematocrit rose from 26.7 percent during the first month of rHuEPO treatment to a peak of 28.9 during the fourth month. Twenty-four percent of patients had a hematocrit greater than or equal to 30 percent in the first month of rHuEPO use compared with 44 percent in the fourth month. Among those patients who received rHuEPO for at least 6 months during the study period and were enrolled in the ESRD program for at

least 6 months prior to initiation of rHuEPO therapy, 27.1 percent were transfused in dialysis centers during the 6-month period prior to initiation of rHuEPO therapy, whereas only 14 percent were transfused in the first 6 months following initiation of therapy.

Manufacturer recommendations included a target hematocrit level of 30 percent. In general, patient hematocrit stabilized at a level lower than expected based on the results of clinical trials, which may be due, in part, to physicians' belief that there are diminishing benefits with regard to the oxygen carrying capacity of blood of increasing hematocrit beyond this level. In contrast to clinical trials where rHuEPO obviated the need for blood transfusions, blood transfusions in routine clinical practice were markedly decreased but not totally eliminated.

In unadjusted analysis, we found that those patients receiving rHuEPO experienced, on average, a rise in percentage of hematocrit of 2.47 points. In multivariate analysis, we found that the change in percentage of hematocrit from the first to fourth month of rHuEPO use was significantly related to the logarithm of average dose from the first to fourth months of rHuEPO use, but that the magnitude of this association was small. Therefore, this observed dose-response relationship was weaker than expected, on the basis of clinical trials conducted prior to FDA approval of rHuEPO that reported strong dose-response relationships.

### **Survival**

We examined the trend in survival rates for the ESRD population from 1985 to 1990 to determine whether rHuEPO appeared to have an effect on overall survival. Patients were considered to have survived a year if they were alive and enrolled in the ESRD

program on July 1 of one year and did not die before June 30 of the following year. We used the technique of direct standardization (Lillienfeld and Lillienfeld, 1980) to adjust for increases over time in the proportion of elderly patients and the proportion of patients with diabetes as an underlying cause of renal failure. Both characteristics are associated with a lower probability of survival. The adjusted survival rate remained constant across all years at approximately 80 percent, suggesting that rHuEPO did not affect overall survival (Powe et al., 1991).

Two caveats should be considered. First, it is possible that we failed to control for other changes in the composition of the ESRD population that influence survival. Second, the followup period may have been too short to observe an effect of rHuEPO.

### Costs

The cost of pharmaceuticals is an increasingly sensitive issue to both policymakers and patients, and was identified as a major target in the President's health care reform proposal. The average Medicare expenditures for rHuEPO per recipient per month increased from \$242 in July 1989 to \$340 in June 1990. This may be due to the fact that in the early months following FDA approval, more patients had less than a full month of rHuEPO therapy because they were just starting therapy, compared with later months, when rHuEPO therapy for most patients was established and such patients were receiving rHuEPO for the whole month. Likewise, the average copayment cost increased from \$61 in June 1989 to \$85 in June 1990. The average copayment cost in June 1990 is more representative of future copayment costs, and it is likely that yearly copayment costs will be at least \$1,020.

However, this estimate ignores the effects of payment changes, to \$11 per 1,000U of rHuEPO administered in January 1991, and to \$10 per 1,000U in January 1994.

