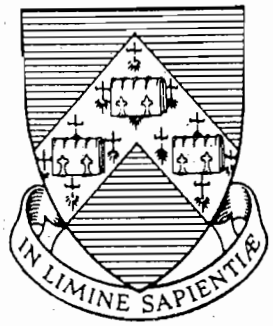

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The Costs and Benefits of the Use of Erythropoietin in the Treatment of Anaemia Arising from Chronic Renal Failure: A European Study

Edited by
Brenda Leese, John Hutton and Alan Maynard

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The Editors

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ABSTRACT

The purpose of this study was to estimate the costs and benefits of the use of erythropoietin (EPO) in the treatment of anaemia arising from chronic renal failure. Recurrent dialysis of chronic renal failure (crf) patients results in their haemoglobin being depleted and the patient becoming listless and weak. The conventional method of mitigating these effects is blood transfusion at regular intervals.

Recombinant human erythropoietin (EPO) maintains the haemoglobin of crf patients at a satisfactory level, avoids the adverse effects of haemoglobin depletion on the patients' quality of life, and removes the risks associated with transfusions. These obvious benefits can only be achieved using the new and expensive drug. However, some resources are saved as blood transfusions are no longer necessary for patients treated with EPO.

To evaluate the costs and benefits of the use of EPO for crf patients a five nation study was funded by Emron Inc. (USA) and managed from the Centre for Health Economics at the University of York, England. An identical research protocol was used by research groups in Italy, France, Spain, Germany and the UK to identify the costs of the use of EPO, the resource savings generated by such a treatment and the effects of this treatment on the patients' quality of life. The impact on patients' quality of life was measured using the Rosser matrix of disability-distress states. The movement between health states in response to the treatment was assessed using expert opinions of nephrologists and a limited amount of patient self-assessment.

The results of the study in the five countries are reported in this paper and show that the use of EPO produces patient benefits at significant cost. Obviously, with such a new technology the cost-outcome (QALY) characteristics of the treatment may change as dosage rates are adjusted to patient responses. However, it seems at present that the use of EPO for patients with end stage renal failure is a high cost way of producing patient benefits, measured in terms of quality adjusted life years (QALYs).

Chapter 1

Overall Summary of results

by B Leese, J Hutton, A Maynard and D Kerr

1.1 STUDY OUTLINE

1.1.1 Objective

A frequent side effect of chronic renal failure is the development of anaemia. This is primarily due to erythropoietin deficiency, although shortened survival of red blood cells and silent blood loss into the gastrointestinal tract (and dialysis equipment) are contributory factors. The traditional treatment has been the use of periodic blood transfusions to alleviate the symptoms. It is now possible to reverse the anaemia by the administration of human type erythropoietin derived from recombinant DNA (Winearls et al, 1986). The purpose of this study is to assess the relative cost-effectiveness of the use of blood transfusions and erythropoietin (EPO) to treat the anaemia of patients undergoing dialysis.

1.1.2 Method

The major impact of the use of EPO is expected to be on the quality of life of renal dialysis patients, rather than survival rates. It is therefore necessary to use a measure of effectiveness which incorporates quality of life assessment as a major element. The study has therefore been conducted as a cost-effectiveness analysis using cost per quality-adjusted-life-year (QALY) gained as the decision criterion.

The calculation of quality-adjusted life years for use in cost-effectiveness studies can be done using different methods (Torrance, 1986). Whichever approach is used the basic steps are as follows:-

a) define the dimensions of health-related quality of life to be measured

b) define different levels on each dimension

c) classify a series of health states comprising one level in each dimension

d) derive a measure of the relative utility of each health state which can be used as a quality-adjustment weight

e) develop a method of determining the health status of any patient at any time

f) estimate the length of patient survival in each health state

g) apply the weights from (d) to calculate the quality-adjusted survival period.

By carrying out steps (f) and (g) for the patient receiving a treatment and not receiving a treatment, and subtracting the latter from the former the net gain in quality-adjusted life years (QALYs) is obtained.

The dimensions and levels of quality of life can be defined in the context of a specific disease or in general terms. The latter approach is more useful in economic appraisal because a generic measure of quality of life can be used to compare the benefits of treating different clinical conditions. It is also preferable that the patients should determine their own health state, since many of the dimensions of health-related quality of life, such as pain and distress, are very subjective. The approach to quality of life measurement used in the study has both these characteristics. It is based on the Rosser classification of health states and full explanation of its practical application can be found in Gudex and Kind (1988). This classification defines 30 possible health states in terms of disability and distress. The classification of illness states and the valuations are shown in Appendix 1.1, together with the associated self-completion questionnaire.

Although experience of the use of EPO is growing, evidence, from controlled studies, of its impact on patient survival and the importance of side-effects is not available. Recently published studies have demonstrated improvements in the quality of life of patients receiving EPO instead of transfusions (Canadian EPO Study Group, 1990; Evans et al, 1990; MacDougall et al, 1990) but the data are not readily adaptable for use in a cost-effectiveness analysis. The time scale of this study did not permit the establishment of prospective trials to generate definitive data. Consequently, the study is based primarily on secondary data, adapting information from published sources and seeking clinical opinion directly on some issues. In assessing the impact on quality of life new data were produced prospectively from small samples of patients in Italy and Spain. This was re-inforced with assessments of patients' quality of life by medical staff in Germany, France and the UK.

1.1.3 Organisation

Separate studies were conducted by health economic institutes in the five countries. The study design and management was undertaken by Emron Inc. and the Centre for Health Economics at the University of York in the UK. A common methodological approach was agreed at the outset and regular consultation took place as the work progressed. The individual study teams in each country were responsible for making contact with local clinicians to obtain data, advice and opinion. An overall review of the studies from a clinical perspective was undertaken at Hammersmith Hospital.

Each individual country study stands as a separate piece of work in its own right, but the common approach has allowed the pooling of data and the formulation of a general view from comparative analysis of the results from different countries.

1.2 BACKGROUND

1.2.1 Renal Replacement Therapy in Five Countries

Detailed factual information on the provision of RRT is given in individual country studies. It is not proposed to repeat this in full but certain points are relevant to the subsequent comparisons. The importance of dialysis, and in particular hospital dialysis, varies very greatly amongst the five countries studied. As can be seen from Table 1.1, the UK differs markedly from the other four in this respect. While these differences will

influence the potential numbers of patients eligible for EPO treatment in each country, they should not affect the estimated effect on a per patient basis provided that equivalent patient groups are being studied.

Table 1.1 RRT patients alive at end December 1986

	Hospital HD	Home HD	IPD	CAPD	Dialysis %	Graft	Graft %	Total	Per m Pop
Germany	15650	1077	119	433	85	3035	15	20314	333
France	9687	1968	154	872	76	3998	24	16679	303
Italy	13049	739	98	1336	88	2121	12	17343	305
Spain	8931	264	66	732	77	3056	23	13049	337
UK	2111	1898	77	2774	51	6638	49	13498	239

Source: EDTA (1987)

1.2.2 Current Use of EPO

The inability to mount specific trials for this study has produced a dependence on secondary data sources. As a consequence of this, the way in which EPO has been used in each country has determined the patient groups for which data on the effects of EPO are available. In some countries, for example the UK, the use of EPO has been restricted by cost considerations and, at the time of the survey, only transfusion dependent patients had received treatment outside formal clinical trials. In other countries such as West Germany, EPO has been available to a wider spectrum of RRT patients.

In estimating the potential impact of EPO, it was agreed that the focus should be "transfusion dependent patients", given that the major advantages of EPO would be expected to give this group most benefits. The definition of such dependence on transfusion is subject to debate and the data used have been determined by the interpretation of dependence at particular clinics and hospitals. In each case, it was vital to know the number of transfusions replaced by EPO, as this not only indicated the severity of the anaemia but also the potential cost savings.

1.3 COST ANALYSIS

1.3.1 Cost Elements

The costs were calculated in four categories: the cost of EPO treatment; costs associated with adverse patient reaction to EPO; the cost of transfusions; and the costs associated with adverse patient reaction to transfusions. The cost of haemodialysis was also included in cases where different survival periods were assumed for patients on the alternative therapies.

1 EPO Costs

EPO costs were taken from the manufacturer and dosages were assumed to be similar between countries. There is some evidence that the dosage could be reduced by the use of subcutaneous rather than intravenous injections.

Studies by Stevens et al (1989), Granaleras et al (1989) and Sinai-Trieman et al (1989) have confirmed the effectiveness of lower dosages in peritoneal dialysis patients. These results would have to be confirmed for haemodialysis patients before they became relevant to the present study. However, the effectiveness of sub-cutaneous EPO would permit alterations in the timing of the dose as well as the reduction of the overall dosage. There is a need for prospective studies to see whether the advantages of daily injections, in terms of reduced adverse reactions, are borne out in practice.

2 Side Effects of EPO

The principal extra cost in dealing with the side-effects of EPO is extra therapy for hypertension. There will also be some consequent costs for extra blood pressure monitoring. Seizures as a complication of hypertension will also lead to hospitalisation costs. The importance of the latter has been documented (Brown et al, 1989), and although the incidence has declined with the more cautious use of EPO, the problem has probably not entirely disappeared.

Some fall in dialysis efficiency occurs with a rise in haemotocrit but the measured effect is small (Casati et al, 1989). As the changes in pre-dialysis creatinine and urea are well within the range accepted in Dialysis Units as day-to-day fluctuations or inter-patient variations, no allowance has been made for any extra costs of dialysis time. Other side-effects which might lead to extra costs are thrombosis of grafts, the need for iron supplements, elevation of plasma potassium, occasional rash and orbital oedema.

3 Cost of Transfusions

The total cost of transfusions is dependent on the frequency of transfusion and the cost of blood units, the first of which varies with the seriousness of the anaemic condition, and the second with the real cost of blood products in different health care systems. The direct cost of blood to the health service will depend on the system of collection, ie. donation or purchase. Even when blood is donated free there is an indirect social cost borne by the donor in terms of lost earnings or leisure time. The costs of screening for blood-borne diseases must also be included with the collection costs. In some circumstances the real cost of red cell concentrates may be much less than the cost of whole blood because the extra demand for plasma leads to the discarding of red cells. However, where plasmapheresis is commonly undertaken this situation will not occur.

4 Side Effects of Transfusions

The principal side-effects of transfusion arise from the risk of transmission of infectious diseases. There is still a risk of AIDS transmission since high risk subjects still persist in donor panels (Leitman et al, 1989) and the rising incidence of AIDS, particularly in the heterosexual population, involves its spread to individuals who do not regard themselves as at high risk (Clumeck et al, 1989). The small risk of transmitting AIDS during the period between acquiring the virus and developing the antibody will presumably be eliminated only when there is routine testing for antigen (Cumming et al, 1989). Costs would not be incurred until infection took place but then the prognosis is poor for those who acquire HIV by blood transfusion (Ward et al, 1989). The worry

engendered in transfusion patients by the risk of AIDS transmission, if serious, might be expected to be reflected in self-assessments of quality of life through the distress dimension.

The screening test for Hepatitis B is for the antigen which should prevent future infections of this type through transfusions.

In recent studies (Alter et al, 1989), the incidence of hepatitis C infection in transfused patients was calculated at 7-12% in the period up to 1980. It is believed to be lower now, but without proof from prospective studies. The illness engendered by hepatitis C is frequently progressive, and lacks a permanent cure (Davis et al, 1989; Di Bisceglie et al, 1989). However, it would be difficult to quantify the ill effects from the present studies, and the major effect is of reduction in life expectancy since the illness is often subclinical until the late stages. It might not, therefore, add much to hospitalisation costs, but its effect should be much more readily seen in the analysis of quality of life.

1.3.2 Cost Results

The inter-country comparisons of the costs of EPO treatment and haemodialysis (in local currencies) are set out in Table 1.2. The costs of EPO per ampoule are similar in all 5 countries, as is the annual EPO cost per patient. The estimated cost of adverse reactions per patient was highest in France, and was considered negligible in the UK. It is, however, clear from the results for all countries, that EPO treatment is considerably more costly than transfusion, by factors ranging from 5 in France to 16 in Spain.

1.4 EFFECTIVENESS ANALYSIS

The effectiveness of EPO treatment was measured using quality-adjusted life-years (QALYs) based on the Kind and Rosser valuation scale for health states. Ideally, the classification of health status is best done by the patients themselves, but this was only possible in a specially conducted experiment in the Spanish study. Data for the German, French and Italian studies were produced by asking clinicians to complete the assessment questionnaire on behalf of their patients. In the UK study, patient-completed assessments of health status using the Nottingham Health Profile were converted to the Kind and Rosser categories by the study team. In all cases, the sample sizes were relatively small, although the German study produced data on a group of 70 patients in one clinic. The German study added in the effect of return to productivity, but it was decided that this approach was best avoided to exclude double counting.

The results are summarised in Table 1.3. The average QALY gain, weighted by patient numbers, is 0.034 with a range from 0.02 to 0.048. The largest average gain was found in the UK. This could have been a reflection of the greater average severity of anaemia in the limited number of patients given EPO in the UK, the initial quality of life score (before EPO) being the lowest for this group. However, the UK data were transformed from the NHP and so could contain bias.

Table 1.2 Inter-Country Comparison Cost Estimates (1988 prices)

	FRG DM	France FF	Spain Pts	Italy L	UK £
EPO per ampule	98-160	350	5,684	73,777	36
Annual EPO Cost per Patient	12,000	36,400	866,000	7,672,808	5,616
EPO Annual Cost of Adverse Reaction per Patient	N/A	1,825	2,150	23,967	N/A
Blood Unit	200	1,282	14,072	138,650	35
Annual Transfusion Cost per Patient	2,400	7,234	53,546	1,096,550	665
Blood Annual Cost of Adverse Reaction per Patient	4,000	10,147	1,630	242,151	N/A
Annual Cost of Haemodialysis per Patient	64,000*	300,000	3,974,052*	35,000,000*	15,000

*Estimate based on £20,000 p.a. assumption

The Spanish figures show relatively high absolute levels and a small average net gain. The study team indicated that this could be a reflection of the adjustment of patients to a disabled life-style which resulted in higher self-estimation of health status compared to the clinical view.

As would be expected, the introduction of the costs of side-effects reduces the cost per QALY figures, except in the UK and Spain where the net cost of side effects of transfusions is thought to be negligible.

No direct evidence of any impact of EPO on survival was discovered, but because of the possibility being confirmed in future, some sensitivity analysis was carried out. The average life expectancy of a patient on hospital haemodialysis is 10 years. The implications of EPO extending this to 11 years were explored. This requires a discounted flow analysis because of the different time periods being compared (eleven years of EPO vs. ten years of transfusions). In the eleventh year, EPO would bring a whole year of extra benefit weighted by the appropriate Kind and Rosser value. It would also bring additional costs of EPO treatment (without compensating savings from avoided transfusions) and an extra year of dialysis treatment.

However, it is improbable that there will ever be an adequate prospective double-blind controlled trial of EPO spread over the five plus years that would be needed to demonstrate convincingly an improvement in life

expectation. Since the potential adverse effects of EPO, such as an increased incidence of vascular thrombosis, might take years to become apparent, a shorter time scale would not be convincing to most clinicians. The difficulty is that such a trial requires matched groups who can be persuaded to stay on their assigned form of treatments over the course of many years, and therefore the need to ask the patients to forego their chance of transplant during this period. If the 2 groups can be whittled down by renal transplantation, then there would be few valid conclusions that could be drawn from the technique survivors at the end of the study.

If the reasons why life expectation improvement has to be assumed rather than demonstrated can be established, one of the major criticisms of this approach will be overcome. The reasons for believing that there will be an improvement in life expectation must then be cogently argued, as shown below:-

	Favouring Better Life Expectation		Favouring Shorter Life Expectation
1	Freedom from blood transfusion	1	Risk of increased hypertension
2	Avoidance of AIDS	2	Risk of vascular thrombosis
3	Avoidance of Hepatitis B	3	Possibility of less efficient dialysis
4	Avoidance of Hepatitis C		
5	Avoidance of CMV infection		
6	Avoidance of iron overload		
7	Avoidance of HLA sensitisation		
8	Probable beneficial effect on general health, greater mobility, exercise, etc		
9	Possible beneficial effects of EPO on amino acid metabolism (Riedele et al, 1988)		
10	Improvement of hormonal status (Schaefermm et al, 1989)		

1.5 COST EFFECTIVENESS

The impact of the assumption of an extra year of survival with EPO is quite dramatic as is shown in Table 1.4. The savings from reduced side effects of transfusions also have a big impact on the French and German figures. The relatively high Spanish cost per QALY is partly explained by the low net change in Kind and Rosser's value observed. Once increased survival has been assumed, the figures come more into line with the results of the other studies.

The range of cost per QALY figures for EPO is from $349,000 to $58,600, depending on the assumption made and the country studied. The weighted average is $137,000.

The range is also the result of different criteria for the selection of EPO patients. The average number of transfusions being given to the samples of patients studied in each country varied considerably.

Table 1.3 Inter-Country Comparison Cost Effectiveness Estimates

	FRG DM	France FF	Spain Pts	Italy L	UK £
Average Patient Quality of Life Score on Transfusion	0.926	0.937	0.965	0.948	0.917
On EPO	0.956	0.974	0.985	0.988	0.965
Net QALY gain per Patient	0.030	0.037	0.020	0.040	0.048
Cost per QALY					
1 Treatment Cost Only	320,000	788,270	40,622,700	164,406,240	103,145
2 Treatment Cost + Side Effects	186,666	563,357	40,648,700	158,957,649	-
3 Treatment Cost* + Side Effects + 10% Increase in Survival	109,701	438,763	12,469,649	82,732,241	53,805

* Discounted analysis using 5% discount rate

Table 1.4 Inter-Country Comparisons
Cost per QALY $US (1988)

	FRG	France	Spain	Italy	UK
$1 =	DM 1.87	FF 6.31	Pts 116.4	L 1373.35	£0.5858
1 Treatment Cost Only	171,123	124,924	348,992	119,712	176,075
2 Treatment Cost + Side Effects	99,821	89,279	349,215	115,740	-
3 Treatment Cost* + Side Effects + 10% Increase in Survival	58,663	69,534	107,127	60,241	91,848

* Discounted analysis using 5% discount rate.

1.6 EPO IN CONTEXT

1.6.1 A summary of some recent quality of life studies

The clinical benefits of EPO are now well recognised and include (1) restoration of haematocrit to normal levels (2) elimination of the need for transfusion (3) relief from symptoms of anaemia. However, although EPO has been accepted as having an important contribution to make to the clinical health status and well being of patients undergoing haemodialysis, there has been some concern that the effect of EPO in raising blood viscosity might increase the risk of thrombotic complications. Also, patients on haemodialysis have greatly reduced exercise capacity and impaired cardio-respiratory function, mainly due to the chronic anaemia. Indeed, cardiovascular complications account for more than half of all deaths in patients with chronic renal failure, and EPO treatment should not exacerbate these problems. EPO patients report subjective improvement in well being and exercise tolerance, but little is known about the secondary effects such as the rise in haematocrit.

Such complications outlined above, have to be balanced against patients' perceived improvement in their quality of life. Until recently, studies on quality of life of patients on EPO have been subjective and unquantified. However, some recently published studies have described attempts to quantify the beneficial effects of EPO, and have indicated that they do, indeed, outweigh the disadvantages, at least in the short term (Evans et al, 1988; MacDougall et al, 1990; Canadian EPO Study Group, 1990).

The Canadian EPO study group carried out a double-blind, placebo controlled trial of 118 patients randomised into three groups; a placebo group, and 2 groups with different EPO dosage regimes. It was found that EPO patients were less fatigued, reported fewer severe physical symptoms, and had moderate improvement in exercise tolerance and depression when compared with the placebo group. However, they did have a higher incidence of hypertension and clotting of the vascular access.

In contrast to the Canadian study, Evans et al reported that, in view of the perceived benefits of EPO, use of a placebo would be unethical, so a study involving 300 patients in 9 centres used baseline and follow up data together with a control group from the National Kidney Dialysis and Kidney Transplantation Study to assess quality of life based on the Nottingham Health Profile. Results were similar to those of the Canadian study with improvements noted in energy activity levels, sleeping and eating behaviour, and well being and happiness. However, there was no change in ability to work or in employment status - a not unexpected finding in view of this group of patients' previous severe problem and the length of time already taken off work. There were similar findings in a small study involving six patients in Manchester (Twomey, 1990).

Bearing in mind the problems of hypertension and blood viscosity noted by the Canadian group, MacDougall et al carried out a study on 10 patients over 12 months to assess the long term cardiorespiratory effects of EPO. This study did not have a control group although patients were assessed before commencing EPO treatment, and again 2, 4, 8 and 12 months afterwards. MacDougall et al found improvements in exercise time, maximum oxygen consumption and anaerobic threshold at 2 months, and these improvements were maintained, but not augmented, subsequently. A substantial reduction in

exercise induced cardiac ischaemia was noted, despite a rise in whole blood viscosity, paralleling the Canadian study. This study also suggested that EPO might have longer term beneficial effects. It is known that anaemic patients have high cardiac output which results in hypertrophy of the left ventricle, an important factor in the survival of haemodialysis patients. MacDougall et al's study found a 30% decline in left ventricular mass after 12 months on EPO, but longer term studies are needed to assess the effect on survival rates.

1.6.2 Other QALY Estimates

A limited range of other clinical interventions have been assessed using QALYs. In Table 1.5 a list is given showing where EPO appears in the ranking. Although the ranking is low, it must be remembered that the list is far from comprehensive, and does not imply that EPO is at the bottom of all clinical priorities. Also EPO is not a life-saving intervention, its benefits come principally in terms of improved quality of life. Haemodialysis itself is the life-saving intervention with an estimated cost/QALY of around $19,000. Viewed from this standpoint, the results of EPO may be regarded more favourably.

1.6.3 The QALY Method

QALY estimates, like all medical evaluation data, are best derived from controlled clinical trials. Given the short-time scale and preliminary nature of this study, the results are remarkably consistent. Obviously, confirmation from specifically designed trials would be desirable before basing any policy decisions on the conclusions, but the message is fairly clear. At current prices, EPO can only produce a competitive cost per QALY for patients with serious incapacity as a result of anaemia. Using EPO for any haemodialysis patients who have transfusions (rather than transfusion-dependent patients) would be an expensive way of gaining health benefits.

The Kind and Rosser scale shows only small variations for movements between health states in low disability categories. This is not a disadvantage for an instrument designed to compare the whole range of clinical interventions. A specific quality of life measure to record the effects most often found with EPO might appear more sensitive, but would not allow comparison with other clinical procedures in a systematic way, thereby rendering the analysis interesting, but not useful for decision-makers.

1.6.4 Cost Benefit Analysis

In some of the studies, the possibility of cost-benefit analysis was examined by valuing the projected productivity gains from the use of EPO. Some transfusion dependent patients might be able to return to work when receiving EPO treatment, and others might be able to return to more appropriate jobs. The results showed that the value of these benefits was well short of the net cost of the EPO treatment. In the absence of sound methodology for valuing some of the other benefits, CBA was considered unsuitable as a means of assessing the value of EPO.

Table 1.5 Comparison of Cost/QALY for Selected Clinical Interventions

	Cost ($US 1987) Per Well Year
Pneumococcal Vaccine, Older Adults	1,500
Phenylketonuria Screening	7,000
Screening for Severe Hypertension (diastolic blood pressure above 105)	9,200
Behavioural Intervention in NIDDM	10,870
Screening for Mild Hypertension (diastolic blood pressure 95-105)	18,600
Estrogen Replacement in Post-Menopausal Women	23,500
Rehabilitation in Chronic Obstructive Pulmonary Disease	24,600
CABG, Two Vessel Disease	32,700
EPO Therapy (with 10% increase in life expectancy)	**
Pneumococcal Vaccine, Young Children	114,900
EPO Therapy (no increase in life expectancy)	**
CABG, Single Vessel Disease	515,000

** Comparative location of EPO treatments

The use of the QALY approach is a form of cost-effectiveness or cost-utility analysis, which includes patients' subjective assessment of quality of life, including the ability to work. To subtract alleged productivity gains from the cost of EPO in such cases would be double-counting the benefits.

1.6.5 Recent changes in EPO dosages

Since the 5 European studies were compiled, there have been attempts by physicians to reduce the high cost of the drug per patient, and to allow more patients to benefit from its use. This has been achieved in a number of ways. One way in which this has been carried out is to give patients a lower dose of EPO than that recommended by the manufacturers.

In the UK, the estimated costs shown in Chapter 6 are based on an average dose of 3 vials of EPO per patient per week. If this were reduced to 2 vials per week, then the annual EPO cost per patient would fall from £5,616 (Table 1.2) to £3,079, giving a cost per QALY (treatment costs only) of £64,146 instead of £103,145 (Table 1.3). Expressed in dollars, treatment costs would then become $109,502 instead of $176,075 (Table 1.4). However,

in these circumstances, it is possible that a lower dose might have a lower impact on the patient's quality of life, which would lead to an increase in the cost per QALY. There are no figures for the quality of life of patients on these lower doses of EPO in the UK, so it is not possible to make any assumptions. It is also possible that the quality of life tool is, in any case, not sensitive enough to detect such small differences.

In the Spanish case study (Chapter 5), estimated costs were based on an average dose of 65U per kg, which was the intermediate dose described in Table 5.6. If the results are recalculated using the lower figure of 50u per kg in Table 5.6, then the annual cost of EPO per patient falls from 866,000 pesetas to 666,200 pesetas (Table 1.2), which in turn leads to a cost per QALY of 30,632,700 pesetas instead of 40,622,700 pesetas (Table 1.3). In dollars, the treatment only cost per QALY becomes $263,168 instead of $348,992 (Table 1.4). The same caveats with regard to changed quality of life effects apply as in the UK case study.

In the German case study (Chapter 3), the cost of EPO treatment per patient per year was given as 10,000 to 15,000 DM, and for the calculations, a mean figure of 12,000 DM was used (Table 1.2). If the lower figure of 10,000 DM is used, then treatment only cost per QALY becomes 253,333 DM against the higher value of 320,000 DM in Table 1.3. In dollars (Table 1.4), the treatment only cost becomes $135,472, compared with the higher figure of $171,123. Again, the quality of life changes have remained unchanged.

The French and Italian studies were both based on a dose of 2 vials per patient per week, so no additional calculations have been made. When the QALY differences, set out in Table 1.3, are compared, there is no dose-related pattern, suggesting that either the QALY is not sensitive enough to pick up small changes in quality of life, or that there were no dose-related differences in quality of life.

In some instances, physicians have switched to subcutaneous administration of EPO, which has a longer plasma half life, so enabling lower doses to be used to achieve the same effect. In Middlesbrough, physicians have divided the total amount of EPO they were able to finance from their budgets, among all patients, so that all have some benefit, but this method has not been evaluated (South Tees Health, 1990).

In the UK, health authorities have been encouraging GPs rather than consultants to prescribe expensive drugs. This helps to cut hospital costs and puts the cost onto GP drug budgets which have not been cash limited. However, problems will arise when GPs have indicative drug budgets (Millar, 1990).

EPO is presented in 1ml ampoules intended as a single dose, which can lead to expensive waste of a valuable drug. A multidose preparation would allow the drug to be used on a more economical basis.

EPO remains an expensive drug, even when the dose is reduced. There will undoubtedly be further dose reductions while still retaining benefits, but the improvement in patient quality of life is likely to ensure that the drug becomes an increasingly important factor in the treatment of patients with chronic renal failure.

Appendix 1.1 Rosser's Classification of Illness States

	DISABILITY	DISTRESS
I	No disability	A. No distress
II	Slight social disability	B. Mild
III	Severe social disability and/or	C. Moderate
IV	Choice of work or performance at work very severely limited Housewives and old people able to do light housework only but able to go out shopping	D. Severe
V	Unable to undertake any paid employment Unable to continue any education Old people confined to home except for escorted outings and short walks and unable to do shopping Housewives able only to perform a few simple tasks	
VI	Confined to chair or wheelchair or able to move around the house only with support from an assistant	
VII	Confined to bed	
VIII	Unconscious	

Valuations for 29 Health States in Rosser Index

Disability	A	B	C	D
I	1.000	0.995	0.990	0.967
II	0.990	0.986	0.973	0.932
III	0.980	0.972	0.956	0.912
IV	0.964	0.956	0.942	0.870
V	0.946	0.935	0.900	0.700
VI	0.875	0.845	0.680	0.000
VII	0.677	0.564	0.000	-1.486
VIII	-1.028	-	-	-

FIXED POINTS: HEALTHY = 1 DEAD = 0

See: Kind, Rosser and Williams (1982)

SELF-COMPLETED QUESTIONNAIRE

GENERAL MOBILITY

Which one of these statements best describes your situation?

I can move around indoors and outdoors on my own easily with no aids or help. ☐

I can move around indoors and outdoors on my own with a little difficulty but with no aids or help. ☐

I can get about indoors and outdoors on my own but I have to use a walking aid e.g. stick, frame, crutch, wheelchair, etc. ☐

I can move around the house without anyone's help but I need someone's help to get outdoors ☐

I spend nearly all my time confined to a chair (other than a wheelchair). ☐

I have to spend nearly all my time in bed. ☐

SELF-CARE

Do you have difficulty with any of the activities listed below? If you do, do you also need help from someone else to do them?

	NO DIFFICULTY AT ALL	SOME DIFFICULTY BUT COPE ON MY OWN	SUCH DIFFICULTY THAT I NEED SOMEONE'S HELP
Washing yourself	☐	☐	☐
Dressing yourself	☐	☐	☐
Eating or drinking	☐	☐	☐
Using the toilet	☐	☐	☐

USUAL ACTIVITY

During the last two weeks has your health affected any of the things you usually do (e.g. at work or study, at home)?

Not at all	☐
Slightly affected	☐
Severely affected	☐
Unable to do usual activities at all	☐

SOCIAL AND PERSONAL RELATIONSHIPS

Does your state of health seriously affect any of the following?

Your social life?	Yes ☐	No ☐
Seeing friends or relatives?	Yes ☐	No ☐
Your hobbies or leisure activities?	Yes ☐	No ☐
Your sex life?	Yes ☐	No ☐

FEELINGS

Over the last two weeks has your state of health led you to experience any of these feelings? If so, how much distress have they caused you? Mark a cross on the line.

	No	Yes	NO DISTRESS AT ALL — EXTREME DISTRESS
Feeling sad or depressed	☐	☐	
Feeling anxious or worried	☐	☐	
Pain	☐	☐	
Dissatisfaction with your weight	☐	☐	
Dissatisfaction with your appearance	☐	☐	
Embarrassment	☐	☐	
Uncertainty about the future	☐	☐	
Anger or resentment	☐	☐	
Guilt	☐	☐	
Loneliness	☐	☐	
Loss of self-confidence	☐	☐	
Feeling dependent on other people	☐	☐	
Feeling dependent on machine for my health	☐	☐	
Feeling sick	☐	☐	
Breathlessness	☐	☐	
Difficulty sleeping	☐	☐	
Lack of energy	☐	☐	
Incontinence (i.e. lack of control over bladder or bowel movements)	☐	☐	

	No	Yes	NO DISTRESS AT ALL	EXTREME DISTRESS
Inability to concentrate	☐	☐		
Poor memory	☐	☐		
Difficulty in speaking	☐	☐		
Difficulty in hearing	☐	☐		
Difficulty in writing	☐	☐		
Difficulty in seeing	☐	☐		
Any other problems that cause you distress?	☐	☐		

Please specify

_____

How much does your state of health distress you overall? Mark a cross on the line.

NO DISTRESS AT ALL — EXTREME DISTRESS

_____

What aspect of your state of health most upsets you?

_____

_____

_____

Chapter 2

The French Case Study

by F Fagnani and R Landman

2.1 INTRODUCTION

An economic analysis of the diffusion of EPO in the treatment of anaemia in patients on dialysis has been performed in France. Most of the physicians directly involved in the process of clinical experimentation and/or playing a role in the diffusion of this treatment in France have been approached and interviewed (see list included in Appendix 2.1). In general, these contacts have been easy to establish and have allowed the collection of a large quantity of information. However, there were two kinds of difficulties.

The first was related to the lack of an existing data base for the population of patients treated for chronic renal failure on a national scale. Aside from the data collected through the EDTA network (EDTA, 1986), no statistical information seemed to exist on the general characteristics of this population as far as demographic variables, physical and social disability, etc were concerned. For instance, no available data was found on the breakdown by age, sex and occupation of the population on dialysis. The only way to manage such a situation seemed to rely on information coming from nephrology units and centres, with the problems of judging their representativeness.

The second type of difficulty was related to the specific context and time period of this investigation. EPO had only recently been certified on the French market, creating a number of controversial reactions from nephrologists and patient organisations. It seemed that the agreement for the marketing of the Cilag product was determined on the basis of a quota of utilisation defined as 10% of the potential group of patients eligible, and at a price of 350 FF/ampule. This way of regulating the diffusion of a pharmaceutical is unique in France and has already produced a number of reactions. In this context, most of the nephrologists interviewed were directly involved in this debate and had not much time left to cooperate in the analysis. Incidently, this specific situation has led to more elaborate questioning of the proposed method for the determination of priorities in the indications of EPO treatment.

2.2 GENERAL CHARACTERISTICS OF DIALYSIS IN FRANCE

At the end of 1986, the number of patients alive on dialysis was 12,407 (at the same time, 3,998 patients were alive with a functioning graft). The breakdown was as follows:

9,296 were treated in hospital (excluding self care), 1,101 were on self care dialysis and 2,010 were on home dialysis.

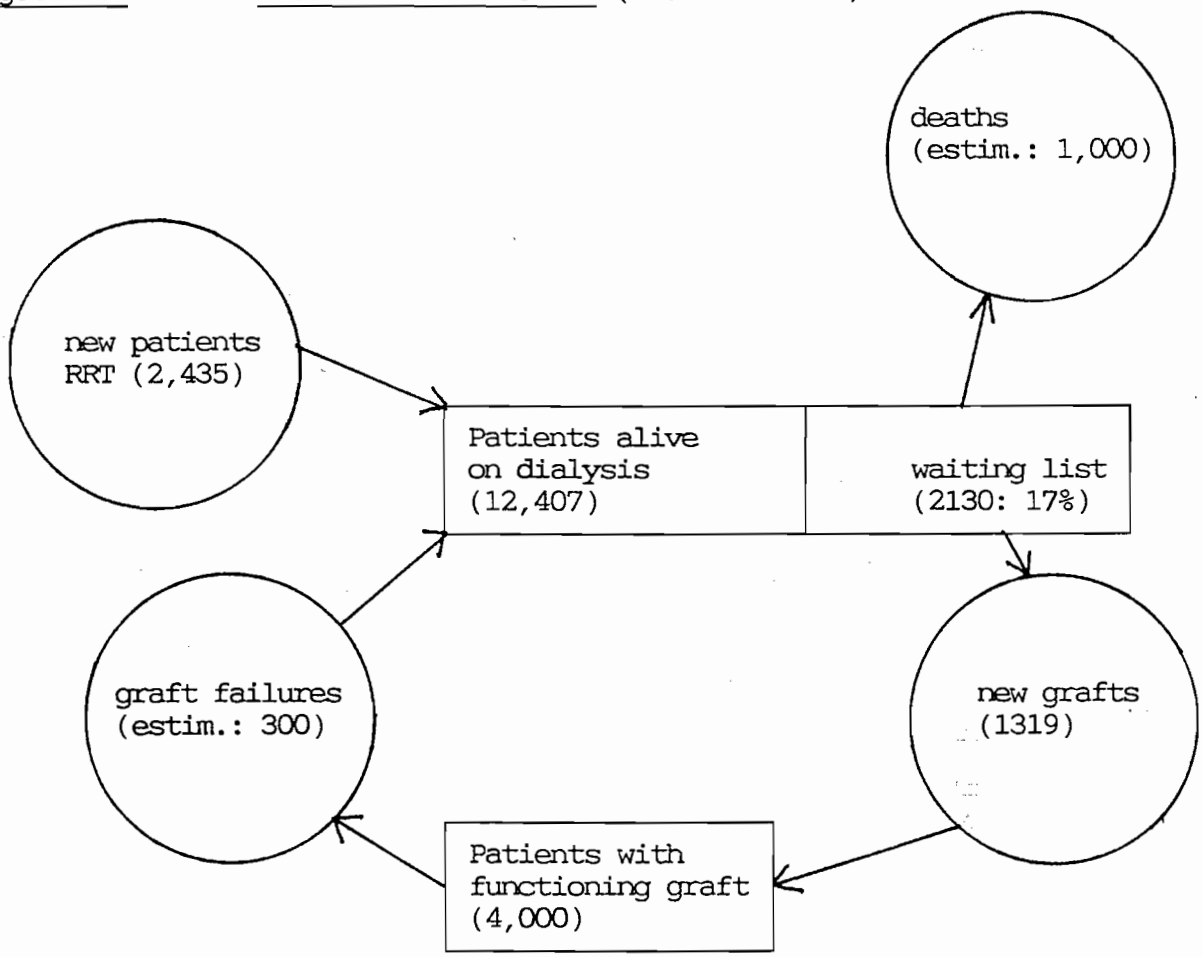
The number of new patients accepted for renal replacement therapy during 1986 was 2,435 (incidence rate of 44.2 per million population). The corresponding number of grafts performed in 1986 was 1,319 (23.9 per million population). The predominant method of renal replacement therapy during the period 1983-85 was haemodialysis (in 83% of cases) and peritoneal dialysis was

used in the remaining 17% of cases. These figures were extracted from the information collected by the EDTA registry and covered 87.3% of the known centres operating in the country.

A more recent estimation of the total number of cases (patients alive on dialysis at the end of 1988) is 16,000. An estimated annual net increment of about 500 to 700 patients is generally quoted by the nephrologists involved.

Figure 2.1 is a tentative summary of the different flows of patients that have to be considered in predicting their future numbers. The figures correspond to the year 1986. Figures appearing in rectangles represent prevalence rates at the end of 1986. Those in the circles are incidence rates during the year 1986, some of which are crude estimates.

Figure 2.1 Flows of Patients RRT (France - 1986)



Although there is no national detailed information on this matter, it appears that this population is getting older. The main reason for this is progressive extension of the indications of treatment to the older population with RRT. Using data from a centre covering a whole region in the south-east of the country (Isere), it appears that the mean age of this population is now around 50-55 years (62% are between 15 and 59 years and, 38% are over 60 years). The patients relying on self care are younger than those treated in hospital.

2.3 OPINIONS OF NEPHROLOGISTS REGARDING EPO

Of the 221 centres known to the EDTA Registry in 1986, the seven centres which have at present experienced EPO therapy through clinical trials in connection with Cilag (French subsidiary of Johnson and Johnson) have been contacted. The first of these trials began in 1986. The number of patients included in these trials varied from 10 to 30, according to the centre. The total experience gained from the trials currently performed concerns 120 patients, mainly adults (only 10 among this total are children under 15 years of age, in the unit of Professor Broyer, Hospital Necker, Paris). Most of the centres involved can be considered, from different points of view, as being leaders in the field of French nephrology. Many are located in large University Hospitals (Paris, Montpellier); their activities are important, their leaders have excellent clinical reputations and are often acting as advisers to the French Ministry of Health and involved in different national and international professional bodies. In consequence, the opinions expressed by these physicians represent the best available expertise on the question in France, and are highly predictive of the likely attitudes of French nephrologists in the near future.

However, it has to be remembered that the indications for the use of EPO will also largely be influenced by administrative constraints in relation to the regulation of the costs associated with them. At present, the situation is still too complex to predict with any confidence the final decisions which are likely to occur.

2.3.1. A large consensus on the importance of the benefits of EPO treatment

Among the nephrologists interviewed, it was generally agreed that EPO was, in their opinion, the most important therapeutic innovation in the field of dialysis, to emerge in the last ten years. These opinions resulted from their personal experience gained through clinical trials with EPO. They considered that the increase in haemoglobin level to 10 g/dl or more in their patients has clearly improved their quality of life in terms of physical performance in day-to-day activities and in relation to psychological well-being.

2.3.2. Medical indications for EPO

In the first stage, the nephrologists were asked what they considered to be the main indications for EPO therapy, leaving aside any considerations of cost constraints or availability of the product. A provisional method of priorities was proposed in order to obtain a ranking of the criteria of eligibility for the treatment. The criteria which were identified relevant were the following:

- history of polytransfusion
- degree of anaemia: three classes were taken (<6; between 6 and 8; >8 g/dl)
- presence of coronary disease
- age
- tolerance to anaemia.

Aside from these "positive" criteria, a set of exclusion factors was also identified:

- patient at risk of thrombosis (due to hyperviscosity)
- severe hypertension
- history of convulsions.

The nephrologists were asked to assign a score expressing their views on the relative importance of each criterion and combinations of criteria for eligibility for EPO treatment. Table 2.1 summarises the results. The scores were assigned on a scale from 0 to 5, with 5 an absolute priority and 0 an absence of indication (the exclusion factors would, in this respect, be attributed a score of zero).

Table 2.1 Tentative Criteria for Expression of Priorities of EPO Treatment

Criteria	Score
- > 1 blood transfusion in the last trimester	5
- Hb < 6 g/dl	5
- 6 < Hb < 8 g/dl	
+ coronary disease	5
+ according to age and tolerance to anaemia	3 to 4
- 8 < Hb < 10 g/dl	
+ coronary disease	4
+ according to age and tolerance to anaemia	2 to 3
- exclusion factors	0 to 1

These criteria do not include the probability of the patient receiving a graft. The French nephrologists considered that this was not a relevant criterion for eligibility for EPO therapy.

Two of the physicians interviewed would not prescribe EPO to patients in their first year of dialysis because the Hb level of those patients was expected to increase normally upon the use of dialysis, in most of the cases. This was only applicable to adults.

The paediatric cases (less than 15 years of age) presented distinctive aspects. In 1988, the total number of patients in that group in France was between 200 and 250. The haematocrit value was 17%, which implied that all ought to benefit from EPO treatment, in the opinion of the paediatric nephrologists. This treatment has to be started at the onset of dialysis because these patients have no chance of improving their anaemia by dialysis alone.

Some physicians have expressed the view that the indications for EPO treatment should integrate assessment of the role of anaemia in limiting the social and physical activities of the patients. In all the cases where other conditions or factors (for example, psychological or medical) were the main causes of disability or distress, they considered that the improvement expected from EPO would not modify significantly the performance and states of health of those patients and therefore, they tended to exclude them from therapy. This can be illustrated by the example of Dr Florence from the centre in Montpellier. Of the total number of patients treated in this centre (137), 37 had cardiovascular function impaired by anaemia and should potentially benefit from EPO on purely clinical criteria. However, 16 of them have been excluded, because it was considered that their general state of health and social condition were limited primarily because of other factors which were not expected to be modified by the suppression of anaemia. This attitude was, however, questioned by other clinicians.

Some nephrologists have expressed concern about a possible negative consequence of the generalised use of EPO therapy in all cases of anaemia i.e. it could lead to a neglect of careful follow-up and adjustment of dialysis, integrating educational aspects, hypertension control, and the diagnosis and treatment of other causes of anaemia. One extreme view on this point was expressed by a nephrologist in Lyon, who is one of the rare French physicians to continue to routinely prescribe and operate dialysis sessions lasting more than eight hours, a method which has the advantage of preventing anaemia and, therefore, of reducing significantly the frequency of EPO indication.

2.4 SEVERITY OF ANAEMIA AMONG PATIENTS ON DIALYSIS

The distribution of haemoglobin concentration among patients on dialysis is not known on a national basis. It was only possible to obtain this information from patients at two regional centres (Grenoble and Montpellier) which represent a total of 337 patients. The proportion of patients with different levels of anaemia are as follows:

- Hb < 6 g/dl : 2 to 4%
- 6 < Hb < 8 g/dl : 25 to 30%
- 8 < Hb < 10 g/dl : 35 to 40%

There was no direct and automatic correlation between the consequences of anaemia in a particular patient and the level of haemoglobin. Furthermore, nephrologists may differ substantially in their attitudes concerning prescription of blood transfusions. All these reasons lead to the conclusion that a more relevant description of the actual modalities of treatment of anaemia was the direct observation of the practice of blood transfusion in patients on haemodialysis.

Some data of this kind have been collected (Rousseau, 1988) for the year 1987 in a sample of six units, located in the Paris region and covering the whole range of categories of French medical institutions (two private, two private not-for-profit, two public centres). The total number of patients in the centres was 309. Three populations of patients could be classified according to the annual frequency of blood transfusions:

- the first category received no blood transfusion during the year; 41%

of the total population;

- the second category received between one and three transfusions (two to six blood units); 39% of the total population;

- the third category had four or more blood transfusions in the year (20% of patients).

2.5 ESTIMATION OF THE NUMBER OF PATIENTS ELIGIBLE FOR EPO

Considering the different previous estimates of patients on dialysis, the frequency of anaemia at different severity levels and considerations of criteria of eligibility, it is possible to get some insight into the potential number of patients who could be treated by EPO in France. It seems appropriate to estimate that on purely clinical considerations, approximately 50% of all patients on dialysis are eligible for EPO, if the reasoning of the French nephrologists involved is followed. This figure yields a number of around 8,000 patients in 1989.

A more realistic approach, integrating both economic considerations and more restrictive clinical criteria (for example, anaemia corresponding to an Hb concentration under 8 g/dl or patients receiving regular blood transfusions) would give a proportion of 30% of patients on dialysis: that is about 5,000 patients. It is this last figure which seems a more realistic estimate of the probable future utilisation of EPO in France, and will be used in subsequent calculations in this report.

In a recent proposal, the French Ministry of Health authorised the use of EPO for only 10% of the group of potentially eligible (1,600) patients. This decision, which was heavily debated, rested on two main arguments. The first related to the costs involved: the Ministry was probably willing to restrict EPO use in the absence of competitors in this market. The second argument was related to the fact that experience with this therapy is still limited and that it seemed appropriate to wait until more information became available on optimal dosage, side effects and efficacy.

2.6 EVALUATION OF THE DURATION OF EPO TREATMENT

Two categories of patients have to be considered, according to the group of nephrologists consulted.

1. The first group are patients on the waiting list or eligible for a graft. This consisted, in France, of 17% of the total number of patients currently on dialysis. The mean expected duration of EPO treatment in that group was around two years. Considering the fact that a proportion of those patients will not be treated in their first year of dialysis (according to the attitude of some nephrologists) it is estimated that the mean duration of EPO treatment in this group, for the purposes of this report, is 2 years.

2. The second group of patients consisted of those who were not eligible for grafting. The question of estimating the duration of EPO treatment raised some methodological difficulties. In principle, this length of time is the life span of those patients. However, different considerations suggest that a shorter period would be sufficient. Considering that the mean age of this potentially treated cohort is around 50 to 55 years of age, the life expectancy of such a cohort in the general population would be around 25

years. There is no direct information concerning the actual corresponding figure for the group of patients under consideration. One plausible estimation would be to reduce this value by a factor of 2. In the context of the present study, even this mean estimated period of 12.5 years is probably too long, because of multiple uncertainties: future costs of EPO in a competitive market, emergence of other therapeutic innovations, increase of the number of grafts performed, improvement of immunosuppressive regimens, etc.

2.7 ESTIMATION OF THE CONSEQUENCES OF EPO TREATMENT

2.7.1 Effect on life expectancy

It could easily be predicted that EPO treatment of patients suffering from anaemia will improve their life expectancy; most of the nephrologists interviewed seem to agree with such a prediction but there is, at present, no way of demonstrating and documenting it quantitatively in any respect. Furthermore, the general information concerning the vital statistics of patients with end stage renal disease is very poor in France. As a result, a 10% increase in life expectancy attributable to EPO treatment has been assumed. Rather than using a life table methodology, the survival of two cohorts of RRT patients (EPO-treated vs transfused) have been compared, using the mean duration as an approximation. Table 2.2 presents the coefficients that must be applied in order to determine the annual number of patients in these two cohorts. Two other assumptions have been made: a) twenty percent of RRT patients are expected to be grafted after a mean period of 2 years, and b) the final health outcome of grafting is similar for the two groups with regard to life expectancy and success of the graft.

Table 2.2 Expected evolution of two cohorts of RRT patients

Year	1	2	3	4	5	6	7	8	9	10	11	12
Dialysis + EPO	1	1	.8	.8	.8	.8	.8	.8	.8	.8	.8	0
Grafted	0	0	.2	.2	.2	.2	.2	.2	.2	.2	.2	0
Dialys. + transfusion	1	1	.8	.8	.8	.8	.8	.8	.8	.8	0	0
Grafted	0	0	.2	.2	.2	.2	.2	.2	.2	.2	.2	0

2.7.2 Assessment of the quality of life

The classification developed by Kind and Rosser (Gudex and Kind, 1988) which defines 30 possible health states in terms of disability and distress and the corresponding questionnaire, have been translated into French. These questionnaires have been presented to the nephrologists in charge of three centres, (Professors Mion and Florence in Montpellier, Dr Foret in Grenoble and Dr Drueke in Hopital Necker in Paris). Each of these centres have used EPO on groups of 20 to 40 patients.