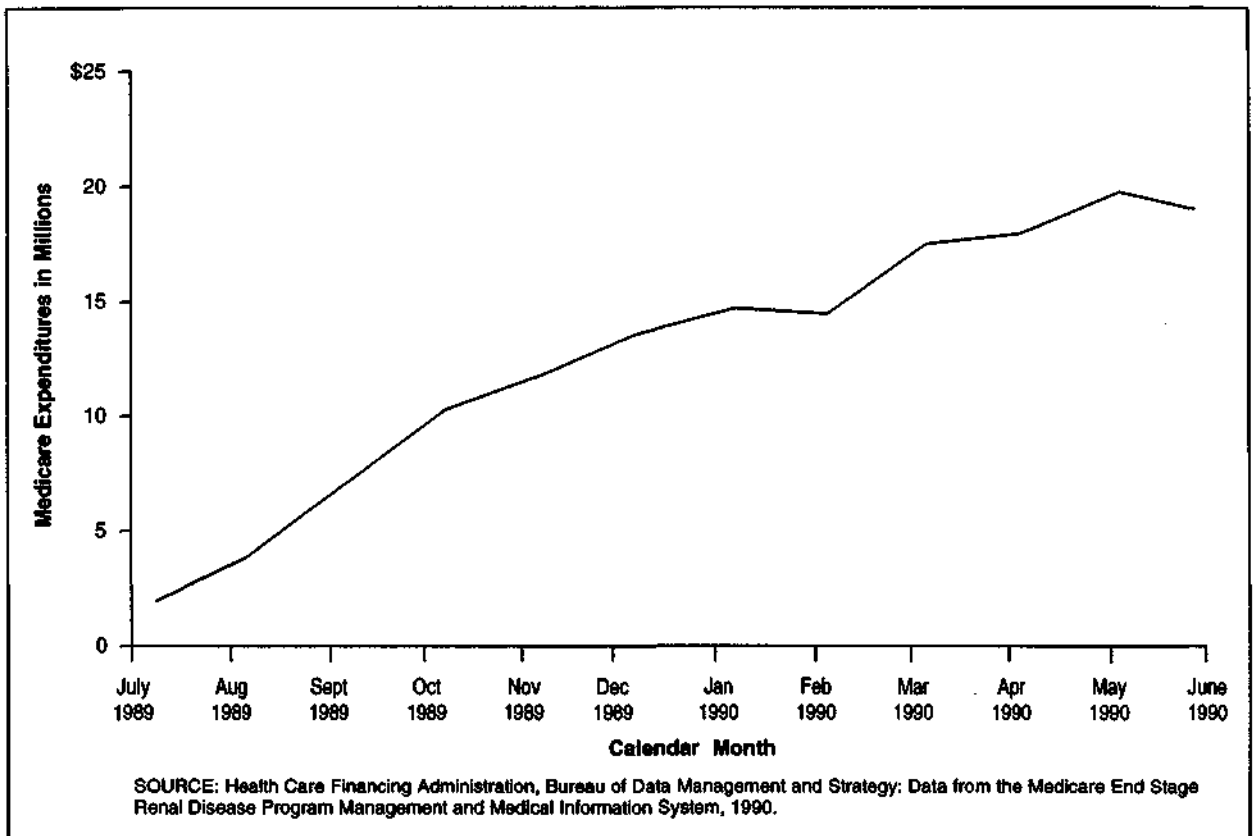
As might be expected, overall expenditures by Medicare (Medicare-allowed charge less 20 percent beneficiary copayment) on rHuEPO increased rapidly during the first year of coverage because of immediate and extensive rHuEPO use (Figure 7). Total expenditures increased from \$923,000 in July 1989 to \$19,200,000 in June 1990. Cumulative expenditures by Medicare during the first year of coverage were \$144 million, while cumulative coinsurance costs were \$36 million. Again ignoring the possible effects of the changes in payment policy, and assuming no additional diffusion, cumulative expenditures by Medicare would be expected to reach \$230 million in the second year following FDA approval, which represents an increase of approximately 5 percent over total Medicare ESRD expenditures in 1988.

It is also worth noting that the incident ESRD population, which continues to grow, contains an increasingly large proportion of elderly patients who are more likely to receive rHuEPO. This suggests that even if all clinical need for rHuEPO is currently satisfied, expenditures and utilization will continue to grow as new patients enter the ESRD program.

It is important to recognize that the Medicare expenditures that we measured are due only to rHuEPO itself, and therefore may not reflect the net impact on Medicare expenditures of rHuEPO. The extent to which expenditures for rHuEPO are offset by savings resulting from the therapeutic benefits of rHuEPO, or are increased because of side effects of therapy, have been projected with decision modeling (Powe, Griffiths, and Bass, 1993). The projected annual cost of rHuEPO for 53,394 patients in

Figure 7

Monthly Medicare Expenditures for Recombinant Human Erythropoietin: July 1989–June 1990



June 1990, adjusted for savings resulting from therapeutic benefits and costs resulting from side effects, is \$227,084,682, compared with the unadjusted cost of \$230,000,000. Information from claims data might be used to provide current estimates for modeling the extent of additional costs or savings resulting from rHuEPO.

## CONCLUSIONS

Several conclusions may be drawn from our study of early rHuEPO use in the Medicare ESRD program. Some of these may be generalizable to the assessment of new biotechnology therapy or other new technologies for which Medicare and other insurers must make coverage and reimbursement decisions.