These nephrologists were interested in this approach; they had no way of quantifying the subjective and functional dimensions of the outcome of the

treatments they prescribe. They found the questionnaire relatively easy to answer but maybe not specific enough to express particular aspects relating to patients with end stage renal disease. Only the last two centres have provided the results of the questionnaire within the time scale of the study. The total population of patients is 57 (36 patients from Hopital Necker and 21 from Grenoble). The 21 patients from Grenoble were all polytransfused, although this was the case for only half of the patients from Hospital Necker. The questionnaire was only used on a subsample and the results presented come solely from the nephrologists' assessment. It was incidently noticed that the patients' evaluation of their own state of health were more optimistic than those of the nephrologists, a situation that seemed normal in the case of a chronic disease. The population of patients who received EPO treatment consisted of 35 females and 22 males. They were relatively younger than the total population of patients on dialysis: eight were under 20, 30 between 20 and 40, five between 40 and 60 and 14 over 60 years of age. 25 patients were currently working, half of them full-time, half on a part-time basis; eight were retired; five were looking for a job.

Tables 2.3 and 2.4 show the distribution of patients in the different health states of the Rosser and Kind classification, before and after EPO. After utilisation of the corresponding valuation matrix (Appendix 1.1), and proper division by the sample size (N = 57), the quality of life indicators for one average patient-year in both groups were as follows:-

- pre-EPO : 0.937
- post-EPO : 0.974

The assumption was made at this stage that this benefit could be directly extrapolated to the whole population eligible for EPO treatment.

Table 2.3 Pre-EPO Treatment Classification of Patients

	A	B	C	D	Total
I					
II		3	5	4	12
III		10	5	3	18
IV		8	7	2	17
V		1	7	2	10
VI					
VII					
VIII					
TOTAL		22	24	11	57

Table 2.4 During EPO Treatment Classification of Patients

	A	B	C	D	Total
I	2				2
II	18	2	1		21
III	10	6			16
IV	4	7	2		13
V	2	2	1		5
VI					
VII					
VIII					
TOTAL	36	17	4		57

According to EDTA data (1988 Report, p 48, Fig 34), the average annual mortality after starting renal replacement therapy in 1980-84 was about 10%. It is therefore possible to calculate an average annual QALY benefit of:

$$\{1 - (0.1 \times 0.5)\} \times (0.974 - 0.937) = 0.0351$$

For the whole population potentially eligible (5,000 patients), the corresponding value is:

5,000 x 0.0351 = 175.5 quality adjusted years of life (QALY)

2.7.3 Effect on productivity

Half of the population of patients on dialysis are considered to be able to work normally either in the labour market or at home. There are no statistical data available on this situation in general, so it is necessary to rely on partial information concerning some centres which have collected such data. Dr Florence (Montpellier) has provided this information on 136 patients. Of those, 75 were in the age group 20 to 60 years, which allowed them to be professionally active. Of those 75 patients, 52% had a full-time job, 11% a part-time job and 8% were housewives with children. It was expected that treatment with EPO would considerably improve the situation for those active patients with anaemia. For the group of patients who were inactive and who were of working age, however, it is difficult to make any serious prediction of their chances of re-entering the labour market. The overall unemployment situation in the country, on the one hand, and the ageing of the group on the other hand, make it difficult to appreciate the real situation in terms of social integration and occupational ability. The financial support of the French Social Security system given to these patients makes this assessment even more difficult. This support reserved for patients

with serious impairment (around 1,800 FF per month in the case of an adult), combined with other social services is at present a disincentive to look for a job for some of these people.

This situation makes it difficult to evaluate whether the improvement in terms of quality of Life for these patients would modify in any way their rate of employment or activity. At this stage of the analysis, it therefore seemed perilous to argue about any indirect benefits in terms of productivity or increase in economic output.

It must be emphasised that the concept of QALY used here as a measure of the outcome of EPO treatment is supposed to integrate a diversity of factors and aspects related to personal well-being. Consequently, this cost/utility methodology is not supposed to include any additional measure of "indirect social benefit", concerning, especially, productivity gains.

2.7.4 Costs of blood transfusion and side effects avoided

A previously mentioned study (Rousseau, 1988) on the indications of blood transfusion in six centres located in the Paris area, provided a detailed comparison of the yearly medical costs of non-transfused and polytransfused patients. The methodology of this study was particularly rigorous even if the sample size was limited. A randomised sample of 15 patients were selected from the two groups. The mean age was 55.5 years and both sexes were equally represented. The two groups were not only different on the criteria of anaemia; the frequency of hypertension, history of angina pectoris and of ischemic heart disease was much higher in the poly-transfused patients. One in three patients were on the waiting list for renal transplantation in each group, a proportion which is two times higher than the national rate of 17%.

The information on costs was divided into the following categories:

a. biological analyses directly related to anaemia follow-up and transfusion (numeration, reticulocytes, haematocrit, platelets, serum iron, anti-HLA antibodies, irregular agglutinins...);

b. other biological analyses and serologies (calcemy, phosphoremy, SGOT, SGPT, vitamin D, HBs antigens, anti-HBs antibodies...);

c. blood transfusion costs (standard and specific blood units; transportation costs from transfusion centres included);

d. other related medical costs: specialised visits, hospitalisation, ECG, radiology... (transportation costs included);

e. other non-related medical costs.

The results are presented in Table 2.5

Table 2.5 Comparison of Medical Costs of Patients with and without Anaemia

Group	Poly-transfused	Non-transfused	Difference
Category of costs*			
a.	3,814	2,777	1,037
b.	8,642	6,755	1,887
c.	10,297 (9,207)*	157 (157)	10,140 (9,050)
d.	42,801 (23,978)**	28,039 (7,896)	14,762 (16,082)
e.	3,584	2,868	716

* French Francs (1987); annual costs (see text for explanations).

** The values in brackets correspond to costs not including transportation.

In conclusion, the previous values yielded an annual mean extra cost related to the follow-up and treatment of anaemia by means of blood transfusion of 28,056 FF per patient (transportation costs excluded) or 37,826 FF (transportation costs included).

These costs, however, would not be avoided completely with the treatment of anaemia by EPO. Some of the biological analyses and treatments would still be prescribed and performed. The costs and side effects of blood transfusion avoided will be considered separately.

Costs of blood transfusion avoided

The first category of economic gain relates mainly to the avoidance of blood transfusion. The current rates in France for blood products have been updated by the Administration as of 30/12/1988. The rate for a standard blood unit is 328 FF. An extra 78 FF has to be added for phenotyped blood, and 347 to 454 FF, according to the method used, for leucocyte and platelet removal (a "specific" blood unit). The test for detection of CMV (cytomegalovirus) costs an extra 99 FF. Among the population of regularly transfused patients (15) 1/3 require standard and 2/3 require specific blood units. The mean frequency of transfusion was 7.8 per year, using two units of blood each time. The annual cost of transfusion is calculated as approximately 10,000 FF (not including the costs of transportation of blood from the transfusion centre to the haemodialysis centre) or 1,282 FF per transfusion.

Of the assumed 30% of patients that are eligible for EPO treatment, then, 20% receive a mean of 7.8 transfusions per year and the remaining 10% receive a mean of 1.5 transfusions per year. The corresponding mean annual cost avoided is then:

$$(1,282 \times 7.8) \times 0.66 + (1,282 \times 1.5) \times 0.33 = 7,234 \text{ FF}$$

With an expected number of 5,000 patients, the annual costs of avoiding blood transfusion can be estimated as: 5,000 x 7,234 = 36.17 MFF (million of Francs).

2.7.5 Side-effects of blood transfusion avoided

The main side effects to be considered are the probability of occurrence of non A, non B hepatitis (a condition for which the prevalence seems to be relatively high among the polytransfused patients considered here: 15 to 20% of cases), other infections (including CMV), ferritin overload, etc. The residual risk of AIDS seems, at present, to be very low and thus insignificant.

The previously-mentioned analysis will be used to estimate the annual extra medical cost of treating these side-effects, including the biological analyses used for follow-up.

According to the nephrologists interviewed, it is estimated that the cost of avoiding side effects of blood transfusion are as follows: 2/3 of the differences in medical costs observed (Table 2.5) between polytransfused and non-transfused patients (aside from the direct cost of transfusion itself). This estimation (12,300 FF per year) applies only to the group of polytransfused patients (20% of those under haemodialysis). The corresponding value for the intermediate group (receiving a mean number of 1.5 transfusions per year) has not been established in the previous study. It is estimated as one-half of the latter value, or 6,150 FF.

With these assumptions, the annual cost of side effects avoided per patient can be estimated as:

(12,300 x 0.66) + (6,150 x 0.33) = 10,147 FF

For 5,000 patients, the corresponding annual cost is then:

5,000 x 10,147 - 50.74 MFF

Another benefit associated with the avoidance of blood transfusions relates to the reduction in incidence of hyperimmunization. Indeed, polytransfusion is generally considered to be the main cause of hyperimmunity, aside from previous transplantations and pregnancies. In France, the proportion of hyperimmune patients on the waiting list for graft is around 20%.

It may be assumed that the use of EPO will probably result in a substantial reduction in waiting time, an increase in the number of candidates for transplantation, and an increase in the final success of grafting. It is extremely difficult to quantify this complex series of events and consequences in monetary terms. One difficulty relates to the limitation of possible transplantations by the lack of donors. Another consequence is the likely reduction in the duration of EPO treatment as compared to the present situation.

Cost of treatment of side-effects: hypertension

One of the main and less controversial side-effects of EPO is probably

the increase of the frequency and severity of hypertension. The proportion of patients affected has not yet been precisely determined. Different publications state an increase of up to 16% (Eschbach et al, 1987), 20% (Foret) and even 60% cases (Drueke et al, 1988). The cost of treatment of hypertension has been investigated. The daily cost of the antihypertensive drugs is very variable and lies between 5 and 14.5 FF. Since those patients are probably difficult to control, it is likely that the actual cost is in the upper range, in the order of magnitude of 10 FF per day in patients with this condition. The corresponding cost is then (using a proportion of 16% of cases):

5,000 x 0.16 x 10 x 365 = 2.92 MFF

2.7.6. Cost of treatment with EPO

The cost of EPO in France is 350 FF/ampule. The maintenance dose is two ampules per week. It seems inappropriate to add other costs relating to medical follow-up or referrals, since these patients are normally under continuous medical surveillance and the drug is given during dialysis sessions. The cost for this year for 5,000 patients is thus estimated to be:

350 x 2 x 52 x 5,000 = 182 MFF

2.7.7 Summary of costs and benefits (without life expectancy effect)

The annual summary of the different medical costs involved (on a basis of 5,000 patients) is then:

2.92 + 182 - 36.2 - 50.74 = 97.98 MFF (sum of indirect, direct and avoided costs) or 19.6 KFF per patient per year.

The related ratio of cost per QALY is: 97.98 M/175.5 = 0.56 MFF

2.7.8 Cumulated costs and QALYs with a consideration of effect on life expectancy

Taking as background the considerations outlined earlier on the probable duration of the treatment in the two groups of patients identified, and using a 5% discount rate, it is interesting to calculate the total discounted cost and QALYs of EPO treatment on the life expectancy period of a cohort of 5,000 patients. (Table 2.6).

The following annual cost per patient will be used:

- EPO + side-effects: 36,984 FF

- Blood transfusion + side-effects: 17,381 FF

- Haemodialysis (hospital): 300,000 FF

The future level of health of the 20% of patients grafted after 2 years is supposedly identical in the two cohorts; therefore, these patients will be eliminated from the calculation after their graft (see Table 2.4).

Discounting factors used (5%, cumulated) are:

- first two years: 1.859

- year 3 to 11: 8.307 - 1.859 = 6.448

Table 2.6: Net medical costs and QALYs on the expected life-span of two cohorts treated with EPO and transfusion (5% discount rate on both cost and QALY; 10% gain in life-expectancy in case of EPO)

EPO	Annual Cost (FF)	Cumul. Cost* (FF)	QALY	Cummul. QALY*
Year 1 & 2	36,984	68,750	0.974	1.810
Year 3 to 10	30,580	197,180	0.779	4.657
Year 11	270,580	158,289	0.779	0.456
Total	-	424,229	-	6.833
Transfusion				
Year 1 & 2	17,381	32,311	0.937	1.742
Year 3 to 10	13,904	81,519	0.749	4.395
Total	-	113,830	-	6.137

* discounted 5%

The marginal cost of QALY gained is then:
(424,229 - 113,830)/(6.833 - 6.137) = 445,975 FF or about 0.45 MFF.

Cost per QALY values can only be interpreted when compared to the corresponding values for related fields of medicine. If as a reference, dialysis performed in the hospital, is taken, for which the current annual medical cost is up to 300 KF per patient in France, and the hypothetical mean QALY value for these patients as 0.8, (in the absence of any additional treatments for side effects), a cost per QALY value of 300/0.8 = 375 KF or .375 MF, can be obtained, as an illustration.

This illustrates that the value obtained for EPO, for which rather restrictive assumptions were taken, leads to a cost/utility ratio that puts this treatment in the range of other existing costly medical technologies, on the same order of magnitude as haemodialysis itself.

2.8 SUMMARY OF RESULTS

Number of patients eligible for EPO:

Up to 50% of patients on dialysis are potentially eligible; a more realistic number is 30%; that is about 5,000 persons in France.

QALY benefit of EPO on that group (annual): 175.5.

Cost of blood transfusion avoided (annual): 36.2 MFF.

Side-effects of blood transfusion avoided: (annual) 50.74 MFF.

Cost of treatment of side-effects of EPO (hypertension; annual): 2.9 MFF.

Direct cost of EPO treatment (current year): 182 MFF.

Cost per QALY:

without life expectancy effect = 0.56 MFF
with life expectancy effect = 0.45 MFF

Appendix 2.1

List of the Physicians Interviewed

Dr Drueke, Clinique Nephrologique, Hopital Necker, Paris (tel: 42738000).

Professor Broyer, Dr Gagnadoux, Service de Nephrologie pediatrique, Hopital Necker, Paris (tel: 42738000).

Professor Jacquot, Service de Nephrologie, Hopital Broussais, Paris.

Professor Jacobs, Service de Nephrologie, Hopital de la Pirie-Salperriere, Paris.

Dr Foret, Association Agduc, Centre d'Hemodialyse, Grenoble (tel: 16 76420363).

Professor Mion, Service de Nephrologie, Hopital Lapeyronie, Montpellier (tel: 16 67339050).

Dr Florence, Dr Rivory, Centre d'Hemodialyse Languedoc-Mediterrannee, Montpellier (tel: 16 67632302).

Mr Volle, FNAIR (tel: 16 72307013).

Dr Mignon, Service de Nephrologie, Hopital Tenon, Paris.

Dr Poisson, Dr Brisset, CILAG, Levallois-Perret (tel: 47481100).

Chapter 3

The German Case Study

by J-Matthias Graf v.d. Schulenburg, S Klein,
U Piojda and O Schöffski

3.1 INTRODUCTION

A frequent complication of chronical renal failure is the development of anaemia, which in the past could only be treated by blood transfusions. Now, renal anaemia can also be treated with recombinant human erythropoietin (r-HuEPO hereafter EPO).

In this study, the cost and benefits of treating anaemia with EPO will be analysed. The results presented in this paper can provide only a rough estimate of the benefit-cost ratio of EPO Therapy for four reasons. Firstly, the main effect of EPO, in comparison with blood transfusions or no treatment at all, is an increase in quality of life. The assessment and evaluation of those effects provides a number of severe methodological difficulties. Secondly, nephrologists expect that EPO increases the life-expectancy of dialysis patients through the improvement of tissue oxygenation, with no iron overload and no risk of blood-borne infections. However, it is impossible to quantify the increase in life expectancy after such a short period of experience with EPO. Thirdly, the cost-benefit ratio depends also on the number of patients who will be entitled to receive EPO. The current situation is that only some patients with anaemia receive blood transfusions, although most would benefit from this therapy. Other factors that affect the cost-benefit ratio are the dosage (depending on the therapeutic goal) and the frequency of administration of EPO. Fourthly, the study is based on a number of critical assumptions which have had to be made in the absence of sufficient experience with EPO.

3.2 THE GERMAN EXPERIENCE

3.2.1 Some basic statistics

Firstly, the demography of dialysis and transplantation in the Federal Republic of Germany is described. All data are taken from the "Combined Report of Regular Dialysis and Transplantation in Europe, XVII, 1986" and/or the report of the "European Dialysis and Transplant Association (EDTA)" presented at the XXVth Congress of the EDTA, Madrid, September 5-8, 1988.

a) Total number of patients alive on a known method of renal replacement therapy on December 31, 1986:

Hospital haemodialysis	:	15,650
Home haemodialysis	:	1,077
Intermittent peritoneal dialysis	:	119
Continuous peritoneal dialysis	:	433
Functioning graft	:	3,035
Total	:	20,314
Per million population	:	333

b) Centres known to the EDTA Registry in 1986:

Population in millions : 61.065
Known centres : 346
Known centres per million population : 5.7

c) New patients accepted for renal replacement therapy during 1986 -

The absolute number of new patients and the acceptance rate per million population:

New patients in 1986 : 4,043
Per million population : 66.2

d) Number of patients alive on special forms of haemodialysis/haemofiltration on December 31, 1986:

Bicarbonate haemodialysis	:	4,290
Haemofiltration	:	861
Haemodiafiltration	:	441
Haemodialysis with haemoperfusion	:	285

e) Transplant activity in 1986. The total number of grafts performed in 1986 as an absolute number and expressed per million population (PMP):

Cadaver:	- 1st graft	:	1,077
	- patients under 15	:	63
	- Total cadaver grafts	:	1,235
Living donor:	- 1st graft	:	39
	- patients under 15	:	9
	- Total living donor grafts	:	42
All grafts		:	1,627
PMP (intern. average)		:	26.7 (14.8)

f) Patients on waiting list for cadaver transplant in 1986:

Per cent of all dialysis patients : 19.9 (25.6, intern. average)
Number of patients : 3,844

g) Hepatitis B diagnosed in patients in 1986:

Hep B (n) : 51
Cases/1000 patients on Hosp. HD : 3.3 (18.1 intern. average)

h) AIDS cases 1986:

Serological evidence : 29
1st detected in 1986 : 15

Outlook:

Subcutaneous administration of EPO seven times a week will reduce the

current dosage per week, because more stable serum levels of EPO are achieved. This is a problem for future clinical research.

With regard to the 20,000 dialysis patients in the Federal Republic of Germany, there are two communities of interest for people with renal disease: The "Interessenverband der Dialysepatienten und Nierentransplantierten Deutschlands e.V. (IVDD)" and the "Verein Urlaubsdialyse e.V". The "IVDD" has more than 13,000 members in 80 local groups. The second union gives financial help for holiday activities for children and people on low income.

On November 25, 1988, EPO obtained a licence to be sold in Germany by the "Bundesgesundheitsamt" (German Federal Drug Administration). Since December 12, 1988, EPO has been sold in Germany.

3.3 ANALYTICAL FRAMEWORK

3.3.1 Number of patients

There were 20,314 patients with ESRD (end stage renal disease) in the Federal Republic of Germany (ie, 332 patients per million population) (EDTA, 1986). This number is probably too low since only 78.6% of the questionnaires were returned. Calculation of the current number of ESRD patients from this data, must include consideration of the increasing rate (= number of new ESRD patients in one year) and the decreasing rate (= death rate of patients with end stage renal disease). These rates are given by an analysis of the IVDD. The increasing rate is between 65 and 75 patients per million population per year, ie 3,900 to 4,500. The average death rate (12%) is an outcome of various studies. Simulations based on these parameters lead to an expected number of 30,278 to 34,295 patients in the year 2000. If EPO has a positive net benefit the yearly net benefit of the introduction of EPO will increase over time.

In this study the current number of 22,500 RRT patients is used, and will concentrate on those patients who are on haemodialysis (18,500). An extended analysis should take into consideration the changes in patient numbers. The number of patients requiring blood transfusions diverge from centre to centre, eg 10% of the dialysis patients at the Heidelberg University Hospital to 30% at other centres. The data given by the Würzburg survey (Dr R Schaefer), where 19% of dialysis patients receive transfusions, will be used for this study.

Also the number of ESRD patients considered for EPO treatment is unspecified. How many anaemic patients will be treated with EPO depends on the treatment goal, how much of the renal anaemia should be corrected, and the potential side effects of EPO. In this survey, the very restrictive assumption that only 30% of the ESRD patients are able to receive EPO treatment, will be used. This rate is supported by the Heidelberg and Würzburg surveys. With time, the rate will probably increase because of growing experience with this treatment. In the US, it is estimated that 80% of anaemia patients will be treated with EPO.

3.3.2 Direct cost and benefits measurement

The manufacturer's estimate for the yearly direct cost of EPO therapy is 10,000 to 15,000 DM. With increasing production, the price will probably decrease in the future. Other costs, eg staff, etc, are less important,

because EPO is given during the dialysis sessions. Another cost could be associated with complications resulting from the increase in blood viscosity during EPO treatment. This may cause the dialysis session to last perhaps 10% longer and also requires a higher heparin addition. For this survey, the direct cost of 12,000 DM per patient per year will be used.

The direct benefits are derived from the omission of blood transfusions, the average patient needing one blood unit per month. The cost for an average blood unit which is billed to the sickness fund by the Hanover University Hospital is 122 DM. 200 DM is taken for this survey (estimation of Professor Bommer, Heidelberg), which is certainly not an overestimation if the cost for the laboratory, cross matching etc is also considered. There is also no cost for the staff, because the transfusion is part of the dialysis session.

3.3.3. Assessment of impact on quality of life

One of the main problems is the measurement of the quality of life of patients with and without EPO treatment. In this study the Rosser matrix is used to assess the impact on quality of life of treatment with EPO. The Rosser matrix is a global model, which means that it is applicable to most diseases. The matrix is divided into eight classes of disability and four classes of distress (see Appendix 1.1) giving thirty-two possible classes. Only twenty-nine states of illness were described, since the combinations of unconscious with mild, moderate or severe distress were excluded. These combinations were not considered because it was felt that an unconscious patient would not experience distress.

A magnitude estimation was used to evaluate the range of states. Seventy subjects (ten patients from medical wards, ten psychiatric in-patients, ten nurses, 20 healthy volunteers and ten doctors) were interviewed. Six cards describing different states of illness which were widely dispersed between the categories of disability and distress had to be ranged by these subjects on a scale comparing two states each time. Then the other twenty-three states had to be ranged. The scale in Appendix 1.1 was calculated from the median results for different subjects, and standardised so that dead = 0 and healthy = 1.

3.3.4 Productivity benefits

There is no doubt that EPO therapy will improve the capacity for work and will lower the rate of permanent disability for dialysis patients. However, the productivity effects are considered to be low, due to the long average period of time renal disease patients leave the workforce. Most of them have great difficulty in re-entering the workforce and they have little incentive to resume work, due to the comprehensive and generous German social health insurance system. In addition, patients with lower levels of education have difficulty finding jobs, because unemployment is relatively high for those groups. This hypothesis is supported by the observation that the rate of self-employed workers is much higher than the rate of employees continuing to work after starting dialysis. Undoubtedly the chance for new dialysis patients to remain in the workforce is much greater with EPO treatment than without.

In general, EPO patients are more active and more efficient, and it is possible that their life expectancy will rise, because of correction of anaemia. It was not possible to give detailed information about this subject,

because EPO is a new therapy and statistical data are not available.

3.3.5 Other costs and benefits associated with side-effects

The aim of this survey is to quantify the cost resulting from side-effects of former treatment and EPO treatment. The following arguments make quantification difficult:

- very different measurements of the side-effects
- different treatment possibilities cause different costs
- different treatment goals, mostly not clearly defined
- the estimated incidence of side effects varies among experts
- related cost data are unpublished
- even side-effects affect productivity, quality of life and life expectancy, and these have to be taken into account
- EPO data, in particular, are lacking, because of limited experience with this therapy.

In this study, a rough estimate of the cost of treating side-effects will be described, because an exact quantification is not possible because of the difficulties listed above.

a) Possible side-effects of treatment without EPO:

i) Administration of androgens

Until now there was no successful therapy for renal anaemia. The administration of androgens had some positive influences but the therapeutic effect was low and there were major side effects:

- hirsutism: abnormal growth of hair, especially beard hair
- liver cell damage.

ii) Blood transfusions

Because of the disadvantages of high androgen doses, blood transfusions were used in the majority of anaemic patients. However, transfusion leads only to a short-term correction of renal anaemia. Moreover, blood transfusion is not a causal therapy, but represents a symptomatic treatment of the anaemia of end stage renal disease.

Risks of blood transfusions include:

- suppression of erythropoiesis
- risk of infection:
  - a) hepatitis: inflamation of the liver resulting in viral infection
  - b) cytomegalie: liver disease, leuko- and thrombocytopenia
  - c) AIDS
  - d) iron overload
  - e) formation of cytotoxic antibodies

The possible cost of treating these side-effects have been discussed with a number of nephrologists. Dr R Schaefer (Würzburg University Hospital) found 4,000 DM per patient per year to be a realistic cost estimate. It should be noted that not all blood transfusion patients experience side-effects. Non-A, non-B hepatitis seems to be a larger problem, with AIDS being

of lower incidence. The estimate presented here is an average figure which has to be considered with caution because hard data could not be provided by any of the sources. Nevertheless, this estimate will be used because large parts of this study are based on the EPO medical study conducted at Würzburg University Hospital, but the final results will also be derived without taking side-effects and their cost into consideration.

b) Possible side-effects of EPO treatment:

- Hypertension (high blood pressure): rise of systolic and diastolic blood pressure.
- Occlusion of the arteriovenous shunt of dialysis patients, attributable to the increase in thrombocytes (increase of blood platelets).
- Flu-like complaints: fever after the injection of EPO, bone aches.
- Decreased serum ferritin: patients who started with low ferritin values may develop iron deficiency.
- Rise of the retention values (creatinine, urea, phosphate and potassium) due to a decline in dialyzer clearance with increasing haematocrit values.
- Skin reactions.
- Palpebral oedema.
- Epileptic seizures.

To reduce the cost of side-effects during treatment, EPO is only administered to patients who are not especially endangered. Consequently EPO will currently only be given to 30% of dialysis patients in the Federal Republic of Germany. Therefore the side-effects of EPO can be neglected. However, if this percentage increases, the side-effects of EPO treatment will have to be taken into account. However, the side-effects of EPO are relatively rare and can normally be properly treated without significant cost, and by simply lowering the dosage of EPO. Hypertension appears to be the most significant problem. Many patients are hypotensive initially so the effect of EPO may only raise the pressure to around normal levels. A few patients already on antihypertensive medication may require only a slight dosage adjustment.

3.4 ESTIMATING COST AND BENEFITS OF EPO

3.4.1 Estimations of the number of potential EPO patients

- In Germany approximately 20,000 to 25,000 patients suffer from renal failure and need dialysis. The calculations will use the number of patients given in Section 3.3.1. This is certainly not an overstatement because the number of dialysis patients has increased significantly over the past few years (22,500).

- Some of these patients do not suffer from anaemia because their kidneys produce sufficient amounts of EPO. According to EDTA-ERA estimates, the percentage of total renal replacement therapy patients on haemodialysis (both hospital and in-home) is 82.3% (16,727/20,314). Applying this haemodialysis subsegment percentage to the estimate of renal replacement patients leads to a number of about 18,500 haemodialysis patients (82.3% x 22,500). The nephrologists who have been consulted in conducting this report believe that the number of anaemic patients is slightly higher, and estimate that about 10 to 15% of all patients do not suffer from anaemia. The average of these percentages leads to 22,500 -12.5% =

19,688.

- EPO has a number of side-effects (eg increase in blood pressure). Professor Koch believes that, from the start, roughly 20% of the anaemia patients should not be treated with EPO. This would reduce the number of patients for whom EPO treatment is without side effects to 15,751. Other nephrologists, eg Dr Winearls, suggest that patients on EPO who experience side effects should not be excluded from EPO treatment since side-effects are relatively rare and can be properly handled. With increasing experience of EPO, clinicians have learned how to avoid some adverse effects through lower dosing (see 3.3.5.b).

- Blood transfusions are associated with a number of side-effects (eg hepatitis, iron overload, formation of cytotoxic antibodies (see 3.3.5a). Therefore, only a certain group of anaemic patients receive blood transfusions. In the literature the percentage of patients with chronic renal failure receiving blood transfusions is estimated at 30%. A recent national survey conducted by the University Hospital of Würzburg, however, observed only 19% of dialysis patients receiving blood transfusions. The number of anaemic patients treated with blood transfusions is between 19% x 19,688 = 3,741 and 30% x 19,688 = 5,906. Both numbers will be used and the first conservative one will be called the "Würzburg estimation".

- The number of patients who will show an improvement in quality of life with EPO treatment but do not receive blood transfusions in the absence of or before EPO treatment can be estimated at 15,751 - 5,906 = 9,845 or taking the "Würzburg estimation" 15,751 - 3,741 = 12,010.

- Very little is known about the sex and age structure of dialysis patients with anaemia, who will be treated with EPO. At the University of Heidelberg, 9.4% of the patients are 30 or younger, 6.3% are between 30 and 40, 25% are between 40 and 50, 43.7% are between 50 and 60, 9.3% are between 60 and 70 and 6.3% are over 70 years. In this study the patient structure of the Würzburg University Hospital is taken as representative of all patients. The following estimates are obtained for all patients who could be treated successfully with EPO at this time:

female	48.6%	7,655
male	51.4%	8,096

<u>female</u>

0 - 20 years	0.00%	0
21 - 30 years	4.18%	658
31 - 40 years	8.31%	1,309
41 - 50 years	6.95%	1,095
51 - 60 years	13.17%	2,075
61 - 70 years	12.54%	1,975
71 - 80 years	3.45%	543

male

0 - 20 years	0.00%	0
21 - 30 years	4.42%	696
31 - 40 years	8.79%	1,384
41 - 50 years	7.35%	1,158
51 - 60 years	13.93%	2,194
61 - 70 years	13.26%	2,089
71 - 80 years	3.65%	575

- The number of anaemic patients who will actually be treated with EPO also depends on the treatment goal and the target correction of renal anaemia. In the Würzburg University Hospital approximately 30% of dialysis patients are treated with EPO. In the US, it is estimated that 80% of the anaemia patients will be treated with EPO. Nephrologists think this percentage too high for Germany and believe 50% is a more realistic future prediction. Nephrologists also believe that only 30% of all dialysis patients will currently be entitled to EPO treatment. Therefore this study is based on the following number of anaemic patients receiving EPO - 6,750.

  The number of EPO patients with prior blood transfusions is estimated at 5,906. In 87.5% of cases, EPO will replace transfusions and in 12.5% of cases, EPO will be given to patients with no prior blood transfusions. The "Würzburg estimation" observed a lower percentage of dialysis patients receiving blood transfusions, namely 3,741. Taking the "Würzburg estimation", EPO replaces blood transfusions in only 55.4% of cases. In 44.6% of cases treated, no transfusions were given before EPO treatment. In the future the number of anaemic patients will increase, due to an increased percentage of dialysis patients being treated with EPO, and an increase in the total number of dialysis patients. Professor Bommer (Heidelberg University Hospital) estimates this number of patients will increase from 7,000, to 12,000 in the near future.

3.4.2 Estimation of life expectancy

It is most likely that EPO patients will have a longer life expectancy than those anaemia patients who are not treated or who receive blood transfusions. The effects of EPO on life expectancy cannot yet be assessed, since it will take about 10 years to have sufficient information to quantify the comparative effects on life expectancy of EPO in comparison with traditional therapies. A very conservative estimation is the following:

EPO will increase life expectancy by 10%.

This implies that rather than the estimate that 12% of the anaemia patients treated with EPO will die in the current year (see 3.3.1), it is only 10.8%. In other words, the average yearly survival probability increases from 0.88 to 0.892.

Table 3.1 provides some information how this increase in life expectancy will change the life expectancy of different age groups of anaemia patients. It should be noted that the estimations in Table 3.1 are based on the assumption that EPO patients have the same life expectancy as the average of the population. Therefore, Table 3.1 is given simply as an illustration of

life expectancy effects. However, results will also be shown using the assumption that EPO has no life-expectancy effects.

Table 3.1 Structure of potential EPO patients

j	Nj	nj1	nj2	Lj2	Lj1
female					
21 - 30	9.6	1.8	2.9	49.57	44.61
31 - 40	19.1	3.6	5.8	40.21	36.19
41 - 50	15.9	3.0	4.9	31.05	27.95
51 - 60	30.3	5.8	9.2	22.35	20.12
61 - 70	28.9	5.5	8.8	14.43	12.99
71 - 80	8.0	1.5	2.4	8.01	7.21
male					
21 - 30	10.2	2.0	3.1	45.06	40.55
31 - 40	20.2	3.8	6.1	35.89	32.30
41 - 50	16.9	3.2	5.1	26.93	24.24
51 - 60	32.0	6.1	9.8	18.75	16.88
61 - 70	30.5	5.8	9.3	11.80	10.62
71 - 80	8.4	1.6	2.6	6.61	5.95
	230.0	43.7	70.0		

Nj : number of dialysis patients (N=230)
nj1: number of patients treated with transfusions (n1=43.7)
nj2: number of EPO-treated patients (n2=70)
Lj2: mean life expectancy with EPO treatment if life expectancy would increase by 10%
Lj1: mean life expectancy

N, n1 and n2 are the numbers of patients in the Würzburg survey which were also used to estimate the quality of life effects.

3.4.3 Estimation of direct cost and benefits

3.4.3.1 Direct cost

The number of patients receiving blood transfusions is

n1 = 5,906 (or 3,741 according to the "Würzburg estimation")

The cost for one patient per year of blood transfusions is approximately

c1 = 2,400.00 DM

The saved direct cost for EPO patients is then given by

$C1 = n1 \times c1$
$= 5,906 \times 2,400$ DM = 14,174,400 DM
(or $3,741 \times 2,400$ DM = 8,978,400 DM)

The cost for EPO treatment for one year and one patient is approximately

$c2 = 12,000.00$ DM.

The number of patients who will be treated with EPO is

$n2 = 6,750$

For all EPO patients the cost is given by

$C2 = n2 \times c2$
$= 6,750 \times 12,000 =$ 81,000,000 DM

3.4.3.2. Estimating Productivity Effects

45 of the 230 dialysis patients at the Würzburg University clinic are currently working. The experience shows that about 3% of patients treated with EPO resume work after one year. This percentage will increase if EPO treatment is started at an earlier stage in renal disease, and if EPO treatment is continued over a longer period of time. In this study it will therefore be assumed that at least 10% of all EPO patients who have not worked before will re-enter the workforce. If 6,750 patients were treated with EPO and if 45/230 have continued working, then 5,430 patients have stopped working. 2221 of all treated patients are over 60 and are assumed not to enter the work force again. 10% of the remaining patients is 321. If an average productivity gain per one working year of approximately 48,600.00 DM is assumed, a productivity gain is achieved for one year of

$CP = 48,600.00$ DM $\times 321 =$ 15,600,600 DM.

The average gross income of employees (blue and white collar workers) was about DM 48,600 in 1987. This can be taken as the productivity value added of one work-man-year, with no market imperfections and other distortions taken into account.

In the final estimates, two cases are presented. The first takes these effects on productivity into account, while the second neglects productivity effects (as is done in a pure cost-effectiveness analysis).

3.5 ESTIMATION OF QUALITY OF LIFE EFFECTS

To assess the impact of EPO on quality of life, a number of leading German nephrologists having experience in EPO therapy have been approached. These are Professor Koch (Medizinische Hochschule Hanover), Professor A Heidland and Dr R Schaefer (Medizinische Universitätsklinik Würzburg) and Professor Bommer (Universitätsklinik Heidelberg). All information used for this study was gathered by these experts. They were asked to classify their patients according to the Kind and Rosser classification matrix. Some had difficulty in classifying their patients according to this matrix, for various reasons. In one case data protection reasons were claimed. In other cases, it was difficult for physicians to classify the patients according to a two-dimensional scale.

In this section assessment of quality of life effects is based on the classification developed in cooperation with the Würzburg University Hospital. At this clinic, 230 chronic renal failure patients receive dialysis, 70 of whom were treated with EPO.

In Tables 3.2 and 3.3, the classification of these patients before and during EPO treatment are shown. The matrix in Table 3.2 will be designated M1 and the matrix in Table 3.3 as M2. Multiply M1 and M2 with the evaluation matrix W (Appendix 1.1), where the fixed points are 1 (I A = healthy) and 0 (VIII D = dead). Those values are added and then divided by the sample size of patients n (n = 70). By this a quality of life indicator is derived for one patient year in both patient groups.

$$Q1 = (M1 \times W) / n$$
$$= 64.82 / 70 = 0.926$$

$$Q2 = (M2 \times W) / n$$
$$= 66.92 / 70 = 0.956$$

The difference between Q1 and Q2 is the average gain in quality adjusted life years per anaemic patient for one year if he or she receives EPO:

$$Q2 - Q1 = 0.03$$

If 0.03 is multiplied by the number of patients treated with EPO, the total gain in quality of life for one year in terms of quality adjusted life years is obtained. Currently, about 6,750 patients are treated with EPO so that the yearly quality of life gain is

$$0.03 \times 6{,}750 = 202.5$$

If the total number of patients who will benefit from EPO are treated, and do not suffer from side-effects, a yearly quality of life gain of

$$0.03 \times 15{,}751 = 472.5 \text{ is estimated.}$$

Table 3.2 PRE - EPO treatment

	A	B	C	D	Total
I	Healthy	0	0	0	0
II	0	4	2	0	6
III	0	2	24	6	32
IV	0	4	8	12	24
V	0	0	6	2	8
VI	0	0	0	0	0
VII	0	0	0	0	0
VIII	0	0	0	0	0
Total	0	10	40	20	70

Table 3.3 During EPO treatment

	A	B	C	D	Total
I	Healthy	0	0	0	0
II	2	5	1	0	8
III	0	20	23	1	44
IV	0	8	5	1	14
V	0	1	2	1	4
VI	0	0	0	0	0
VII	0	0	0	0	0
VIII	0	0	0	0	0
Total	2	34	31	3	70

3.5.1 The impact on life expectancy

Currently only 88% of anaemic patients are still alive at the end of the year. 12% of patients die, on average, in every given year. To measure the effect it is necessary to adjust Q1 and Q2 for life expectancy. If n is the number of patients before EPO treatment, 88% will have the full quality of life of 0.926. The other 12% will die during the present year and will have an average rest life of half a year. The total quality of life of all patients before EPO is therefore

$$(n \times Q1 \times 88\%) + (n \times Q1 \times 12\%/2)$$
$$= n \times Q1 \times 0.94$$

If these n patients receive EPO they might have the same life expectancy, ie the same survival or death-rate as before. In this case, the total quality of life can be obtained as before:

$$n \times Q2 \times 0.94$$

The total gain of quality and life expectancy adjusted life years is then given by

$$\text{QALY-Gain} = n \times 0.94 \times (Q2 - Q1)$$
$$= 190.35 \quad \text{if } n = 6{,}750 \text{ or}$$
$$= 444.18 \quad \text{if } n = 15{,}751$$

However it is most likely that EPO increases life expectancy by at least 10% (see 3.4.2.). As Table 3.1 indicates, this would imply an increase of about one year or less for patients over 60, of about 2.5 years and less for patients over 40, and for more than 2.5 years for younger ones. According to the procedure described above, the total quality of life adjusted for life expectancy is given by

$$n \times Q2 \times 0.946$$

The life expectancy adjusted yearly quality of life years gained by EPO is per patient

$$\text{QALY-Gain} = (Q2 \times 0.946 - Q1 \times 0.94)$$
$$= \underline{0.0339}$$

For all patients treated with EPO, a yearly QALY-Gain of

$$\text{QALY-Gain} = \underline{228{,}825} \quad \text{if } n = 6{,}750 \text{ or}$$
$$= \underline{533.959} \quad \text{if } n = 15{,}751$$

for one year is obtained.

3.5.2 Estimation of the critical value for one quality of life year

With the given data, the critical value for one quality of life year for one patient can be estimated. The critical value represents the DM value for the Qaly-Gain of one year and one patient where the benefits of EPO treatment are as high as the cost.

The expected net-benefits NB of EPO for one given year, say 1990, can

be estimated by the following equations. It should be noted that all cost and benefits should either be adjusted to the life expectancy of the patients in the given year, which is estimated to be 0.946 for EPO patients and 0.94 for anaemic patients not treated with EPO (or before treated with EPO), or should neglect survival rates. An adjustment to the life expectancy or survival rates has to be done because a patient who dies during the current year will only add cost and benefits to our estimation for a fraction of that year. Table 3.4 summarizes the results derived in the analysis up to this point as a basis for the further calculations of the net-benefits.

The benefits of EPO for one year are calculated by the following equation where the results for the conservative "Würzburg estimation" are also given in parentheses:

the saved cost for blood transfusions
13,323,936 DM (8,439,696 DM)
+ the product of Qaly-Gain and Qaly-value
228.825 x QV
+ the benefits of the side-effects of blood transfusions
22,206,560 DM (14,066,160 DM).

The cost for EPO treatment for one year is estimated to be

76,140,000.00 DM

if EPO has no life increasing effects and

76,626,000.00 DM

if EPO has a life increasing effect by 10%.

This leads to

$$NB1\ (QV,\ t) = -41,095,504 + 228.825 \times QV$$
$$(-54,120,144 + 228.825 \times QV)$$

where NB (QV, t) is the net benefit of EPO in the year t for a given value of QV. Unfortunately, there is no value for QV. An impression of the critical value of QV will be provided where NB (QV, t) = 0. If QV is higher than this critical value the net benefit of EPO is positive. If it is lower the cost of EPO is higher than its benefits. The critical value is given by

$$QV^*\ (1) = 179,594\ DM\ (236,513\ DM)$$
if n = 6,750

Table 3.4 Cost and Benefits of EPO

	Patients	Unadjusted	Life expectancy adjusted
Direct Cost Saved for Blood Transfusion(1)	5,906 (3,741)	in DM 14,174,400 (8,978,400)	in DM 13,323,936 (8,439,696)
Direct Cost of (3) EPO	6,750	81,000,000	76,626,000 (76,140,000)
Productivity (2) Effects	321	15,600,600	
Side Effect Benefits (1)	5,906 (3,741)	23,624,000 (14,964,000)	22,206,560 (14,066,160)
		in QALYs	in QALYs
QALY Gain per year (3)	6,750 15,751	202.5 472.5	228.825 (190.35) 533.959 (444.18)

(1) Estimation of the "Würzburg survey" in parentheses.

(2) Those who work will have on the average a much lower death rate than other anaemic patients. That is why the value will not be adjusted.

(3) In parenthesis: if EPO would have had no life-increasing effect, ie. would not increase the yearly survival rate from 0.94 to 0.946.

If the survival rates are not taken into account, assuming that EPO has no life increasing effects, the estimated Qaly-Gain per EPO patient is:

190.35 for n = 6,750.

This leads to the following critical value of QV:

$$QV^*(2) = 40,609,504 / 190.35 \text{ DM}$$
$$= 213,341 \text{ DM } (281,766 \text{ DM})$$

The critical value of QV will also be derived for the case where not only the survival rates including the life increasing effect of EPO, but also the side-effects of blood transfusions are neglected. This leads to the pure

cost-effectiveness ratio with respect to quality of life which is the major aim of normal cost effectiveness analysis:

$$QV^* (3) = 62,816,064 / 190.35$$
$$= 330,003 \text{ DM } (355,662 \text{ DM})$$

The analysis of the patient structure of potential EPO recipients shows that the net benefit of EPO is very much dependent on the ratio of the patients who have had blood transfusions before, and those who did not receive blood transfusions, prior to EPO treatment. In this study it is assumed that only 5,906 or 87.5% (55.4% according to the "Würzburg estimation") of all EPO recipients have had blood transfusions before. If all EPO recipients got blood transfusions before they were treated with EPO, then only those 87.5% would be entitled to receive EPO. The net benefit of EPO would then be given by

$$NB\ (QV, t, BL) = 13,323,936 + 22,206,560 + (228.825 \times QV \times 0.875) - (76,140,000 \times 0.875)$$

This leads obviously to a lower critical value, namely

$$QV^* (4) = 155,288 \text{ DM}.$$

The reader should note that QV* (4) is the same if the conservative number of the "Würzburg estimation" is taken. The net benefits of EPO for a given value of one adjusted quality of life year, or the critical value of QV, depends obviously on the "generosity" of physicians in administering EPO. If the productivity effects are not considered, the lowest critical value of one QALY is 155,288 DM. A realistic estimate taking into account all cost and benefits is 179,594 DM. The cost-effectiveness ratio with respect to one quality of life year is given by 330,003 DM. The last two numbers are slightly higher if only 19% and not 30% of all dialysis patients receive blood transfusions as is claimed by the "Würzburg estimation".

3.5.3 The discounted value of future net benefits of EPO

In the above calculations the net benefit of an unrestricted use of EPO for one given year, say 1990, has been derived. To receive the total net benefits of EPO the cost and benefits of all subsequent years have to be taken into account. If NB (QV, t) is the net benefit for a given value of a quality adjusted life year for the year t, the discounted value is obtained of all future net benefits (DNB) of licencing EPO in Germany by

$$DNB = \sum_{t=0}^{s-1} NB\ (QV, t)\ q^t$$

with $$q = \frac{1}{1 + i}$$

where s-1 is the time horizon, ie the number of years EPO will be employed, and i the social discount rate.

If it is assumed that NB is constant over time, that means the net

benefit is the same for all years. In this case

$$DNB = NB \sum_{t=o}^{s-j} qt = NB \frac{qs - 1}{q - 1}$$ is obtained.

For an infinite time horizon this will be

$$DNB = NB \frac{1 + i}{i}$$

For instance, if the social rate of discount is given by 4.5% (which is a normal rate for public projects = bank rate for loans on securities) the discounted value of all net benefits is

$DNB = NB \times 23.2$ for $s = \infty$
and $DNB = NB \times 8.4$ for $s = 10$.

A yearly Qaly-Gain has been estimated of between 228.825 and 533.959 quality adjusted life years. Taking 4.5% as discount rate ($s = \infty$) the total present value of all current and future quality of life years is at least

$$228.825 \times 23.5 = 5,377 \text{ QALYS}$$

and is most likely to increase to

$$533.959 \times 23.5 = 12,548 \text{ QALYS}.$$

Certainly n depends on the technical progress in the field of pharmaceutical therapies. For three reasons the calculation of NB by the equation given above will probably lead to an underestimation. Firstly, the cost of EPO will decrease over time due to market competition in this field and the ending of patient protection. Secondly, the quantity needed to treat one patient will decrease once patients have learned to inject EPO themselves, as is usual for diabetic patients. This would make possible a more frequent injection of EPO, and this allows a reduction in the yearly dosage. Thirdly, the number of patients over time will increase (see 3.3.1) and therefore NB (QV, t) is not time invariant but increasing, too.

3.6 SUMMARY

This paper presents an analysis of the cost and benefits of Erythropoietin (EPO), a new compound for the treatment of anaemia arising from chronic renal failure. The productivity effects, the cost of side effects, the effects on life expectancy and the direct cost of EPO are discussed and evaluated. The main focus of this paper is however on the effect EPO therapy has on increasing the quality of life. Employing data from 70 patients (out of 230) being treated with EPO, the quality of life effects are estimated and assessed following the Rosser and Kind method. The study calculates a critical value of one quality adjusted life year to be between 87,111 DM and 179,594 DM depending on the percentage of patients treated with EPO. The quality of life cost-effectiveness ratio is estimated to be 349,333 DM.

Acknowledgements

We are indebted to a number of nephrologists, especially Professor K M Koch, Professor J Bommer and Dr R Schaefer, for the provision of information, data and patient experience. We also would like to thank Professor Alan Maynard and Mr J Hutton for their information on methods of assessment and evaluation of effects on quality of life, and Myron Z Holubiak from EMRON Inc. for information on the universal problem of treating anaemic patients and his careful review of previous versions of this paper. His comments were most valuable for our study.

Chapter 4

The Italian Case Study

by C Lucioni and F Rossi

4.1 A NEW TREATMENT FOR ANAEMIC PATIENTS WITH CHRONIC RENAL FAILURE

Patients with chronic renal disease are often anaemic. The main cause of the anaemia is the inadequate production of the hormone erythropoietin (EPO) from still unidentified sites in the kidney that are damaged by the disease.

Anaemic patients experience chronic fatigue which limits their ability to work and affects their leisure. In the worst cases there is the need for regular blood transfusions, which provide only temporary respite. Furthermore, treatment by transfusion is as far as possible avoided because of risks of infection, iron overload and sensitisation to transplantation antigens.

Renal dialysis is carried out in patients with renal failure, with correction of many of the metabolic consequences of the disease, but not of the anaemia. Several other factors are believed to contribute to anaemia in dialysis patients, including uraemic suppression of bone marrow, shortened red cell survival, chronic occult blood loss, iron deficiency and aluminium intoxication. However, anaemia is largely a consequence of deficiency of EPO in almost all anaemic patients on dialysis.

Unfortunately, regular administration of EPO was, in the past, precluded by its scarcity. After the hormone was isolated from human urine, the amino acid sequence was determined and, as a final consequence, human EPO prepared by recombinant DNA technology is now available in quantity.

Clinical trials have shown the effectiveness of EPO made by recombinant technology in correcting the anaemia of end stage renal disease in patients maintained on haemodialysis. The anaemia could be completely reversed, despite the persistence of all other contributing factors. Patients who had previously required regular blood transfusions no longer needed these. The response was accompanied by increases in appetite, energy and well-being.