## Value of Early Monitoring

First, contrary to a previous appraisal of HCFA policy in establishing mechanisms to routinely monitor rHuEPO dose and patient response (Sisk, Gianfrancesco, and Coster, 1991), we found that the decision to monitor early utilization of rHuEPO provided a valuable base of experience for HCFA and Congress in their evaluation of payment policy (Herdman and Sisk, 1990). Observation of changes in rHuEPO utilization over time, projection of costs and evaluation of effectiveness became possible, and shed light on how various factors influence the way new technologies may be used in clinical practice.

As shown, rHuEPO made a dramatic entry into ESRD patient care after its



approval by the FDA, in large part fueled by uniform health insurance coverage for patients with ESRD. The rate and extent of diffusion, and the effectiveness of rHuEPO, have been shaped by a variety of factors. Patients appear to have obtained access to rHuEPO based on clinical need, but economic incentives created by Medicare payment policy may also have influenced facilities' decisions with respect to rHuEPO use and dosing. Furthermore, although rHuEPO was effective in increasing hematocrit, the hematocrit levels achieved during rHuEPO treatment were lower than anticipated on the basis of experience in clinical trials. Factors that appeared to be responsible for the outcomes we observed, while specific to rHuEPO, the ESRD patient population, and the ESRD provider community, provide valuable insights regarding the relative importance of factors that may influence how technology is used in clinical practice during the early period of its adoption.

### **Usefulness of Data Reporting Requirements**

Second, data collection was designed not only to facilitate evaluation of utilization of services but also to provide a specific mechanism for monitoring effectiveness and quality of care. HCFA included in its data collection measures of the intensity of rHuEPO utilization (dose and number of administrations) and a proxy for health status (hematocrit). The incorporation of these measures facilitated a rapid, unobtrusive and relatively inexpensive means for evaluation of the effectiveness of rHuEPO therapy throughout all dialysis facilities in the United States. Typically, such evaluations through primary data collection efforts require a commitment of substantial resources and often provide selected

and possibly unrepresentative samples of patients. In the late 1970s, however, HCFA made a substantial investment in creating, through collaboration between the Office of Research and Demonstrations, the Bureau of Data Management and Strategy, and the Health Standards Quality Bureau, the ESRD PMMIS. The adaptation of the PMMIS permitted an evaluation of the impact of rHuEPO to take place in a cost-efficient manner.

One limitation of the data was that hematocrit was only available for those who received rHuEPO. As a result, although use was rapid and extensive, we cannot confirm that everyone with a clinical need received rHuEPO. Hematocrit data for all ESRD patients, irrespective of rHuEPO use, might be particularly useful in determining the importance of non-clinical factors in shaping access to rHuEPO. A second limitation was that information on patient weight, an important determinant of rHuEPO dose in clinical trials, and on iron supplementation, which is important to clinical effectiveness of rHuEPO, were not available. Therefore, variability in dosing and effectiveness may have been due to unobserved variability in patient weight and rates of iron supplementation.

One outcome that we could not obtain from claims data was change in quality of life associated with rHuEPO therapy. Improved quality of life may be the most important dimension of rHuEPO's benefits to ESRD patients. To collect such data, HCFA or the National Institutes of Health United States Renal Data System could administer health status surveys to samples of ESRD patients, either by phone or in person. Medical record review, to identify clinical barriers to rHuEPO effectiveness or appropriateness of prescribing, might be coordinated through the ESRD networks, because their responsibility

includes an assessment of quality assurance. These activities, coupled with analysis of claims data, would provide a more comprehensive estimation of effectiveness, cost-effectiveness and quality of care.

### **Payment Policy Revision**

Third, payment policy changed from \$40 for less than 10,000U of rHuEPO and \$70 for 10,000U or more in July 1989 to \$11 per 1,000U of rHuEPO in January 1991. This payment was further reduced to \$10 per 1,000U in January 1994. These revisions were possible, in part, because of the availability of representative data on access, cost, practice patterns, and effectiveness from this early monitoring system and because the U.S. Congress Office of Technology Assessment (OTA) (1990) had previously identified the merits and drawbacks of several alternative payment policy options. For instance, the OTA had evaluated the incentives and disincentives to ESRD providers associated with reimbursement based on the number of rHuEPO U administered, increasing the dialysis capitation payment to allow for the expected cost of rHuEPO, and providing two levels of reimbursement based on dose (the coverage policy selected for use during the first year following FDA approval). Therefore, when data on rHuEPO use during the first year of coverage began to appear, HCFA and Congress were in a position to evaluate the incentives created by the initial payment policy and their impact on access, quality and cost, and to make an informed decision on whether and in what way policy should be revised (Herdman and Sisk, 1990).