From the trials so far reported there seem to be few adverse effects. There is no evidence of immune elimination or antibody formulation. Only one side effect, the raised level of haemoglobin, seems to be noteworthy: hypertension and its complications may develop or increase.

News of the success of EPO in the treatment of the anaemia of chronic renal failure has resulted in a number of suggestions for additional uses. The availability of EPO from rDNA has led to the study of its use in other conditions, such as the anaemias of chronic disorders, including rheumatoid arthritis and neoplastic disease. Since such clinical trials are still in the early stages, the usefulness of EPO in these other conditions is not yet known.

4.2 STUDY AIMS AND METHODOLOGY

The aim of this study was to assess the economic impact on the community of the new EPO treatment for anaemic patients on renal replacement therapy (RRT). Lacking definitive clinical results, other possible therapeutic uses of EPO have been ignored.

The hypothesis formulated is that EPO treatment entirely does away with the need for such patients to undergo periodic transfusions. Anaemia in patients with chronic renal disease may develop before the need for RRT arises. However, the study ignores these potential patients to concentrate attention on patients already on dialysis, since they form a definite and easily identifiable group.

Assessment of costs was based on direct costs of treatment (costs of treatment and relative side effects). Where appropriate, indirect components of costs (eg productivity losses), were included in assessment of transfusion costs.

On the assumption that life expectancy of patients treated with EPO is slightly higher than that of patients on transfusions, the marginal costs of RRT during this period of longer survival were also attributed to EPO treatment. For both treatments, solely marginal components of costs were taken into account.

The benefits derived from a reduction of anaemia do not seem to prolong life expectancy (even though this hypothesis was taken into consideration), as much as to give an improvement in the quality of the patient's life. Particular attention was consequently paid to evaluating this improvement, using the methodology based on QALY assessment. Initially therefore, assessment of the impact of EPO therapy was achieved by cost/effectiveness (C/E) analysis, calculating the cost per QALY and the cost per QALY gained, compared with traditional treatment based on transfusion.

In view of the limited number of patients for whom it was possible to calculate the Quality of Life Index devised by Kind and Rosser, extension of the results to the entire population on RRT in Italy was considered inopportune.

To establish the potential monetary benefit for the entire community, a separate analysis was made to assess the positive consequences, in terms of productivity gains, determined by the greater psychophysical well-being of patients on EPO. Assessment of benefit was confined to considering the improved working capacity of EPO patients, utilizing a cost/benefit (C/B) approach. From information supplied by a number of clinicians, a hypothesis was formulated as to the percentage of patients that might presumably avoid suspension of working activity because of EPO treatment. For both treatments, the classical (B-C) and (B/C) ratios were thus calculated. Moreover, in the case of EPO treatment, it was felt that assessment should also establish:

- what average EPO price would: a) result in a (B/C) ratio equal to that of transfusion; b) balance costs and benefits (B-C = 0) or (B/C = 1);

- what percentage of patients would have to be able to continue working in order to obtain: a) (B/C) ratio equal to that of transfusion; b) balance of costs and benefits (B-C = 0) or (B/C = 1).

4.3 THE QUANTIFICATION OF DIRECT COSTS

Direct costs of treatment of anaemia in patients on dialysis comprise:

a) cost of implementing treatment, and
b) cost of side effects.

Direct costs for both treatments within the present study were first estimated on the basis of a single patient per year course of treatment. The average costs were subsequently applied to the entire population of anaemic patients. The following procedures were used to determine the direct costs of EPO treatment;

1. Dosage in EPO therapy: The following three sets of figures were examined to establish dosage:

a) The manufacturer-advised dosage is 3-5 vials for the first 20 weeks of treatment, followed by a maintenance dosage of 2 vials per week, the total of which is 134 vials in the first year and 104 in each subsequent year;

b) Patients examined for quantification of quality of life received six vials per week without appreciable variations in dosage. This results in an annual dosage of 312 vials per year;

c) Certain dialysis centres contacted for the purposes of ascertaining the number of patients undergoing transfusions reported dosages of up to 9 vials per week (468 vials per year).

The explanation for such a wide range lies in the time required to reach the haemoglobin target: a higher dosage abbreviates time. As clinical experience today seems to favour gradual attainments of the target (3-5 months), it was decided to adopt the 104 vials per year as the lower limit of dosage. Such a limit can be waived in sensitivity analysis. It does, in any case, represent a conservative estimate; the cost of EPO can only be in excess of the figure adopted for the purposes of comparison;

2. Cost per vial: 73,777 lire, the price in force in Italian hospitals, was adopted;

3. Side-effects ascribable to EPO therapy: Although in one centre hypertension was reported to affect over 10% of patients, this phenomenon was not significantly reproduced in other centres. An average incidence of 5% is therefore held to be acceptable. Anti-hypertension therapy employs various pharmaceuticals. One of the most frequently used products is an ACE inhibitor (Capoten), annual consumption of which may be estimated at 30 packages (50 mg) at a price of 15, 918 lire per package to hospitals.

Total direct costs for EPO treatment on a single patient/one year basis were therefore estimated to be:

- EPO cost =
  (annual dosage) x (average price)
  104 vials x 73,777 = 7,672,808

- Cost of treatment of side-effects =
  (annual dosage ACE inhibitor) x (average price) x (average incidence)
  30 vials x 15,978 x 0.05 = 23,967

- Total direct costs for EPO treatment = 7,672,808 + 23,967 = 7,696,775

The annual cost of treatment of an anaemic patient on dialysis with repeated transfusion of red cells was estimated by summation of the sole marginal costs of a transfusion, which are as follows;

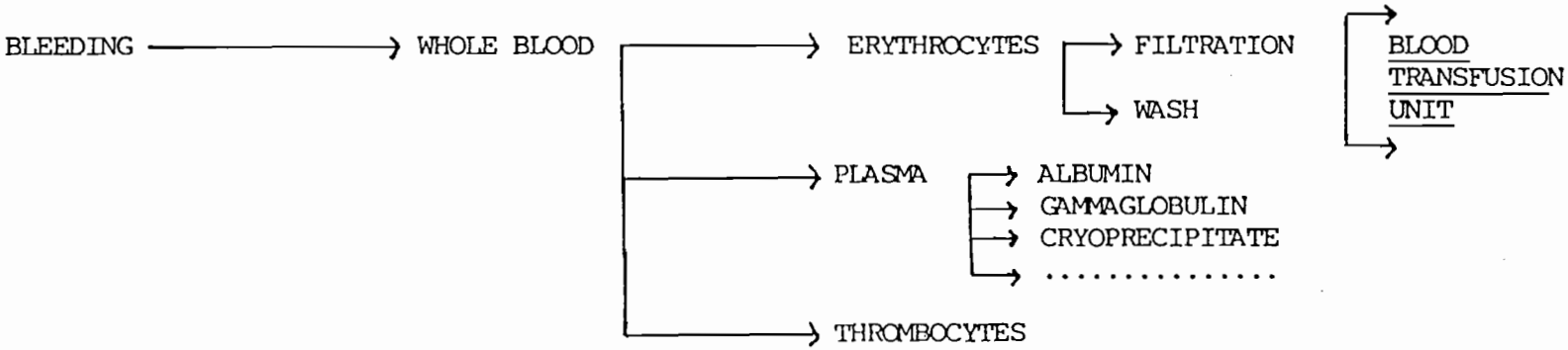
- bag of red cells
- material for transfusion
- pre-transfusion tests
- side-effects

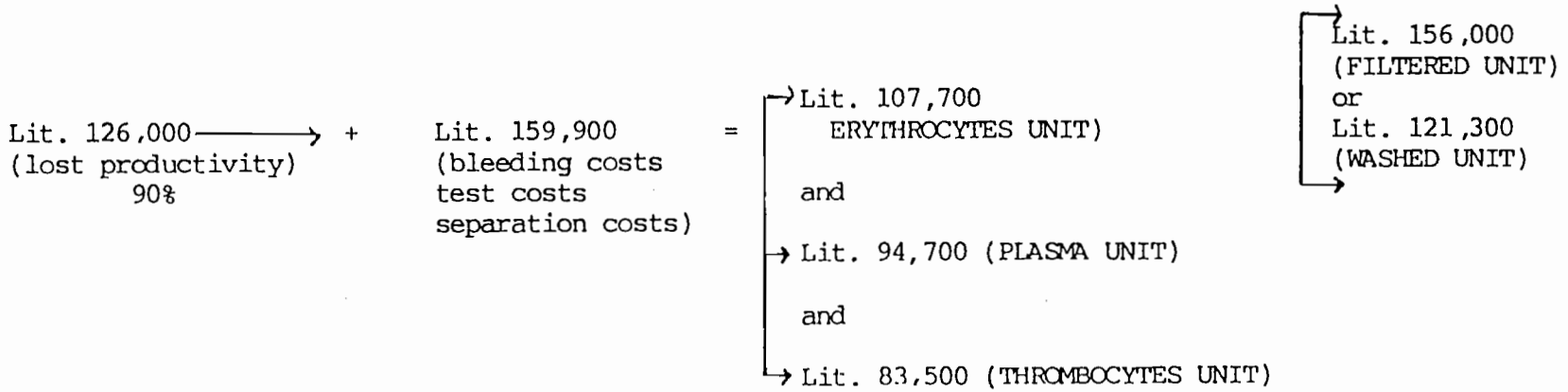
The cost per bag of red cells was estimated on the basis of the tariffs in force in the National Health Service (89,300 lire for washed erythrocytes and 124,000 for filtered erythrocytes). This includes testing for antibodies to the more common infectious diseases (hepatitis B, AIDS, etc). Such tariffs were adjusted in order to distribute more equitably the costs of dividing a whole blood unit into its three haemo-derivatives (erythrocytes, plasma, thrombocytes). It was decided to incorporate into the figure obtained, the cost (indirect) deriving from loss to production caused by absence of a donor from his or her place of work, because of blood donation. On the basis of inquiry it was estimated that 90% of blood donors belonged to the employee category (white and blue collar). The cost of work days lost was estimated by dividing the share of Gross National Product ascribable to income from working employees, inclusive of social charges. A cost per working day equivalent to 140,000 lire was thus obtained for 1988, of which only 90% is to be considered, representing the proportion of employees to the total donors. This loss of productivity was also equitably distributed over all haemo derivatives. Finally, it was noted that the transfusion is generally composed of 50% each of filtered and washed erythrocytes.

With the adjustments illustrated, the opportunity cost of a bag of red cells seemed to vary between 121,300 lire for washed cells and 156,000 lire for filtered cells (Table 4.1) with a mean value of 138,650 lire. the annual frequency of transfusion to an anaemic patient (HMC 15-20 or HMG < 8-9) in the dialysis centres contacted appeared to vary between an average minimum of 4 and a maximum of 9. On the whole, 7 annual transfusions per patient was judged to be plausible. The cost of material (set) needed for a transfusion, apparently almost always required in the course of dialysis, was valued at 2,000 lire; to which 16,000 lire must be added to cover the biocompatibility test.

With regard to side-effects emerging from transfusion of red cells, the 4 centres contacted provided the following information: a) in the last two years (1987 and 1988) there had been no instance of AIDS transmitted by this channel to patients on dialysis; b) an incidence equal to 0.7% of infections such as hepatitis B and hepatitis nA/nB was judged to be plausible by the

Table 4.1 - BLOOD TRANSFUSION UNIT FLOWSHEET AND COSTS





Source: Istituto di Economia Sanitaria, Milano 1989

various nephrologists interviewed; c) 50% of the multiple transfusion patients seemed to display an iron overload; d) 100% of the multiple transfusion patients seemed to become highly sensitized (with reduced chances of kidney transplants).

The cost of acute viral hepatitis (hepatitis B and non A non B hepatitis) without complications, destined to be neutralized over a one year term and inclusive of the value of working days lost, was estimated on the basis of previous inquiries to equal 9,234,00 lire.

The cost of treatment for iron overload, involving administration of approximately 5 packages of deferoxaminum (Desferal) annually, at a price of 45,150 lire (to hospitals) may be valued at 121,905 lire per year.

The cost of immunity against transplant is hard to estimate. While it is true that the inevitable immunity of multiple transfusion patients is an important factor in the exclusions of transplant, it is equally true that the likelihood today of even non-multiple transfusion patients on dialysis obtaining a kidney transplant seems very remote. The data available show that the average survival on constant dialysis is approximately 10 years. This is due to two contrasting phenomena: the improvement in dialysis technology and the increase in the average age of patients accepted for dialysis (see later). The ten year survival period is paralleled by a waiting list for transplant exceeding ten years. As the number of Italians on the 1987 waiting list for transplant (in Italy and abroad) was about 9,300 and the number of transplants was 835, the average waiting period, unfortunately, seems to be longer than the average survival period. These reflections, in addition to the absence of information concerning the immunity response to transplant in patients treated with EPO, have urged shelving of the problem.

Totalling the various entries, the annual cost of transfusion treatment of anaemia in a patient on dialysis is as follows:

- cost per erythrocyte bag x no. of transfusions:

- 138,650 x 7 = 970,550

- cost of transfusion materials:
  2,000 x 7 = 14,000

- cost of biocompatibility test:
  16,000 x 7 = 112,000

- cost of treatment of hepatitis B:
  9,234,000 x 0.007 = 64,638

- cost of treatment of non A non B hepatitis
  9,234,000 x 0.007 = 64,638

- cost of treatment of iron overload:
  45,150 x 5 x 0.5 = 112,875
  Total direct cost of transfusion therapy:
  = 1,338,701 lire

Table 4.2 gives the main cost elements of the 2 therapies, expressed in Italian lire and US dollars.

Table 4.2 - EPO AND TRANSFUSION TREATMENT COSTS PER PATIENT
Italian Lire and US Dollars
(1 dollar = 1,350 lire)

1 EPO	AVERAGE VALUES (Lit.)	AVERAGE VALUES (US $)
1.1 EPO unit price	73,777	54.65
1.2 EPO units/year	104	104
1.3 EPO cost/year	7,672,808	5,684
Other Drugs		
1.4 ACE inhibitor unit price (Capoten)	15,978	11.84
1.5 Capoten units/year	30	30
1.6 Anti-hypertension treatment cost	479,340	355
1.7 Anti-hypertension treatments/year (rate)	.05	.05
1.8 Anti-hypertension treatment cost/year	23,967	18
EPO TREATMENT COST/YEAR	7,696,775	5,701
2 TRANSFUSION		
2.1.0 Blood unit cost	138,650	102.70
2.1.1 Blood units/year	7	7
2.1.2 Blood units cost/year	970,550	719
2.2.0 Transfusion material cost	2,000	1.48
2.2.1 Transfusion material units/year	7	7
2.2.2 Transfusion material cost/year	14,000	10
2.3.0 Pre-transfusion test cost	16,000	11.85
2.3.1 Pre-transfusion test units/year	7	7
2.3.2 Pre-transfusion test cost/year	112,000	83
Side Effects		
2.4.0 HB treatment cost	9,234,000	6,840.00
2.4.1 HB infections/year (rate)	.007	.007
2.4.2 HB treatment cost/year	64,638	48
2.5.0 HnA/nB treatment cost	9,234,000	6,840.00
2.5.1 HnA/nB infections/year (rate)	.007	.007
2.5.2 HnA/nB treatment cost/year	64,638	48
2.6.0 Desferal (deferoxaminum) unit price	45,150	33.44
2.6.1 Desferal units/year	5	5
2.6.2 Iron overloading treatment cost	225,750	167
2.6.3 Iron overloadings/year (rate)	.50	.50
2.6.4 Iron overloading cost/year	112,875	84
TRANSFUSION TREATMENT COST/YEAR	1,338,701	992

Source: Istituto di Economia Sanitaria, Milano 1989

4.4 ASSESSMENTS OF BENEFITS

Two aspects which may be taken into consideration when assessing the benefits of a specific therapy are their contribution to:

1. life expectancy
2. quality of life.

Both transfusion and EPO are able to prolong the life of the patient. There are no comparative studies to confirm that EPO guarantees a longer life expectancy than does transfusion. Notwithstanding, clinicians widely believe EPO should increase life expectancy for patients on dialysis. Consequently, this opinion has been taken into consideration in the assessment of benefits. However, in view of the impossibility of quantifying the longer life expectancy, a conservative estimate of a 10% increase of life expectancy has been attributed to patients on EPO treatment. The average life of patients on dialysis has been calculated on the basis of ANED (Associazione Nazionale EmoDializzati) data. Unfortunately, these data do not take into account the age of patients at the start of dialysis treatment.

It is believed, however, that in Italy, as in other countries, there is a rise in the average age of those undergoing dialysis. It is clinicians' opinion that the phenomenon is more marked in Italy (probably due to the absence of a restrictive upper age limit when accepting patients for dialysis). According to available ANED data, 36% of patients starting dialysis in 1977 were over 65. There are no figures available for annual mortality rates of patients on dialysis in Italy, broken down on the basis of time spent under treatment. The EDTA data indicate that for patients who began dialysis in the 1980-84 period, the survival rate was 5 years in 76% of the cases when the age at start of treatment was between 15 and 44, and 56% when the age at start of treatment was between 45 and 65. This points to a marked improvement compared with the 1970-74 period, for which EDTA gave a survival rate of 60% for the 15 and 44 group.

As there is no equivalent to the EDTA model in Italy it is necessary to rely on ANED data (Tables 4.3 and 4.4). ANED figures suggest that on average, deaths in a specific year are approximately 10% of patients on dialysis at the end of the previous year, unexpectedly, without significant variations from year to year. The expected improvement in survival rate is neutralized by the increased average age at the start of dialysis. It seems realistic, therefore, to estimate a life expectancy of ten years for patients at present on dialysis with transfusion, whereas patients undergoing EPO treatment would have a life expectancy of 11 years (+10%). Inclusion of the expected improvement in quality of life among benefits is an important step forward in the assessment of a therapy. While life expectancy may not be significantly improved by new treatment, there may be a sensible improvement in the patient's ability to meet his or her daily needs, carry on working, and keep up social contacts.

It is therefore necessary to assess the quality of life of patients undergoing EPO treatment with respect to those on transfusion. A hypothesis formulated, shared by clinicians, is that quality of life is better for patients on EPO. Further, it is felt that quality of life does not change

Table 4.3 - RENAL REPLACEMENT TREATMENT IN ITALY: 1976 - 1987 BALANCE

	RRT patients (1 Jan)	transplanted (Italy & abroad)	deceased	back from transplant	new patients	in/out dialysis due to other reasons	balance	RRT patients (31 Dec)
1976	6,974	230	n.d	n.d	n.d	n.d	n.d	8,294
1977	8,294	295	906	(47)	(2,384)	(90)	1,320	9,763
1978	9,763	213	997	(34)	(2,653)	-8	1,469	11,285
1979	11,285	260	1,152	(42)	(2,889)	n.d	1,552	12,759
1980	12,759	419	1,319	(67)	(3,107)	(38)	1,474	14,515
1981	14,515	456	n.d	(73)	n.d	n.d	1,756	16,051
1982	16,051	565	1,586	(90)	(3,541)	(56)	1,536	17,450
1983	17,450	653	1,797	104	3,799	-54	1,399	18,826
1984	18,826	638	n.d	(102)	n.d	n.d	1,376	20,248
1985	20,248	702	2,150	122	3,987	(165)	1,422	21,587
1986	21,587	681	2,417	111	4,206	(120)	1,339	22,940
1987	22,940	826	2,400	142	4,501	-64	1,353	24,000
1988	24,000	n.d	n.d	n.d	n.d	n.d	n.d	n.d

Source: ANED and our estimates (in brackets)

Table 4.4 - RRT PATIENTS IN ITALY: MAIN TRENDS

(years: 1976 - 1988)

	RRT patients annual rates %	Transplanted RRT patients %	RRT patients deceased/ RRT patients %	New RRT patients/ RRT patients %
1976	-	3.30	-	-
1977	18.93	3.56	10.92	28.74
1978	17.71	2.18	10.21	27.17
1979	15.59	2.30	10.21	25.60
1980	13.06	3.28	10.34	24.35
1981	13.76	3.14	-	-
1982	10.58	3.52	9.88	22.06
1983	8.72	3.74	10.30	21.77
1984	7.89	3.39	-	-
1985	7.55	3.47	10.62	19.69
1986	6.61	3.15	11.20	19.48
1987	6.27	3.60	10.46	19.62
1988	4.62	-	-	-

Source: Calculations on ANED data

during treatment, either on EPO or on transfusion.

No study has been made in this field and there is now insufficient time to undertake such an initiative. The method of assessment evolved by Kind and Rosser delineating 30 possible states in terms of disability and distress, might be usefully applied in this case, using information acquired for other purposes.

However, the information needed to use the QALY questionnaire (Gudex and Kind, 1988), was not available. Reprocessing clinical trial data and interviewing specialists, it was discovered that a small group of 11 patients (data shown in Table 4.5) had been asked to fill in an "ad hoc" EPO questionnaire dealing with "physical activity performance", "energy", "social life", "emotional state", "sleep", and "sexual activity". Specialists confirmed the view that similarities between this questionnaire and that developed by the York QALY team were sufficient to calculate the scores for disability ("general mobility", "usual activity", "self care" and "social and personal relationships") and distress, in a similar way to the York questionnaire.

All the 11 patients to whom the EPO questionnaire was submitted before starting EPO treatment were on transfusion therapy. For that reason the responses to this first questionnaire, filled in between two transfusions to obtain average conditions, were assumed to be representative of the "transfusion group". The results of the second questionnaire, completed after the start of EPO treatment, at the moment Hb target was reached, were assumed to be representative of the "EPO group".

Patients' disability/distress states on transfusion and on EPO are shown in Table 4.6. The improved outcome of EPO treatment is self explanatory.

QoL scores for each patient were discounted at a 5% rate. (See Table 4.7 for individual patient results). Table 4.8 summarises discounted QALY gains for each patient. In general gains from EPO represent an average 12.1% improvement. The small number of patients interviewed is evidently inadequate to represent the general Italian situation.

4.5 RESULTS

Results are summarised in Tables 4.9 and 4.10. Table 4.9 shows the marginal cost per QALY gained. This final index has been calculated solely for the eleven patients who completed the Kind and Rosser questionnaire. The following assumptions were made:

- the outcome and costs were constant for the entire period of treatment;
- an average life expectancy for patients on RRT is 10 years;
- there is a 10% improvement in life expectancy for patients on EPO;
- the eleventh year brought RRT costs in addition to EPO costs;
- a 5% discount rate.

There is no solid basis for these assumptions, but they cannot be significantly improved at present. Consequently, results of the cost-effectiveness for the eleven patients are not fully satisfactory and cannot

Table 4.5 - PATIENTS PREVIOUSLY ON TRANSFUSION TREATED WITH EPO

Patient N°	Sex	Age	Period on dialysis (years)	HMB (g/dl) baseline	target	Time to target (months)
1201	F	42	17.0	7.3	10.3	3.5
1202	F	42	2.0	6.7	8.6	3.5
1203	F	27	4.0	6.2	9.4	2.0
1212	F	37	2.0	7.2	10.6	3.0
1213	F	23	13.0	7.0	10.6	3.5
1215	F	25	7.0	7.3	10.7	1.5
1221	F	36	4.0	7.0	9.5	3.5
1222	M	33	6.0	6.1	11.0	3.0
1231	M	44	11.0	6.9	10.3	1.0
1232	M	22	1.0	8.7	10.1	1.0
1251	F	67	.5	6.7	10.7	1.5

Source: Clinical Trials on EPO in Italy, 1988

Table 4.6 - PATIENTS' DISABILITY/DISTRESS STATE ON TRANSFUSION AND EPO

Classification of patients on transfusion

Disability State	Distress State				Total
	A	B	C	D	
I	1	0	0	0	1
II	0	0	0	0	0
III	4	2	1	0	7
IV	1	0	0	0	1
V	1	0	0	1	2
VI	0	0	0	0	0
VII	0	0	0	0	0
VIII	0	0	0	0	0
Total	7	2	1	1	11

Classification of patients on EPO

Disability State	Distress State				Total
	A	B	C	D	
I	3	1	0	0	4
II	0	3	0	0	3
III	4	0	0	0	4
IV	0	0	0	0	0
V	0	0	0	0	0
VI	0	0	0	0	0
VII	0	0	0	0	0
VIII	0	0	0	0	0
Total	7	4	0	0	11

Source: Instituto di Economia Sanitaria, Milano 1989

Table 4.7 - CALCULATION OF DISCOUNTED QoL SCORES

TRANSFUSION					EPO				
Patient: n° 1222 Date: 06/08/87					Patient: n° 1222 Date: 09/11/87				
Year	QoL level	QoL scores	Discount factor	Discounted QoL scores	QoL level	QoL scores	Discount factor	Discounted QoL scores	GAINS
1	IIIA	.980	.952	.933	IB	.995	.952	.947	.014
2	IIIA	.980	.907	.889	IB	.995	.907	.902	.014
3	IIIA	.980	.864	.847	IB	.995	.864	.860	.013
4	IIIA	.980	.823	.807	IB	.995	.823	.819	.012
5	IIIA	.980	.783	.767	IB	.995	.783	.779	.012
6	IIIA	.980	.746	.731	IB	.995	.746	.742	.011
7	IIIA	.980	.711	.697	IB	.995	.711	.707	.011
8	IIIA	.980	.677	.663	IB	.995	.677	.674	.010
9	IIIA	.980	.645	.632	IB	.995	.645	.642	.010
10	IIIA	.980	.614	.602	IB	.995	.614	.611	.009
11	IIIA	.980	-	.000	IB	.995	.585	.582	.582
	TOTAL			7.568				8.265	.698

Table 4.8 - CALCULATION OF QALY GAINS

TRANSFUSION			EPO		
Patient	QoL Level	Discounted QALYs (5% rate)	QoL Level	Discounted QALYs (5% rate)	GAINS
1201	VA	7.305	IIIA	8.141	.836
1202	VD	5.405	IIB	8.191	2.876
1203	IIIC	7.382	IIB	8.191	.809
1212	IIIB	7.506	IIIA	8.141	.635
1213	IA	7.722	IA	8.307	.585
1215	IIIA	7.568	IIIA	8.141	.573
1221	IIIB	7.506	IIB	8.191	.685
1222	IIIA	7.568	IB	8.265	.697
1231	IVA	7.444	IIIA	8.141	.697
1232	IIIA	7.568	IA	8.307	.739
1251	IIIA	7.568	IA	8.307	.739
Total		80.542		90.323	9.781
average		7.322		8.211	.889
min.		5.405		8.141	.573
max.		7.722		8.307	2.786
s.d.		.645		.072	.634

Source: Istituto di Economia Sanitaria, Milano 1989

be extended to the RRT population.