### **RECOMMENDATIONS**

Based on our experience from this analysis of Medicare insurance claims, we make

several recommendations that form the basis of a paradigm for monitoring emerging medical technologies of extreme importance to patients, providers and payers. First, we recommend that, prior to the coverage of a technology, payers establish an advisory group that includes experts from administrative departments of insurers (program management, claims processing, and data base management), from clinical medicine, and from health economics and finance. Second, this advisory group should define the outcomes (e.g., access, effectiveness, and costs) that are important to patients, providers and payers and should develop specific measures of these outcomes. Third, the advisory group should identify the data needed to construct these measures. Fourth, the feasibility (advantages and disadvantages) of requiring providers to collect and to report various types of data to construct these measures should be weighed. Finally, a timely decision (prior to insurance coverage) about the most optimal strategy for monitoring the technology should be reached and its implementation should be facilitated rapidly.

### **SUMMARY**

Accurate and timely data were essential in evaluating early use of rHuEPO in ESRD patients. Data will play an increasingly important role if policymakers expect to make informed and prompt decisions on how payment policy should be revised to promote use of pharmaceuticals in a way that results in equitable access, containment of costs, and improved patient outcomes. In the case of rHuEPO, with a change in payment policy, which was then implemented by Congress based on more precise levels of dosing, the economic incentives have been altered in a way to promote higher

doses than those administered during the first year of coverage. Continued observation is necessary, and now possible, to assess not only changes in dosing but changes in health status and costs which are likely to result from the payment change.

The findings from this study illustrate the value of post-marketing surveillance, an important aspect of pharmacoepidemiologic research (Strom, 1989). Such research recognizes that drug effects measured during clinical trials designed to provide information for FDA approval can be markedly different from those measured in routine clinical practice. According to the principles of pharmacoepidemiology, a variety of influences that are excluded from or controlled for in the assessment of the efficacy of a new drug in a clinical trial are important in shaping care in clinical practice, and can play a major role in determining whether patients obtain clinical benefits at a reasonable cost. Some of these include the extent to which the patient population in clinical trials differs from the general population that can potentially receive the drug, the amount of pressure for provider economic viability created by coverage policy, and the quality of patient care in clinical practices throughout the United States.

The relative importance of clinical and non-clinical factors in shaping technology use may change over time as the epidemiology of disease in the patient population changes (growth in numbers of elderly ESRD patients), as the provider community changes (growth of for-profit and free-standing facilities), as technology delivery is changed (administration of rHuEPO subcutaneously rather than intravenously) and as payment policies at the State (Medicaid or State kidney disease-specific programs) or Federal level change. As a result, promotion of the optimal use of rHuEPO and other expensive drugs should be a

dynamic process which pays attention to the changing environment of health care. Therefore, the arrival of promising yet expensive new recombinant pharmaceutical products, such as rHuEPO, makes data systems for early and sustained evaluation more important than ever before.