The discounted cost per QALY is on average equal to $8,406 for EPO and $1,046 for transfusion. It is clear that EPO treatment allows longer life and better quality of life at an increased cost for society. The cost per QALY will rise in the eleventh year of treatment, when patients surviving, thanks to EPO, will continue their RRT for an additional year. Consequently, in that year, the EPO cost will be increased by the marginal cost of RRT treatment ($37,000 per patient). For that year (11th) the cost per QALY goes up to $43,232. Notwithstanding this increase, the additional year of life expectancy significantly decreases the cost per QALY gained, equal to $69,011 (Table 4.9). Without that additional year, the cost per gained QALY would have been significantly higher ($117,000).

Table 4.10 shows a different way of assessing the impact of the two treatments (EPO and transfusion). An approximation to a cost-benefit methodology is used in an attempt to evaluate consequences deriving from the extension of EPO treatment to all anaemic RRT patients able to benefit from such treatment.

Benefits in this case are expressed in monetary terms, assigning a value to the recovery of patients' working capacity deriving from the treatment of anaemia. If anaemic patients on RRT treated with transfusion or with EPO are able to continue their activities, then a benefits assessment can be calculated on the basis of value of avoided productivity loss.

Problems arise when the following must be evaluated:

- the number of anaemic RRT patients that can be successfully treated with EPO, far greater than the number of patients at present on transfusion;
- the percentage of such patients that not only could but also would continue to work;
- how many productivity differential gains are linked to EPO treatment.

Drawing on clinicians' opinions, the following assumptions were made:

- anaemic patients potentially treatable with EPO equal 30% of patients of working age (24-65) on RRT;
- 5% of RRT patients of working age (24-65) and at present on transfusion in Italy are considered able to continue to work normally;
- 5.5% of the 30% of patients of working age on EPO (+10% in respect of transfusion) have been considered able to continue to work normally;
- the same productivity gain, $22,000 per year on average (see section 4.3) has been assigned to all patients working normally.

Due to the approximate nature of these assumptions, analysis has been limited to the first year of treatment. The same cost (as shown in Table 4.2) has been used to obtain the results in the upper part of Table 4.10. Cost-benefit ratios, shown in the lower part of Table 4.10, are negative for both treatments, particularly for EPO, which shows a B/C ratio of 0.14, with a surplus of costs of $32 million for one year of treatment.

Table 4.9 - Eleven Years EPO and Transfusion Treatment Costs and QALYs (eleven patients).

US Dollars
(1 dollar = 1,350 lire)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11	Total
EPO												
Dialysis treatment cost/year (*)	0	0	0	0	0	0	0	0	0	0	288,300	238,300
EPO treatment cost/year (*)	59,704	56,882	54,185	51,614	49,105	46,785	44,590	42,458	40,451	38,507	36,688	520,969
Total cost/year (*)	59,704	56,882	54,185	51,614	49,105	46,785	44,590	42,458	40,451	38,507	274,988	759,269
QALYs (*)	10,351	9,862	9,394	8,948	8,514	8,111	7,734	7,361	7,013	6,676	6,361	90,322
Cost/QALY	5,768	5,768	5,768	5,768	5,768	5,768	5,768	5,768	5,768	5,768	43,232	8,406
TRANSFUSION												
Treatment cost/year (*)	10,384	9,893	9,424	8,977	8,541	8,137	7,756	7,385	7,036	6,697	-	84,231
QALYs (*)	9,929	9,460	9,012	8,564	8,167	7,781	7,416	7,061	6,727	6,404	-	80,540
Cost/QALY	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	1,046	-	1,046

MARGINAL COST OF QALY GAINED = (759,269 - 84,231) / (90,322 - 80,540) = 69,011

(*) discounted at 5% rate. Source: Instituto di Economia Sanitaria, Milano, 1989.

Table 4.10 - EPO and Transfusion Treatment Costs and Benefits. All RRT-HD-Patients
U.S. Dollars
(1 Dollar = 1,350 lire)

	PATIENTS (units)	PATIENTS (%)	TREATMENT COSTS (u.s. dollars)	GAINED PRODUCTIVITY (u.s. dollars)
RRT (HD) Patients	22,000	100.0%	-	-
- of working age	14,520	66.0%	-	-
TREATED WITH TRANSFUSION	2,200	10.0%	2,182,400	-
- of working age	1,452	6.6%	-	-
- returned to work	73	.3%	-	1,613,333
TREATED WITH EPO	6,600	30.0%	37,630,560	-
- belonging to labour force	4,356	19.8%	-	-
- returned to work	240	1.1%	-	5,324,000

cost/benefit indexes:	B - C	B/C
- TRANSFUSION TREATMENT	-569,067	.74
- EPO TREATMENT		
. actual price = $54.65	-32,306,560	.14
. with a price of $10.3	-1,864,720	.74
. with a price of $7.58	0	1.00
. returned to work (1.1%)	-32,306,560	.14
. returned to work (5.7%)	-9,655,360	.74
. returned to work (7.7%)	0	1.00

Source: Istituto di Economica Sanitaria, Milano 1989

In order to observe how results would be affected by changes in EPO price and the percentage of EPO patients able to continue working, sensitivity analysis was applied. This analysis showed (lower part of Table 4.10) that a lower price of EPO ($10.30, approximately 1/5 of the existing price) could equalize the B/C rate of the two treatments (0.74). To equalize costs and benefits, the price of EPO would have to be lowered to $7.58.

However, at the existing price of EPO ($54.65), 5.7% of RRT patients of working age (instead of 1.1%) would have to continue working to equalize the B/C ratio (0.74), and the same would apply to 7.7% of RRT patients to equalize costs and benefits.

4.6 DISCUSSION

The first point to be made is that commissioning of this study urged preparation within three months. There have been two main consequences:

- thorough checking of all hypotheses was ruled out; and,
- ad hoc inquiries had to be restricted.

Estimation of costs had to be confined to examining the situation in a limited number of dialysis centres. Assessment of benefits in terms of QALYs had to be confined to an even greater extent: sources for this measure were clinical literature and pre-existent clinical trials. It was thus only possible to estimate QALYs for a few patients (11). Furthermore, the Italian study was carried out using internationally-accepted methodology in order to guarantee that the results would be comparable to those of other countries. In addition, the weights used in applying the Kind and Rosser index were tailored to UK social values and may, therefore, apply only roughly to the actual social/cultural situation in Italy.

Two separate techniques were used to assess the impact of EPO treatment: cost effectiveness (C/E) and cost-benefit (C/B) analyses.

From a C/E standpoint, this study shows that the marginal cost of QALY gained with EPO treatment in comparison to transfusion is nearly $69,000. However, the limited number of patients and lack of a fully checked hypothesis prevents generalization. Moreover, the QALYs calculation is restricted to one year; the future trend remains unknown, unless constancy can be hypothesized.

This high QALY gain is derived mainly from the EPO dosage cost agreed upon internationally (two vials per week).

It should be kept in mind that longer survival with EPO (+10%) involves additional costs of dialysis treatment. Another consideration centres upon whether EPO treatment increases the likelihood of renal transplant, since this additional cost would be partially compensated by the benefits of transplantation. Unfortunately, incorporation of these factors is currently prevented by a lack of definitive studies and by the long waiting list for renal transplant in Italy.

From a C/B perspective, the results for both EPO and transfusion treatments are negative, and even more so in the case of EPO. However, sensitivity analysis shows that the right price for EPO would allow benefits

to balance costs if an increase of seven times the number of patients currently working (1,700 vs. 240) could be attained.

The question of just how realistic this target is must be answered before it can be determined how worthwhile this new treatment is in terms of C/B for the community. An effective answer will only be obtained, however, when more information on EPO becomes available, specifically on the subjects of dosage and the kinds of patients that are likely to benefit from treatment. Meanwhile, key information is required about the real attitude of these patients - anaemia patients with chronic renal disease (both on or not on RRT) - toward continuing to work.

Chapter 5

The Spanish Case Study

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5.1 INTRODUCTION

5.1.1 Objectives of the Study

The objective of the study is to assess the cost-effectiveness of treating anaemia in haemodialised patients with Erythropoietin as opposed to the traditional management with blood transfusions.

An estimation will also be provided of the global impact on the health system of the substitution of transfusion by Erythropoietin therapy.

5.1.2 Methodology

The evaluation of the two treatment alternatives will take the form of a cost-utility analysis, ie the excess direct costs of Erythropoietin treatment over traditional transfusion treatment will be contrasted with the excess health benefits measured in terms of quality-adjusted life years, and the results expressed in terms of cost per QALY gained.

5.1.3 Data sources

As Erythropoietin is still not generally available in Spain and only a very small number of patients have been treated on an experimental basis, the costs and benefits of this treatment are difficult to assess in a reliable way. Therefore, some assumptions will often have to be made based on partial evidence or on the literature available on the experience of the other countries.

The main Spanish data sources used in the study are listed below:

a) Demographic structure of the population of patients with chronic renal failure:

   * EDTA Registry
   * Registry of Dialysis Patients in Catalonia

b) QoL data. Questionnaires on QoL passed to patients in the following Dialysis Centres:

   Hospital de San Gervasio, Nephros, Hospital Cruz Roja, Can Ruti, Institut Nefrologic, Hospital Bellvitge (Barcelona);

   Hospital Gregorio Marañón, Centro de Diálisis Los Enebros (Madrid).

c) Cost data. Data on cost have been obtained from the Hospital General de Asturias and from personal communications indicated in the text.

d) Clinical information. Clinical information on the treatment assessed

has been obtained from published studies and from personal communications from Dr Valderràbano and other leading nephrologists, and the Cilag representative.

5.2 DESCRIPTION OF ALTERNATIVES ASSESSED

5.2.1 Anaemia in dialysis patients

Anaemia is a constant complication in patients suffering from Chronic Renal Insufficiency (CRI) who are in haemodialysis programmes (HD), and its seriousness ranges from stable cases to those requiring blood transfusions on a bi-weekly or monthly basis.

The clinical repercussions of anaemia vary widely, and in many cases are not related to the haematocrit value but depend instead upon the tolerance of the patient (Praga, 1989). Several pathologies which are aggravated by a worsening of the anaemia, particularly cardiovascular pathologies, are frequent among dialysis patients. The therapeutic alternatives centre around blood transfusions, since androgens present many complications. The most serious cases require 10 or more red blood cell concentrates in one year. The appearance of recombinant human Erythropoietin (R-HUEPO) has opened a new therapeutic perspective at a time when transfusion therapy is becoming increasingly restricted in certain regions of Spain.

5.2.2 Transfusion: Management, outcomes, side effects

The decision to give a transfusion to a patient in haemodialysis does not rely upon a mechanical pattern, nor upon exact parameters; instead, it is above all a question of the quality of life.

It is generally accepted that with a haematocrit value of less than 20% a transfusion is necessary; however, individual adaptability varies, and there are patients with a haematocrit of less than 20% in stable condition and patients with a haematocrit of more than 25% (normally with associated cardiovascular disease) who require a transfusion.

Accordingly, and in the opinion of the kidney specialists consulted, patients can be divided into three groups:

* Haematocrit less than 20% (normally requiring more than 5 transfusions per year)

* Haematocrit between 20-25% (1 to 5 transfusions per year, without associated cardiovascular disease)

* Haematocrit more than 25% (1 to 5 transfusions per year, with associated cardiovascular disease)

One of the problems of transfusion therapy is that it is difficult to stabilize the patient over long periods of time, and patients are subject to a progressive worsening of the anaemia until the next transfusion. This has important clinical repercussions as well as consequences for the quality of life.

Transfusions, moreover, subject patients to considerable risks, notably the hepatotrophic virus nonA-nonB which could evolve into chronic hepatitis,

whereas hepatitis B is monitored due to its serological detection in blood donors. The prevalence of post-transfusion hepatitis in dialysis patients is estimated to be 10.6% (Matesanz et al, 1983).

AIDS, immunological sensitisation and an excess of iron (hemosiderosis) constitute other important adverse effects of transfusion therapy on dialysis patient survival.

5.2.3 Erythropoietin: Management, outcomes, side effects

The R-HUEPO obtained by techniques for gene recombination is comparable to human erythropoietin, acting at the haematological synthesis level, stimulating the production of red blood cells (Aguilera, 1988). In situations of CRI, the kidney is not able to secrete the hormone, which contributes significantly to the anaemia suffered by haemodialysis patients. In Spain, R-HUEPO is available through two pharmaceutical firms, Cilag and Boehringer Mannheim.

At present, Spanish experience with EPO treatment is based on the ongoing clinical trials by the pharmaceutical firms who have supplied it to several haemodialysis centres, since it is not yet generally available. In Catalonia, clinical specialists and health administration personnel have drawn up guidelines for EPO treatment in patients with CRI (Table 5.1).

Indications for EPO treatment under conditions of CRI, which had originally seemed to be restricted to transfusion-dependent patients, are becoming more liberalized, and may come to include the majority of CRI patients with anaemia.

EPO is administered endovenously for at least two minutes in order to palliate any possible immediate side-effects (pain, headache, fever), using the artery-vein fistula at the conclusion of each dialysis session. The recommended initial dosage varies between 40-50 IU per kg body weight, three times per week, increasing by 25 IU per kg weight every four weeks, if no response is obtained, up to a maximum of 200 IU/kg per week. The maintenance dosage, normally reached 6 to 12 weeks after the commencement of treatment, varies widely among patients. If the response is favourable, clinical maintenance of the patient is achieved.

The adverse reactions described in the literature (Casati, 1987) are related to the increase in haematocrit produced, and the individual's sensitivity to the drug. According to a European multi-centre study, the following adverse effects were found in 150 patients treated with EPO (Valderràbano, 1988):

* Increase in antihypertensive dosage or onset of arterial hypertension (20.7%)
* Vascular Access Thrombosis (9.3%)
* Pruritus (9.3%)
* Flu like symptoms (pain, fever, headache) (13.3%)
* Allergy (0.7%)

Table 5.1 Indications for EPO Treatment in CRI

A. Children with Renal Insufficiency (between 2 and 15 years old)

- Terminal Renal Insufficiency patients in dialysis. Dialysis should be well tolerated:

    1. Transfusion-dependent patients

    2. Haematocrit of less than 25% in the last two controls, at 3 month intervals.

    3. Special clinical situations justified on an individual basis.

    4. Pre-terminal Chronic Renal Insufficiency patients glomerular filtrate less than 10% of the assumed normal level, undergoing a conservative treatment.

B. Adults with Renal Insufficiency: restricted to patients in dialysis for more than 6 months and in stable condition. There is no age limit.

1. Transfusion-dependent patients: 10 or more red blood cell concentrates per year; or 4 concentrates every 3 months.

2. Haematocrit under 25% in the last two controls (3 month intervals).

3. Haematocrit over 25% and organic situations aggravated by the anaemia:

    a) Ischaemic cardiovascular disease.

    b) Haemosiderosis.

    c) Special clinical situations that must be justified in detail.

Other side-effects have also been described, such as a slight alteration in the biology of the liver, decrease in effectiveness of dialysis and increase in iron requirements, hyperkalaemia, increase in weight.

It is not clear that there is an increase in vascular access thrombosis attributable to treatment with EPO, according to the specialists consulted; in the majority of cases it depends upon the type of fistula used.

The benefits of the hormone described lie in its capacity to alleviate and stabilize the anaemia, with the resulting clinical repercussions and consequences for the quality of life for the patient. The following have been described: increased tolerance for exercise (Clarck et al; Mayer et al, 1988); increased sexual potency and fertility (Bommer et al, 1988); and increased capacity for work (Mayer et al, 1988).

The effect of EPO upon the quality of life and functional capacity of anaemic patients on chronic haemodialysis has been evaluated with the sickness impact profile and physical and fatigue dimensions of a kidney-disease-specific questionnaire. EPO appears to improve the quality of life and

functional capacity of anaemic haemodialysis patients statistically and clinically (Laupacis, 1988).

It is too soon for data on whether EPO treatment has an effect on the survival of patients in haemodialysis.

5.3 COSTS ESTIMATION

5.3.1 Erythropoietin

In this section the costs of treatment with EPO are evaluated according to the clinical practices that are being developed in Spain.

5.3.1.1 Cost of EPO

As mentioned above, the marketing of EPO is not yet authorised in Spain. It is now being tested in two clinical trials, carried out in Hospital Gregorio Marañón (Madrid), Hospital Clíinico (Barcelona) and Hospital Reina Sofía (Córdoba) and other institutions. Those trials began in September 1988 and will be finished in March 1990. The second will last six months and there are eleven hospitals involved.

According to the results obtained in the on-going clinical trials it seems that the mean dose for maintenance treatment, after the adjustments referred to in paragraph 5.2.3, would be 65 units per kg. The average weight of patients is about 60 kg.

The probable price in Spain may be about 5,694 Pt for 1 ml, equal to 4,000 units (information directly provided by Cilag-Spain). Therefore the yearly cost per patient would be about 886,000 Pt for the mean dose.

(3 sessions/week x 52 weeks x 60 kg x 65 u/kg x 1.4235 Pt/u = 866,000 pt).

5.3.1.2 Cost of side effects

Withdrawal of treatment due to adverse reactions is very rare, about 1-2%.

Lack of response to the treatment is not frequent either. It is associated mainly with iron deficiency and the efficacy of EPO is restored when iron is supplied. An evaluation of these factors is not included in the analysis because of their low incidence and low cost.

Two main adverse reactions that need some discussion are hypertension and "Thrombosis of Fistula".

Hypertension is found in 15 to 30% of patients. About ten per cent were already suffering hypertension before EPO was administered and need higher doses of hypotensive drugs. Another ten per cent need a new treatment with hypotensive drugs. The drugs most frequently used to treat hypertension and yearly costs are as follows:

Hypotensive drugs	Cost/year (Pt)
Atenolol	11,680
Nifedipine	21,900
Captopril	28,470
Average (approx)	20,000

The average cost for the 10% of patients who develop this condition as a result of EPO would therefore be 20,000 Pt. For the other 10% of patients who only have their treatment reinforced with higher doses of hypotensors, the extra cost is assumed to be 10,000 Pt per year.

Thrombosis of fistula has been found to be very similar in the group of patients treated with EPO and in those treated with transfusion, and consequently no costs are charged for it.

5.3.2 Transfusion

5.3.2.1 Cost of blood unit and tests

In Spain, due to ethical and legal constraints, there is not an open market for blood. Furthermore, lack of transparency in the organisation and operation of blood banks makes it difficult to calculate the cost of production of blood units. A recent survey carried out by the Ministry of Health has found variations in estimated costs per unit of blood of between 3,266 Pt and 25,878 Pt as a result of different accounting criteria followed by hospitals and blood banks, and due to varying degrees of efficiency and scale of the operations (Ministerio de Sanidad y Consumo, 1986).

Another recent study in Valencia obtained the following estimates, which seem reasonable as an approximation of full production costs for red cell concentrates in different institutions in 1986:

	Cruz Roja	INSALUD	CTCV
red cell concentrates	5,500	7,500	5,280

(1986 prices)
Source: Gandia Balaguer, 1986

Direct information was obtained from the Centro de Transfusiones del Principado de Asturias which charged the different hospitals of the region the price of 3,474 Pt per unit of red cell concentrates.

As a rough mean, therefore, the amount of 6,000 Pt per unit is taken together with a range of 1,500 Pt around it to cover differences in scale and efficiency. Taking into account the rate of inflation for 1987 and 1988 (consumer prices index variations of 4.6 and 5.8), the following estimations are arrived at:

	A	B	C
Blood (red cell concentrates) cost per unit	4,980	6,640	8,300

(1989 prices)

In addition to the blood, the costs have to be evaluated arising from the laboratory tests performed to guarantee the appropriateness of blood. Two items have to be considered, according to the best practice of nephrology units and blood-banks in Spanish hospitals:

- Cross-test to check compatibility
- RIA, Radio-immuno-assay, to detect the antigen to the hepatitis B virus. Although not performed in all hospitals, it is thought that it should be done in all cases and therefore it is included (Cannata, Allende, Serrano et al (1985) and Fernandez, Vina Fernandez, Serrano, Arias, Gutierrez Arias et al (1985) strongly support the generalisation of RIA as standard procedure for transfusions to CRI patients).

The direct costs of these two tests have been estimated to be the following, according to direct information from the Hospital General de Asturias:

Item	Cross-test - Pt	RIA - Pt
- Personnel	614	2,150
- Materials	254	2,214
- Cleaning	42	-
- Fixed costs (buildings, equipment)	26	332
	936	4,696

The current accountancy conventions used to estimate the cost of a unit of red cell concentrates tend to over estimate the real economic opportunity cost of this product.

At present haemotherapy is characterised by the generalisation of component therapy: whole blood is broken down into its natural components, which are transfused separately to different patients for specific purposes, as most patients do not need all the components of whole blood, but only one or some of them. The components for which demand is higher are the derivatives of plasma. This means that if a country is able to attain the level of whole blood donations needed to meet the demand for plasma derivatives - Factor VIII (antihaemophilic) and albumin - a surplus of red cell concentrates will appear. This situation explains the increasing tendency towards plasmapheresis, a procedure which consists of the separation

of plasma from red cells during donation and the reinfusion of red cells to the donor. Plasmapheresis allows a higher amount of plasma to be collected from each donor, as plasma is replaced by the body much quicker than red cells.

But the inconveniences of plasmapheresis - longer donation sessions - and its generalised stigmatization by voluntary donors as a retributed form of donation, has prevented plasmapheresis from expanding to the point where the relative supply of plasma derivatives matches its demand. Therefore most countries have an oversupply of red cell concentrates which are sometimes transferred free to other countries or result in a high rate of outdated units.

Insofar as there is an oversupply of red cells, no general costs of the process of blood component production should be allocated to the red cell units as this procedure clearly overstates its true opportunity cost, which may be near zero. This apparently surprising conclusion does not hold, of course, when there is a real scarcity of red cell concentrates (Rovira, 1982).

5.3.2.2. Administration costs

After careful consideration and according to the opinion of nephrologists and nurses in Madrid, Asturias and Barcelona, it has been concluded that no cost should generally be charged to compensate for professional work insofar as transfusions are performed during hospital haemodialysis sessions by and under the supervision of the same health professionals. HHD is the most commonly used dialysis procedure in Spain. 68.4% of patients were in HHD in 1986 in Spain and only 7.6 in home and peritoneal dialysis. 23.4% had been transplanted (Garcia and Valles, 1988). In some cases it seems that transfusions make dialysis last a little longer, but it seems so rare that no charge is made for it.

On the other hand, it seems sensible to charge for the extra time implied by transfusions when the patient has dialysis in an out-patient unit without blood facilities, and has to move to the reference hospital to be transfused. The additional cost incurred in these cases over costs already calculated, is one hour of the professional work of a nurse (the transfusion may last up to five hours but the effective time employed by nurses is about 20%, according to direct information gathered at Hospital General de Asturias and Hospital Gregorio Marañón). One hour of nurse time is estimated to cost 1,800 Pt.

Only a rough estimate of the patients under such circumstances can be provided; 58% of HHD patients were in 1983 treated in private units (Direccion General de Planificacion Sanitaria, 1984); it is assumed that half of them have to move to reference hospitals to be transfused, and that public units are all in hospitals with blood transfusion facilities. Therefore 30% of HHD patients have transfusions with this extra cost.

5.3.2.3 Side effects

In this section there is an evaluation of the costs that may arise from the emergence of side effects or adverse reactions caused by transfusions to CRI patients. The consequences of Hepatitis B; Hepatitis non-A non-B; AIDS; ferritin overload and hyper-immunisation will be considered.

* No charge will be made for the risk of B-Hepatitis though 40 cases were reported in Spain by EDTA in 1986 (EDTA, 1987). The reason is that present stage medical technology practically guarantees, if sound practices are followed, the eradication of this infection among CRI patients. The RIA test guarantees the absence of risk of infection of the blood transfused to patients, and the vaccine assures the protection of medical and nursing personnel. In fact, no case of hepatitis B has been reported in the last two years in either of the two hospitals worked with.

* Non-A Non-B Hepatitis is an actual risk that cannot be dismissed. The best estimate of its incidence among CRI patients in Spain was obtained in a sample of 154 patients treated at Hospital Ramón y Cajal in the period 1977-1981 (Matesanz et al, 1983). According to this study 10.6% of all CRI patients are hit every year by an infection classified under this heading.

Patients with transfusions suffer more often from this condition. 64% of the hepatitis cases were in-patients who had had at least one transfusion in the last eight months. There is no treatment as such for this condition but it may be accepted as reasonable that its costs are similar to those of B-Hepatitis, for which some estimations are available (Rivera et al, 1984, Grupo Espanol de Estudio de la Hepatitis B, 1987).

* AIDS. About twenty CRI patients out of 10,000/12,000 have developed AIDS in Spain probably linked with transfusions (twenty more are affected by this disease due to other causes). In all cases the infection was related to blood transfused before the ELISA test was available. The nephrologists interviewed are convinced that AIDS infected via transfusion is no longer a threat to their patients and therefore no costs are charged for it.

* Ferritin overload. About 1% of CRI patients transfused develop hypersiderosis (Valderràbano, personal communication). But taking into account that clinical relevance of this condition is much discussed; to the fact that treatment with Desferroaxiamine (DCI) for six to twelve months was not agreed upon by the different groups of nephrologists consulted, and to the fact that the cost would anyhow by very low, additional costs under this heading are not included.

* Hyperimmunization. A serious problem related to frequent transfusions is that patients may become hyper-immune and therefore have to be excluded from transplantation waiting lists; even if this condition does not reflect itself in positive pre-transplant tests, the rate of failure is higher. According to Dr Valderràbano, about ten per cent of patients in transplantation lists are hyper-immune, most of them because of transfusions, and a few because of previous transplantations or pregnancy. This undoubtedly implies costs associated with transfusions but lack of data and the complexities of the matter made it impossible to evaluate this issue.

For some time transfusions of whole blood before transplantation were carried out as a way of improving the immunological response of patients and increasing the survival of the graft (Terasaki, 1984). Nowadays, with the availability of Cyclosporine (INN) there are no benefits and the risks involved in transfusion have made this practice obsolete (published literature strongly supports this view. See Fernandez et al, 1985 and Cannata et al, 1985). Although in Spain at least one unit still performs routine transfusions on these grounds they have not been considered as a source of costs or benefits.

5.3.2.4 Frequency and incidence of transfusions

The records for 1988 of 346 CRI patients in the following haemodialysis units have been studied;

- Hospital General de Asturias (Oviedo)
- Hospital Covadonga (Oviedo)
- Club de diálisis de la Cruz Roja (Oviedo)
- Hospital Gregorio Marañón (Madrid)
- Centro de diálisis Los Enebros (Madrid)

The basic distribution of this sample is as follows:

Patients	%	Units Transfused
143	41.3	None
110	31.8	One to three
93	26.9	Four or more
TOTAL 346	100.0	Average: 3.7

Therefore, it has been taken that 58.4 per cent of CRI patients suffer transfusions and that they receive about 3.7 red cell units per year.

It should be noted that there seem to be important differences in transfusion patterns of CRI patients within Spanish regions. According to the information supplied by five HD units, a lower average of patients are transfused in Catalonia than in Madrid and Asturias (about 22 per cent) and they receive on average 3.3 transfusions of two red cell units, which means an average of 6.6 units per transfused patient per year. The comparison of both sets of data suggests that in Catalonia the transfusion is prescribed only in more severe cases, say to patients with a lower haematocrit. These two transfusion patterns will be referred to in the tables of results as hypothesis 1, (Madrid and Asturias) and hypothesis 2, (Catalonia) respectively.

Table 5.2a Transfusion costs summary

	A	B	C
- Red cell concentrate	4,980	6,640	8,300
- Cross Test	936	936	936
- RIA Test	4,696	4,696	4,696
- Additional administration cost in out-patient dialysis units	1,800	1,800	1,800
- Direct cost of one transfusion for patients in out-patient dialysis units	12,412	14,072	15,732

5.4 ESTIMATION OF BENEFITS

Quality of life assessment

The existing literature on EPO suggests that the main benefits of this new therapy compared to the existing ones would materialize much more in the form of an improvement in the quality of life than in the saving of health care costs. Therefore it seemed of the utmost importance to assign the highest priority to this part of the study.

However, the fact that Erythropoietin has still not been commercialised in Spain at the date of completion of the study and that the only patients of EPO treatment were those participating in clinical trials, made this intention difficult to implement. An initial test trying to gather the relevant information from a small number of leading specialists proved unreliable, as these professionals lacked the close contact with their patients that could allow them to act as judges or evaluators of their health status. Therefore, it was decided to base the evaluation on self assessment of health status by the patient, coupled with the judgement of a nurse or - as a second choice - a physician who had had a long-lasting and frequent direct contact with the patient.

Table 5.2b Direct cost of one transfusion for patients in Hospital dialysis units (Pts)

Red cell concentrates per transfusion	A	B	C
Hypothesis 1	10,612	12,272	13,932
Hypothesis 2	15,592	18,912	24,032

Direct cost of one transfusion for patients in out-patient dialysis units

Red cell concentrates per transfusion	A	B	C
Hypothesis 1	12,412	14,072	15,732
Hypothesis 2	17,392	20,712	24,032

Three groups of patients have been included in the study:

Group A: These were transfused patients interviewed before starting EPO therapy. Assuming the clinical evolution of their quality of life outlined in Section 5.2, they were asked to locate on the Rosser and Kind matrix their health states:

a) just before the transfusion
b) two days after the transfusion

c) in the middle of the period between two transfusions.

Subgroup A 1: Seven patients in group A were interviewed again about 6 weeks after the start of EPO therapy. The results are shown in Appendix 5.1.

Group B: These were patients already stabilised in EPO therapy at the time of the interview. Only the present health state was recorded.

Group C: These patients were also on EPO treatment, but this group was asked to assess not only their present health state, but also the health states at the pre-EPO period, QA, QM and QD.

Table 5.3 summarises the average values of the various health states: QA (before), QD (after), QM (between transfusions) and QR-HUEPO (after EPO treatment). For the sake of simplicity no account is taken of the initial period of EPO treatment until the target haematocrit or haemoglobin levels is reached and stabilised.

QT is the estimated average value of the QoL in the transfusion period and (QR-HUEPO-QT) is the average QoL gain.

As this figure is only available for two small groups of patients, two additional estimations of QoL gains have been computed; (QD-QT) would be the gain if EPO treatment placed the patients stably at the post-transfusion level QD. (1-QT) would be the gain if the QoL level attained by EPO treatment was 1, that is, the completely healthy state, indicating, therefore, the maximum benefit to be obtained given the pre-treatment level.

Although the methodology used is rather crude and the sample size is not very large, the results allow the acceptance of an evident improvement which can conservatively be quantified at around 0.02 QALYs per patient and year.

One of the problems of analysis relying on self assessed health status in the case of chronic diseases is that the patients may tend to get used to their situation and to identify their usual impaired health state with the normal or healthy one. After a transfusion some transfused dialysis patients assigned themselves to health state I.1 in the Rosser and Kind matrix, which may look rather optimistic to an external observer (some health professionals however made the same assignment) (see Appendix 5.1). When these patients are changed to EPO therapy, it will be impossible to record any eventual improvement in their quality of life.

5.5 COST-UTILITY ANALYSIS

Tables 5.4 and 5.6 show the estimated yearly costs of the treatment alternatives assessed. Patients maintained on transfusion therapy are grouped in two different modalities. Patients transfused during dialysis sessions amount to 70 per cent of the transfused patients. For them no administration costs are counted, as transfusion is supposed to require no extra time from health care personnel. Other patients, however (the remaining 30 per cent), receive transfusion at a different time and place from dialysis. Therefore, the cost of administering the transfusion has been added. The figures in Table 5.4 also include the nurse time needed. Capital costs and patient time should also be added, but this would not make a significant difference to the final results.

Table 5.3 . Valuation of Quality of Life With EPO and With Transfusion

(Average values)	Group A (n=23) Transfused patients		Subgroup A1 (n=7) Transfused-EPO pat.		Group B (n=15) EPO Patients		Group C (n=7) EPO Patients	
	Self assessment	Health care personnel**	Self assessment	Health care personnel*	Self assessment	Health care personnel**	Self assessment	Health Care personnel**
QA: Quality of life before transfusion	0.780	0.833	0.816	0.814	-	-	0.917	0.958
QM: Quality of life between transfusion	0.961	0.953	0.974	0.971	-	-	0.976	0.968
QD: Q of life after transf. (2 days)	0.968	0.961	0.987	0.987	-	-	0.981	0.978
QT: Average QoL of transfus. patient	0.917	0.937	0.938	0.936	-	-	0.962	0.968
QEPO: QoL of pat. in EPO treatment	-	-	0.983	0.975	0.971	0.979	0.985	0.985
QD - QT	0.050	0.023	0.049	0.051	-	-	0.018	0.010
QEPO - QT	-	-	0.045	0.039	-	-	0.023	0.017
1 - QT	0.083	0.063	0.062	0.064	-	-	0.038	0.032

* Only nurses ** Nurses and physicians

Three different cost estimates have been computed attending to the likely costs of a blood unit, giving a variation of about 50 per cent in the medium estimate for the average transfusion cost between the lower and the higher estimates.

The cost estimates have also been computed separately for the two hypotheses considered regarding the transfusion patterns found. The results are not as sensitive to this factor as would be expected because some of the cost components of transfusion therapy, namely cross-test, RIA test, and the additional administration cost in out-patient dialysis units are independent of the number of units transfused in each session. So, the cost in the second hypothesis is a third higher than in the first one.

Side effect costs of transfusion therapy related only to non-A-nonB hepatitis infection have been computed (Table 5.5). The proportion of non-A, non-B hepatitis attributable to transfusion (HAT) has been estimated by the formula (Rothman, 1987):

$$HAT = \frac{RR-1}{RR + \frac{1}{Pe} - 1}$$

RR is the relative risk, that is, the quotient between non-A, non-B hepatitis incidence in patients having received one or more transfusions and the incidence in those having received no transfusions. Pe is the prevalence of the risk factors, that is, the proportion of the population that have received one or more transfusions. From data published by Rotellar (1988) and by Matesanz et al (1983), the relative risk, RR=1.64 and the prevalence of the risk factor, Pe=0.52 have been calculated. Consequently HAT is 0.25. So it can be concluded that there is a 0.0265 (0.25 x 0.106) probability that a dialysed patient has non-A, non-B hepatitis attributable to transfusions.

There are no studies available on the cost of non-A, non-B hepatitis. It will therefore be assumed that they are similar to those of B-hepatitis.

One study by Rivera et al (1984) estimates the direct costs of a BHV case as 43,000 Ptas at 1982 prices. Adjusting this figure for inflation gives an estimate of 71,000 (43,000 x 1.657), at 1989 prices.

Another study by Grupo Español de Estudio de la Hepatitis B (1987) offers a more disaggregated breakdown of the data which allows the estimation of the expected five years cost of B-hepatitis at 135,000 Ptas at 1983 prices. Adjusting again for inflation a 1989 cost estimate of 202,000 (135,000 x 1.469) Ptas is obtained.

Multiplying these estimates by the probability of having non-A, non-B hepatitis caused by transfusion, the following values for the likely cost of this side effect of transfusion therapy are obtained:

High estimate: 0.0265 X 202,000 = 5,350 Ptas.
Low estimate: 0.0265 X 71,000 = 1,800 Ptas.

If it is accepted that there is, according to the Grupo Español de

Estudio de la Hepatitis B study, a 0.005 probability of death from non-A, non-B hepatitis, there would be an (undiscounted) loss of 0.000063 life years per dialysed patient. The resulting gain in QALYs of EPO therapy would then go up by less than 0.3 per cent. The inclusion of this effect would therefore have a negligible effect on the cost per QALY obtained and has therefore not been considered in the results.

Hepatitis B has not been considered a side effect of transfusion as the direct costs of this therapy include the RIA test, which seems to preclude any significant possibility of HB infection. Not all blood banks in Spain carry out this test at present, although there is no precise data available. However, in the case where the increased costs of this particular side effect were to be included, they would be counterbalanced by the reduction in the direct costs of transfusion. Given the relatively low expected cost of hepatitis side effects, the likely impact on the total expected cost of the therapy would probably be negligible.

Parallel studies carried out in other European countries (see other chapters in this paper) have obtained much higher estimates for the cost incurred as a result of the side effects of transfusion. The French estimated amounts to an equivalent of 186,000 pesetas annual cost per patient. The German estimate amounts to 248,000. However, these figures are rough estimates based on intuitive opinions of clinicians and no detailed break-down, nor justification is provided to support them, although they suggest that this point might merit further research.

A second major point of divergence with studies from other countries which may affect the total cost of blood therapy is the average number of transfusions which in this study was estimated to be 3.7 transfusions per patient per year. The value for this variable is 7 in the Italian study and 19 in the United Kingdom study. However, it should be noted that the relevant variable for the estimation of the transfusion costs saved by EPO therapy is not the average number of red cell concentrates per patient transfused, but the average per patient receiving EPO therapy, which will depend on the criteria applied in each country for prescribing.

The estimated yearly costs of EPO treatment are shown in Table 5.6. Again, three cost estimates have been computed for the three assumed values of the average EPO dose administered, resulting in a 2:3 ratio between the lower and the higher estimate.

As to side effects of this treatment, only hypertension has been quantified, assuming that:

* 10 per cent of patients will become new cases of hypertension and will require a specific treatment for this condition.

* An additional 10% are patients with hypertension and hypotensive treatment before starting EPO treatment, but whose condition has worsened and required an increase of 50% in the amount of the drug prescribed.

As can be seen from Table 5.6, the expected cost of this side effect represents a very modest amount when compared to the cost of the drug.

Table 5.4 Transfusion Therapy. Estimated Yearly Costs per Patient (1989 Pt)

Treatment modality	Proportion of patients in each treatment modality	COST ESTIMATES Medium	High	Low
A. Patients transfused in Hospital dialysis units	0.7			
Hypothesis 1		45,406	51,548	39,264
Hypothesis 2		62,401	60,256	51,454
B. Patients transfused in out patient dialysis units	0.3			
Hypothesis 1		52,066	58,208	45,924
Hypothesis 2		68,350	79,306	57,394
C. Average transfusion cost				
Hypothesis 1		47,404	53,546	41,262
Hypothesis 2		64,186	79,971	53,236

Side effects	Incidence of nonA-nonB Hepatitis attributable to transfusion	Average cost of treating HB		
D. Expected cost of nonA-nonB Hepatitis treatment	0.0265	High: 202,000	5,350	
		Low: 71,000		1,800
		Average: 136,500	3,575	

E. Total cost E = C + D			
Hypothesis 1	50,979	58,896	43,062
Hypothesis 2	67,761	85,321	55,036

Hypothesis 1: Average number of transfusions: 3.7
Red cells concentrates per transfusion: 1

Hypothesis 2: Average number of transfusions: 3.3
Red cells concentrates per transfusion: 2

Table 5.5 Average Cost (in Pesetas) per Case of a Clinical B-Hepatitis

Expenditure	Evolution (frequency)			
	Cure (0.74)	A-symptomatic carrier (0.115)	Chronic Hepatitis (0.14)	Death (0.005)
First year	73,000	107,000	370,000	119,000
Second to fifth year*	-	32,000	92,000	-
TOTAL	73,000	139,000	462,000	119,000

* Not discounted

Source: Adapted from Grupo Español para el Estudio de la Hepatitis B (1987:234)

Table 5.6 EPO Therapy Estimated Yearly Costs Per Patient (1989 Pt)*

			COST ESTIMATES		
			Medium 65 U/Kg	High 80 u/Kg	Low 50 u/Kg
A. Cost of the drug			866,000	1,066,000	666,200
Side effects	Probability	Cost of treatment	Expected cost		
B. Hypertension					
B1. New cases	0.1	20,000	2,000	2,000	2,000
B2. Worsening of previous HT patients	0.1	10,000	1,000	1,000	1,000
TOTAL Side Effects			3,000	3,000	3,000
C. TOTAL EPO TREATMENT C = A + B			869,000	1,069,000	669,000

* (rounded to 1,000)

Table 5.7 shows the excess cost of EPO vs transfusion therapy, which ranges from 625,000 to slightly over a million pesetas per patient per year, the medium estimate amounting to 820,000 pesetas. Given the relative importance of the costs of the alternatives considered, the results are very much more sensitive to the assumptions about EPO treatment than to any other factor, and it seems unlikely that the inclusion of additional side effects of the EPO would produce significant variations in the estimated results. The results may, however, be sensitive to different assumptions about transfusion therapy. If it is assumed that the cost of the side effects are those estimated in the German study, the previous figure of 820,000 pesetas would come down to 570,000. Similarly, if the figures given in the Italian or the British study are taken as the average number of transfusions, the medium excess cost would come down from 820,000 to 770,000 or to 620,000 respectively.

The results of the valuation of the quality of life summarised in Table 5.8 show that the gain in QALYs of EPO over transfusion treatment can be tentatively estimated at about 0.020 QALYs per patient and year, which would give a cost of additional QALY gained by EPO over transfusion therapy of 40.9 million Pt ($ 356,000) per QALY. This figure varies dramatically if the most favourable or unfavourable combination of assumptions are taken.

The results are not very sensitive to the transfusion pattern hypothesis chosen (Tables 5.7 and 5.9).

Table 5.7 Cost per patient on EPO vs Transfusion Treatment*

	Medium estimate	High estimate	Low estimate
A. EPO	869,000	1,069,000	669,000
B. Transfusion			
Hypothesis 1	51,000	59,000	43,000
Hypothesis 2	68,000	85,000	55,000
C = A - B			
Hypothesis 1	818,000	1,010,000	626,000
Hypothesis 2	801,000	984,000	574,000

* (rounded to 1,000)

Table 5.8 Cost per QALY of EPO vs Transfusion Treatment
Million Pt (1000 $)

Hypothesis 1

Estimated gain in QALYs		Estimation of excess cost of EPO treatment		
		Medium	High	Low
Medium	0.020	40.9 (356)	50.5 (440)	31.3 (272)
High	0.050	16.4 (143)	20.2 (176)	12.5 (109)
Low	0.010	81.8 (712)	101.0 (878)	62.6 (554)

1 $ = 115 Pt

Hypothesis 2

Estimated gain in QALYs		Estimation of excess cost of EPO treatment		
		Medium	High	Low
Medium	0.020	40.1 (349)	49.2 (428)	28.7 (250)
High	0.050	16.0 (139)	19.7 (171)	11.5 (100)
Low	0.010	80.1 (696)	98.4 (856)	62.6 (544)

1 $ = 115 Pt

Although some researchers believe that EPO therapy may increase the survival of dialysed patients, there is at present no evidence for such an effect. Indeed, several years will pass until the follow-up studies can be completed that can support these hopes. It may, however, be interesting to estimate the impact of a hypothetical increase in life expectancy. For illustrative purposes Table 5.9 shows the effects of the cost per QALY gained under the hypothetical but plausible assumption of a 10 per cent increase in life expectancy of 10 to 11 years for transfused patients. The figures in

Table 5.9 show the dramatic change that this effect would produce in the cost-utility indices.

The figures in Table 5.9 take into account the fact that an additional life year gained would require an additional year of haemodialysis treatment. It is a matter of debate whether this type of cost should be taken into account in a cost-effectiveness analysis. If these factors are considered, then there is no reason why other health care costs should not be taken into account, or even food, shelter and other costs.

If the results are computed on the assumption of 1 year's increase in survival taking into account the cost of 1 year's haemodialysis (approx 2.5 million pesetas) at a discount rate of 5 per cent, the cost per QALY comes down from 40 to a figure of between 10.4 and 11.8 million Pesetas, depending on the discount rate applied.

Some patients may discontinue the therapy because of serious adverse effects or because they do not respond to it. The costs of these eventualities should also be imputed to the successful treatments.

Assuming a drop-out rate of F = 0.02, an average time between start and withdrawal of t = 2 months, and an excess yearly cost of EPO therapy over transfusion of 800,000 Pt, the yearly cost per successful treatment would increase by

$$\text{Cost of withdrawals} = F \times \text{Excess Cost} \times \frac{t}{12}$$

$$= 0.02 \times 800{,}000 \times \frac{2}{12} = 2{,}666 \text{ Pt}$$

Again this is negligible when compared to the global cost of the therapy.

5.6 ECONOMIC IMPACT OF THE INTRODUCTION OF EPO

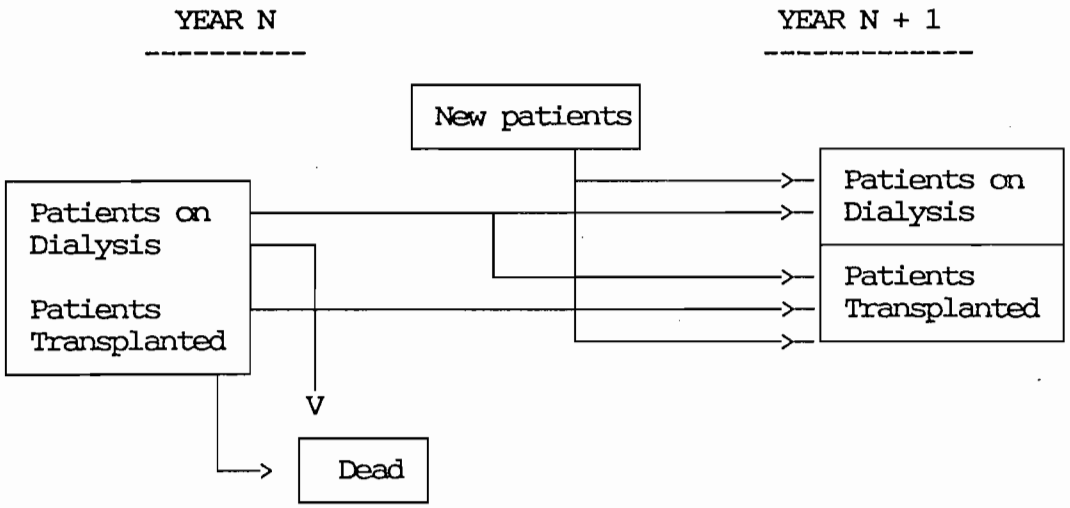
1986 is the last year for which data are available on CRI patients in Spain. These data are part of the EDTA register and can be found in Garcia et al, 1988.

Table 5.9 Sensitivity of the Results to an Increase in Life Expectancy

Rate of discount	No Increase: Discounted additional cost of EPO over transf	No Increase: Discounted additional QALYs	No Increase: Cost per QALY (millions)	Increase by 1 year in survival: Discounted additional cost of EPO over transf	Increase by 1 year in survival: Discounted additional QALYs	Increase by 1 year in survival: Cost per QALY (millions)
2%	7.186	0.1796517	40.0	9.840	0.9437060	10.4
3%	6.680	0.1670040	40.0	9.064	0.8353303	10.6
4%	6.488	0.1622178	40.0	8.631	0.7793187	11.1
5%	6.225	0.1544346	40.0	8.154	0.7098792	11.5
6%	5.888	0.1472017	40.0	7.626	0.6476493	11.8

Assumptions:
Additional costs of EPO over transfusion treatment:
800,000 Pt per patient/year.
Annual cost of haemodialysis: 2.5 million Pt per patient.
Increase in quality of life by 0.02 points.
Life expectancy in transfusion modality: 10 years.
Life expectancy with EPO: 11 years.
Average QoL of additional year: 0.95.