## REFERENCES

- Canadian Erythropoietin Study Group: Association Between Recombinant Human Erythropoietin and Quality of Life and Exercise Capacity of Patients Receiving Haemodialysis. *British Medical Journal* 300:573-578, 1990.
- de Lissoyoy, G., Powe, N.R., Griffiths, R.I., et al.: Role of Provider Characteristics in Erythropoietin Administration to Hemodialysis Patients. *Journal of the American Society of Nephrology* 2(3):386, 1991.
- Erslev, A.J.: Erythropoietin. *New England Journal of Medicine* 324(19):1339-1344, 1991.
- Eschbach, J.W., Egrie, J.C., Downing, M.R., et al.: Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin: Results of a Combined Phase I and II Clinical Trial. *New England Journal of Medicine* 316:73-78, 1987.
- Eschbach, J.W., Abdulhadi, M.H., Browne, J.K., et al.: Recombinant Human Erythropoietin in Anemic Patients with End-Stage Renal Disease: Results of a Phase III Multicenter Clinical Trial. *Annals of Internal Medicine* 111:992-1000, 1989.
- Evans, R.W., Rader, B., Manninen, D.L., and the Cooperative Multicenter EPO Clinical Trial Group: The Quality of Life of Hemodialysis Recipients Treated with Recombinant Human Erythropoietin. *Journal of the American Medical Association* 263:825-830, 1990.
- Herdman, R.C., and Sisk, J.E.: Testimony Before the House of Representatives Ways and Means Subcommittee on Health. U.S. Congress, 1990.
- Jordan, C.D., Flood, J.G., Laposata, M., and Lewandrowski, K.B.: Normal Laboratory Reference Values. *New England Journal of Medicine* 327:718-724, 1992.
- Laupacis, A., for the Canadian Erythropoietin Study Group: Changes in Quality of Life and Functional Capacity in Hemodialysis Patients Treated with Recombinant Human Erythropoietin. *Seminal Nephrology* 10(Supplement)1:11-19, 1990.
- Leaf, A., and Cotran, R.: *Renal Pathophysiology*. New York, NY. Oxford University Press, 1976.

Lillienfeld, A.M., and Lillienfeld, D.E.: *Foundations of Epidemiology*. New York, NY. Oxford University Press, 1980.

National Kidney Foundation, Ad Hoc Committee: Statement on the Clinical Use of Recombinant Erythropoietin in Anemia of End-Stage Renal Disease. *American Journal of Kidney Disease* 14:163-169, 1989.

Nissenson, A.R., National Cooperative rHu Erythropoietin Study Group: National Cooperative rHu Erythropoietin Study in Patients with Chronic Renal Failure: A Phase IV Multicenter Study. *American Journal of Kidney Disease* 18(4)Supplement 1:24-33, 1991.

Powe, N.R., Griffiths, R.I., de Lissovoy, et al.: Access to Recombinant Erythropoietin by Medicare-Entitled ESRD Patients in the First Year After FDA Approval. *Journal of the American Medical Association* 268(11):1434-1440, 1992.

Powe, N.R., Griffiths, R.I., Greer, J.W., et al.: Early Dosing Practices and Effectiveness of Recombinant Human Erythropoietin. *Kidney International* 43:1125-1133, 1993.

Powe, N.R., Griffiths, R.I., Bass, E.B.: Cost Implications to Medicare of Recombinant Erythropoietin Therapy for the Anemia of End-Stage Renal Disease. *Journal of the American Society of Nephrology* 3:1660-1671, 1993.

Powe, N.R., Griffiths, R.I., Whelton, P., et al.: Short-Term Survival Associated with Use of Recombinant Erythropoietin in ESRD Patients. *Journal of the American Society of Nephrology* 2(3):386, 1991.

Rettig, R.A., and Levinsky, N.G., Eds.: *Kidney Failure and the Federal Government*. Washington, DC. National Academy Press, 1991.

Sisk, J.E., Gianfrancesco, F.D., and Coster, J.M.: Recombinant Erythropoietin and Medicare Payment. *Journal of the American Medical Association* 266(2):247-252, 1991.

Strom, B.L., Ed.: *Pharmacoepidemiology*. New York, NY. Churchill Livingstone, 1989.

U.S. Congress, Office of Technology Assessment: *Recombinant Erythropoietin: Payment Options for Medicare*. OTA-H-451. Washington, DC. U.S. Government Printing Office, May 1990.

U.S. Dept of Health and Human Services, Office of the Inspector General, Office of Audit Services: *The Effect of the Interim Payment Rate for the Drug Epogen on Medicare Expenditures and Dialysis Facility Operations*. CIN Number A-01-90-00512. Washington, DC., 1990.

Watson, A.J., and Spivak, J.L.: Recombinant Human Erythropoietin Therapy in End Stage Renal Failure. *Journal of Clinical Pharmacology* 28:1086-1088, 1988.

Winnerls, C.G., Oliver, D.O., Pippard, M.J., et al.: Effect of Human Erythropoietin Derived from Recombinant DNA on the Anaemia of Patients Maintained by Chronic Haemodialysis. *Lancet* 2:1175-1178, 1986.

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Reprint Requests: Robert I. Griffiths, M.S., Sc.D., Johns Hopkins University School of Medicine, 1830 East Monument Street, Room 8061, Baltimore, Maryland 21205.