From these data a projection has been estimated up to the year 1993 according to the following model:



The projection has been made according to the following ideas:

a) Total population estimates for Spain have been taken from Instituto Nacional de Estadística and (De Miguel Castano and Aguero Menendez).

b) The number of new patients per year and per million population in 1986 have been considered to increase slightly during the period to reflect the effect of an ageing population on prevalence rates for CRI.

c) The yearly mortality rate has been considered to remain constant. This may not be totally precise since mortality rates may vary if treatment improves mainly by means of transplantations. It might have been better to calculate mortality rates for each treatment category. As transplants have reached a certain plateau in recent years, the first procedure has been followed, which is simpler.

d) The assumptions already made give the annual increase rate of CRI patients that can be calculated for the period considered.

e) The distribution of patients among the four treatment categories was carried out based on the following assumptions: a decrease in HHD patients from 68.4% in 1986 to 61.4% in 1993; An increase in transplanted patients from 23.4% in 1986 to 29% in 1993; An increase in both DHD and CAPD patients of 0.1% yearly. The results are in Table 5.10.

It is, however, difficult to foresee how many dialysis patients will be receiving EPO therapy in the next few years. A plausible assumption would be that EPO therapy will completely replace transfusion in the future. But unfortunately, the EDTA Registry does not provide this particular information and the partial data available report very different figures ranging from 25 to 50 per cent of all patients, as can be seen from the following table:

Region	Centre	Percentage of HD patients receiving one or more transfusions in 1988	Average number of transfusions per patient transfused in 1988
Asturias	A	57.4	3.6
Asturias	B	52.2	3.4
Madrid	C	81.4	5.9
Madrid	D	50.7	3.2
Catalonia	E	39.0	4.0
Catalonia	F	8.3	2.2
Catalonia	G	19.0	2.6

Moreover, the aims of the transfusions are not always clearly stated - some of the transfusions may be given for other reasons than for correcting anaemia. On the other hand, not all the types of patients who are presently transfused will necessarily be put on EPO treatment, while other types not receiving transfusions will probably be treated with EPO.

A preliminary survey conducted by the Catalan Health Authorities in 15 dialysis centres involving a total of nearly 1,000 adult dialysis patients found that physicians believed that EPO should be prescribed for 40% of these patients. This percentage varies among centres from 28% to 58% (mean: 40, SD: 10.8).

Assuming that 25% and 50% may be plausible, extreme values for the likely range of the future percentage of HHD patients receiving EPO, the net global cost of EPO therapy in Spain in 1989 and in 1993 (at 1989 prices) would fall between the following amounts:

1a High estimate 1989
$$10.976 \times 0.50 \times 800{,}000 = 4.390 \text{ million Pt}$$

1b Low estimate 1989
$$10.976 \times 0.25 \times 800{,}000 = 2.195 \text{ million Pt}$$

2a High estimate 1993
$$13.760 \times 0.50 \times 800{,}000 = 5.504 \text{ million Pt}$$

2b Low estimate 1993
$$13.760 \times 0.25 \times 800{,}000 = 2.752 \text{ million Pt.}$$

Table 5.10 Projected Evolution of CRI Patients

	1986	1987	1988	1989	1990	1991	1992	1993
Population (M)	38.5	38.7	38.9	39.1	39.3	39.5	39.75	39.9
New patients	(52.2 pM) 2,009	(53.2 pM) 2,058	(54.2 pM) 2,108	(55.2 pM) 2,158	(56.2 pM) 2,208	(57.2) 2,260	(58.2) 2,213	(59.2) 2,362
Mortality (22.2 pM)	854	859	863	868	872	876	882	885
Patients Net increase	1,155	1,199	1,245	1,290	1,336	1,384	1,431	1,477
Total Patients	13,009	14,248	15,493	16,783	18,119	19,503	20,934	22,411
HHD Patients	8,900	9,603	10,287	10,976	11,668	12,364	13,063	13,760
%	(68.4)	(67.4)	(66.4)	(65.4)	(64.4)	(63.4)	(62.4)	(61.4)
Transplanted	3,044	3,448	3,873	4,330	4,819	5,343	5,903	6,499
%	(23.4)	(24.2)	(25.0)	(25.8)	(26.6)	(27.4)	(28.2)	(29.0)
	338	385	434	487	544	604	670	739
% DHD	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3
	728	812	898	996	1,087	1,189	1,298	1,412
% CAPD	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3

5.7 DISCUSSION

The results obtained in this study refer to an average patient. However, cost and benefits, and hence, the cost per QALY of the alternatives assessed may vary widely among different patient groups.

With the data available at present and the limited number of patients on EPO treatment, it is not possible to estimate cost-utility ratios for selected groups of patients with specific characteristics. This kind of approach would, however, be very useful for establishing priorities, for example, when there is a need to ration the drug, ie when not all the patients likely to derive a benefit, however small, from EPO treatment are going to be treated.

There are some side effects mentioned in the literature which have not been included in the estimation of costs and benefits; it has been claimed, for instance, that repeated transfusion may increase the probability of rejection of the graft in the case of a future renal transplantation. This would mean an additional benefit to be imputed to EPO therapy.

The number of transplantations is limited at present by the availability of organ donors; therefore, the short term effects of the introduction of EPO would result only in an increased number of transplantable patients previously excluded because of hyperimmunisation from the transplantation programme and the consequent increase in waiting lists. But insofar as the results also reflect an increased survival time for the transplanted grafts, the proportion of patients with a graft in the global population of patients on renal replacement therapy would increase. As the former is usually shown to be a cheaper and more effective form of treatment, the costs of the global renal programme would come down, or alternatively, a higher number of patients could be treated with a given budget. However, the empirical evidence available at present does not unambiguously support this hypothesis, at least after the introduction of immunosuppressive treatments for transplanted patients.

The efficiency of the EPO treatment may also be sensitive to its targets, ie to the degree of correction of the anaemia - or haematocrit values - to be attained.

More ambitious targets will probably mean a larger increase in QALYs gained, but also in costs. Beyond a certain level decreasing marginal gains are likely to appear, leading to an increase in the cost per QALY. This issue could also be investigated within the cost-utility framework, when the required type and amount of data become available.

The results are shown to be very sensitive to the cost of the drug, which depends on the price and on the dose prescribed. In the foregoing analysis, only variations in the dose have been considered, but the sensitivity analysis could easily be extended to explore the consequences of a given range of prices, which would alter the costs but not the benefits of the treatment. A 23% increase or decrease in the assumed unit cost of the drug, for instance, would affect the cost of the treatment by the same amount as the alternative hypothesis on dosage (50, 65 and 80 u/Kg) shown in Table 5.6.

5.8 CONCLUSIONS

There is no doubt that the general availability of Erythropoietin will have a positive impact on health care expenditure. In Spain, given the characteristics of the health care system, the burden will fall almost exclusively on the public budget. The diffusion of the drug is attracting great attention on the part of the health authorities, who will try to guarantee value for money in the use of EPO, as has already happened with other efficacious but expensive drugs, namely Zidovudine, human growth hormone or calcitonin.

As a point of reference for comparison, it may be mentioned that expenditure on these last two drugs amounted to 4,500 and 3,000 million pesetas in 1988 (total drug expenditure: 253,000 million).

Erythropoietin is clearly an expensive drug, but the convenience of its prescription should be considered in the context of treatment of chronic and end-stage disease patients, and not only on the isolated consideration of its cost but on the cost-utility ratio of EPO vs other treatments. As far as EPO is concerned, the present study shows that the magnitude of the cost utility ratio is very sensitive to assumptions about its impact on survival and quality of life. Therefore this should be the main area for research in the future.

Appendix 5.1

ROSSER'S MATRIX : TRANSFUSED PATIENTS (Group A)

BEFORE TRANSFUSION

	1	2	3	4	Total
I		1			1
II	1				1
III	1	4	1		6
IV	1	1	4		6
V	1	1	3		5
VI			2	1	3
VII				1	1
VIII					0
Total	4	7	10	2	23

Table 1. Patients

	1	2	3	4	Total
I					0
II			1		1
III	1	1	8		10
IV	1		1	1	3
V		1	4		5
VI			2		2
VII		1		1	2
VIII					0
Total	2	3	16	2	23

Table 2. Health Professionals

AFTER TRANSFUSION

	1	2	3	4	Total
I	4		1		5
II	1	1			2
III	1	8			9
IV	2	2			4
V		2			2
VI		1			1
VII					0
VIII					0
Total	8	14	1	0	23

Table 3. Patients

	1	2	3	4	Total
I	2	1	2		5
II		4	5		9
III		4			4
IV		1			1
V		3			3
VI		1			1
VII					0
VIII					0
Total	2	14	7	0	23

Table 4. Health Professionals

MIDDLE TERM

	1	2	3	4	Total
I		1	1		2
II	2	3			5
III	2	4			6
IV		5	1		6
V	1	1	1		3
VI		1			1
VII					0
VIII					0
Total	5	15	3	0	23

Table 5. Patients

	1	2	3	4	Total
I		1			1
II		2	6		8
III	1	1	4		6
IV		4			4
V		3			3
VI		1			1
VII					0
VIII					0
Total	1	12	10	0	23

Table 6. Health Professionals

ROSSER'S MATRIX : EPO TREATED PATIENTS (Group B)

	1	2	3	4	Total
I	2	4			6
II					0
III		4	1		5
IV		3		1	4
V					0
VI					0
VII					0
VII					0
Total	2	11	1	1	15

Table 7. Patients

	1	2	3	4	Total
I		1	2		3
II	3	2	1		6
III		4	1		5
IV		1			1
V					0
VI					0
VII					0
VIII					0
Total	3	8	4	0	15

Table 8. Health Professionals

ROSSER'S MATRIX : EPO PATIENTS (Group C)

BEFORE TRANSFUSION

	1	2	3	4	T
I		1			1
II					0
III		2	1		3
IV			3		3
V					0
VI					0
VII					0
VIII					0
Total	0	3	4	0	7

Table 9. Patients

	1	2	3	4	T
I					0
II			1		1
III			6		6
IV					0
V					0
VI					0
VII					0
VIII					0
Total	0	0	7	0	7

Table 10. Health Professionals

AFTER TRANSFUSION

	1	2	3	4	T
I	1		1		2
II	1				1
III		4			4
IV					0
V					0
VI					0
VII					0
VIII					0
Total	2	4	1	0	7

Table 11. Patients

	1	2	3	4	T
I			2		2
II			5		5
III					0
IV					0
V					0
VI					0
VII					0
VIII					0
Total	0	0	7	0	7

Table 12. Health Professionals

MIDDLE TERM

	1	2	3	4	T
I		1	1		2
II	1				1
III		3			3
IV			1		1
V					0
VI					0
VII					0
VIII					0
Total	1	4	2	0	7

Table 13. Patients

	1	2	3	4	T
I					0
II			5		5
III			2		2
IV					0
V					0
VI					0
VII					0
VIII					0
Total	0	0	7	0	7

Table 14. Health Professionals

WITH EPO TREATMENT

	1	2	3	4	T
I		4			4
II					0
III		3			3
IV					0
V					0
VI					0
VII					0
VIII					0
Total	0	7	0	0	7

Table 15. Patients

	1	2	3	4	T
I		1	2		3
II		2	2		4
III					0
IV					0
V					0
VI					0
VII					0
VIII					0
Total	0	3	4	0	7

Table 16. Health Professionals

BEFORE TRANSFUSION

	1	2	3	4	T
I					0
II					0
III	1	3			4
IV		1			1
V		1	1		2
VI					0
VII					0
VIII					0
Total	1	5	1	0	7

Table 17. Patients

	1	2	3	4	T
I					0
II					0
III	1	1	2		4
IV					0
V		1	1		2
VI					0
VII			1		1
VIII					0
Total	1	2	4	0	7

Table 18. Nurses

AFTER TRANSFUSION

	1	2	3	4	T
I	3				3
II		1			1
III	1	1			2
IV					0
V					0
VI					0
VII				1	1
VIII					0
Total	4	2	0	1	7

Table 19. Patients

	1	2	3	4	T
I	2	1			3
II		2			2
III		2			2
IV					0
V					0
VI					0
VII					0
VIII					0
Total	2	5	0	0	7

Table 20. Nurses

MIDDLE TERM

	1	2	3	4	T
I					0
II	1	1			2
III	2	1			3
IV		2			2
V					0
VI					0
VII					0
VIII					0
Total	3	4	0	0	7

Table 21. Patients

	1	2	3	4	T
I		1			1
II		1	1		2
III	1		1		2
IV		2			2
V					0
VI					0
VII					0
VIII					0
Total	1	4	2	0	7

Table 22. Nurses

WITH EPO TREATMENT

	1	2	3	4	T
I	2				2
II	2				2
III	1		1		2
IV	1				1
V					0
VI					0
VII					0
VIII					0
Total	6	0	1	0	7

Table 23. Patients

	1	2	3	4	T
I					0
II	3	2			5
III					0
IV		1	1		2
V					0
VI					0
VII					0
VIII					0
Total	3	3	1	0	7

Table 24. Nurses

Chapter 6

The UK Case Study

by J Hutton, B Leese and A Maynard

6.1 INTRODUCTION

A frequent side-effect of chronic renal failure is the development of anaemia. This is primarily due to erythropoietin deficiency, although shortened survival of red blood cells and silent blood loss into the gastro-intestinal tract (and dialysis equipment) are contributory factors. Treatment has relied largely on damage limitation ie. ensuring there is no haematinic deficiency and limiting blood loss as much as possible, with blood transfusion being reserved for the most severely affected patients. It is now possible to reverse the anaemia by the administration of human type erythropoietin derived from recombinant DNA (Winearls et al, 1986). The purpose of this study is to assess the relative cost-effectiveness of the use of blood transfusions and erythropoietin (EPO) to treat the anaemia of patients undergoing dialysis.

The remainder of the paper will follow the stages of the study from the background information on renal replacement therapy (RRT) in the UK and description of the alternative treatments for anaemia, through the cost and effectiveness assessment, to the presentation and discussion of the results. The main impact of treatment for anaemia is on patients' physical and social functioning, and accordingly, an effectiveness measure has been chosen which encompasses improvements in the quality of life enjoyed by patients, as well as improved survival. The classification developed by Rosser and Kind (1978) has been used to measure impact of treatment on health status, and following the approach of Kind, Rosser and Williams (1982) quality-adjusted life-year gains have been estimated.

Experience of the use of EPO is still very limited (Cotes, 1988) so that hard evidence, from controlled studies, of its impact on survival and quality of life, and the importance of any side-effects, is not available. This preliminary study, using secondary data sources, cannot claim to be definitive, but it is hoped that the presentation of available information can contribute to short-term decision-making and act as a guide for further research to clarify the uncertainties.

6.2 BACKGROUND

The UK, in common with the Nordic countries, places particular emphasis on transplantation as a long-term treatment for renal failure, in marked contrast to other Western European countries as Table 6.1 shows.

It can also be seen that of the UK patients receiving dialysis, 40% were on CAPD, 28% on home haemodialysis, and only 30% on hospital haemodialysis. For the other four countries the percentage of dialysis patients receiving their treatment in hospital ranges from 79-90%.

It is important, however, not to underestimate the role of haemodialysis in the UK, as the preferred treatment is not always immediately available and interim therapy is often required. Long-term survival rates show that fifteen years after beginning RRT, 73% of surviving UK patients had a functioning graft, 19% were on home haemodialysis, 5% on hospital haemodialysis and 3% on

CAPD (EDTA, 1987). Of new patients in the 1983-85 period, 55% were put on hospital haemodialysis, 30% on CAPD, 13% on IPD, and 2% were grafted, as a first treatment mode (EDTA, 1987).

Table 6.1 RRT patients alive at end December 1986

	Hospital HD	Home HD	IPD	CAPD	Graft	Total	Per m Pop
Germany	15650	1077	119	433	3035	20314	333
France	9687	1968	154	872	3998	16679	303
Italy	13049	739	98	1336	2121	17343	305
Spain	8931	264	66	732	3056	13049	337
UK	2111	1898	77	2774	6638	13498	239

Source: EDTA (1987)

Patients awaiting transplant are usually placed on hospital haemodialysis, the average waiting period being just over 2 years in the UK. Of the 3521 patients on the waiting list in February 1989, 35% had been on the list for less than one year and 37% for over two years. Not all patients are placed on the list, the main reasons for exclusion being clinical unsuitability (23%), refusal of transplant (18%) and the patient being too old (10%). If age continues to be a limiting factor there will always be patients for whom transplantation is not suitable, and the average age of patients commencing RRT has risen between 1981 and 1985 (EDTA, 1987). The main reason for delay in transplantation in the UK, as elsewhere, remains the shortage of donor kidneys.

It has been estimated that around 90% of dialysis patients have some anaemia and that for 40% this is a major problem. In all cases it leads to a reduction in physical and social activity but for those awaiting transplant there are further complications. The use of blood transfusions to treat the anaemia can lead to sensitisation of patients and increased risk of failure of eventual transplantation (Winearls, 1988). The UK figure for such highly sensitised patients is 11% of those on the waiting list (EDTA, 1987). On the other hand, some studies have shown a link between transfusions and successful transplantation (Opelz and Terasaki, 1978).

Because of the problems associated with transfusions, patients suffering from anaemia may tolerate a lower quality of life than would otherwise be the case, by avoiding them. A proportion of patients with very low haemoglobin levels (<6g/dl) require transfusions on a regular basis to avoid hospitalisation. These patients, about 10% of those on dialysis (Winearls, 1988), are most likely to benefit from EPO treatment.

6.3 ALTERNATIVES FOR COMPARISON

Before embarking on the analysis it is necessary to make clear exactly what question is being addressed. The cost-effectiveness of RRT itself is not under study. The comparison is between the use of EPO to treat anaemia in dialysis patients, and the use of blood transfusions for the same purpose.

Like all sectors of the NHS, renal services must operate on a fixed budget so that the adoption of new treatments such as EPO must be financed by cost-savings elsewhere. An assessment is therefore made of the extra costs (less any savings) of using EPO, rather than transfusions, and the extra benefits to patients which might ensue. Data is available in the UK only for the effect of EPO on previously transfusion-dependent patients, but estimates will be made of the benefit of its use on other groups. It should be emphasised that when comparing the efficacy of erythropoietin and blood transfusions, the latter is slight and transient.

The marginal calculations will permit comparisons of the effectiveness of using NHS funds to offer EPO to dialysis patients, and expanding other parts of the health service (for which similar information exists). This methodology cannot answer the question "should EPO be used?" per se, but can assist decision-makers by indicating the consequences of providing (or not providing) EPO treatment.

6.4 COST COMPARISON

6.4.1 Direct Costs

The major items of cost for the two options are blood costs on the one hand and the costs of EPO on the other. Apart from the cost of the blood, the other costs incurred by transfusion-dependent patients are those for administration and cross-matching. These latter costs may involve outpatient visits and staff time, which are difficult to separate out from general running costs. These costs are no longer incurred for patients treated with EPO. However, costs for patients receiving EPO include the cost of the drug, and its administration, together with additional blood tests and blood pressure checks, all involving staff time, and possible outpatient visits. The staff time and administration costs for EPO treatment are difficult to quantify, and will to some extent be offset by similar costs no longer incurred for blood transfusions. According to Winnearls, as experience in EPO use increases, staff confidence will also increase and the effect on staff time will be minimal.

Generally speaking, this group of patients is in very frequent contact with the health service, and the marginal cost in terms of staff time of extra tests and consultations is likely to be small. For hospital haemodialysis patients, both blood transfusions and EPO can be administered at one of the patient's regular visits to the renal unit. However, this is not the case for patients on CAPD or home dialysis. Such patients need to travel to the renal unit to have a sample taken for cross-match and then return 2 days later for the actual administration, involving a considerable amount of travel and inconvenience for the patient. Because of the financial system in the NHS, costs per procedure are not readily available. Consultation with those involved in treatment indicates that the costs of support services are unlikely to differ greatly between the two forms of treatment. A major exercise to produce precise costings of every procedure was not considered worthwhile in the context and time period of this study.

6.4.2 Costs of Side Effects

Side effects associated with blood transfusions include sensitisation, iron overload, hepatitis B and AIDS. There are no figures for the cost of iron overload or sensitisation. The incidence of hepatitis B in the UK is low

with only 2.8 cases per 1000 patients on hospital haemodialysis (6 patients in all), and considerably lower than the levels in other countries. The same situation applies to AIDS patients where only 3 have shown serological evidence of AIDS, 3 were detected in 1986 and 2 developed symptoms in 1986. Major cost savings from avoidance of treatment of hepatitis and AIDS are not therefore anticipated in the UK from the reduction of blood transfusions for RRT patients. Non A non B hepatitis (NANB) is much less common in the UK than in the USA. It results in raised levels of hepatic enzymes, is asymptomatic, and usually declines without treatment. NANB hepatitis may, however, be more likely than hepatitis B to progress to chronic liver disease in a very small number of patients.

The major side effect associated with EPO is hypertension. 25% of patients suffered from this when EPO therapy was introduced, but by adjusting the dosage, this has become rare. Shivering, 2-4 hours after dosage, has been reduced by the administration of aspirin. The limited experience of the use of EPO has already indicated that side-effects can be controlled, so that historical experience is not necessarily a good guide when projecting future cost consequences.

In the absence of conclusive evidence either way the cost implications of side effects are treated as equivalent in each treatment. The implication of side effects for patients' quality of life will be reflected in the effectiveness measurements.

6.4.3 Blood Costs

The real cost of a unit of blood in the UK health service has been estimated from a variety of sources. McClelland (1987) gives the official handling charge by the Blood Transfusion Service as £23 (£28 at 1988 prices). Winearls (1988) has estimated the cost of a unit of blood transfused at a renal unit to be between £30 and £40. The figure used in the following calculation is £35 per unit, the mid-point of this range. Each transfusion dependent patient is assumed to use 19 units of blood per year (Winearls, 1988).

6.4.4 EPO Costs

The current UK price of EPO is £36 per vial. The dosage rate varies with body weight and propensity to develop side effects, such as hypertension. The initial dose rate can vary from 3 to 5 vials per week and once an acceptable haemoglobin level has been reached, a maintenance dose of 2 vials per week reduces the incidence of hypertension, but delays the achievement of target haemoglobin levels. For the costings below an average of 3 vials per week per patient has been used.

6.4.5 Annual Cost Comparison

For each transfusion dependent patient the annual cost of transfusion will be:

$$19 \times £35 = £665$$

For the same patient the cost of EPO would be

$$3 \times £36 \times 52 = £5616$$

This gives a net direct cost difference of £4951 per patient per year (at 1988 prices).

6.5 EFFECTIVENESS COMPARISON

6.5.1 Life Expectancy

According to EDTA, survival rates for RRT patients have been increasing. Patients aged 15-44 who started RRT in 1970-74 had a mortality of 14% in the first year, decreasing to 5% per year for the 5-15 years group. By 1980-84, the same age group of patients would have had a mortality of 7.5% in the first year, and 4% per year by the fifth year. In general, 40% of patients are still alive after 15 years, and 50% after 10 years.

The EDTA have listed 5 year patient survival rates for all countries depending on the age of starting RRT. These figures are given in Table 6.2.

Table 6.2 5 Year Patient Survival Rates

Age of Starting RRT	All Countries % Survival After Starting RRT (1981-5)
0-15	83
15-25	85
25-35	78
35-45	71
45-55	62
55-65	49
65+	32

Wood et al (1987) listed life expectancy for standard and high risk RRT patients undergoing different therapies, as shown in Table 6.3. From the data a reasonable assumption would be that standard risk patients have a life expectancy of around 10 years. There are no observed data for life expectancy of patients on EPO, as opposed to transfusions, because the treatment has not been available for long enough. There is the possibility that the increase in viscosity and blood pressure in EPO patients may predispose to cardiovascular events, although no evidence of this is available as yet.

Two main reasons have been put forward for possible increases in life expectancy for patients using EPO rather than blood transfusions. The reversal of anaemia may reduce cardiac size and hence reduce the risk of cardio-vascular problems, a major cause of mortality in this patient group. It is also suggested that the generally improved quality of life achievable on EPO may lead to patients being fitter at the time of eventual transplantation, and hence increase the success rate of grafts. In the absence of evidence some sensitivity analysis is carried out below to demonstrate the impact on effectiveness of a positive effect on life expectancy.

Table 6.3 Life Expectancy of Patients with RRT

	Life Expectancy (years)
Standard Risk;	
Independent dialysis	11.6
Successful transplant	9.3
Hospital dialysis	8.3
High Risk;	
Independent dialysis	7.0
Successful transplant	6.8
Hospital dialysis	4.6

Source: Wood, Mallick and Wing, 1987

6.5.2 Quality of Life

While the use of blood transfusions alleviates the symptoms of anaemia the effect is not permanent and health status declines gradually during the period between transfusions. Using EPO can maintain the improvement at a constant level, so even if it did no more than raise patients to the immediate post-transfusion level there would be a net gain because of the avoidance of fluctuations. However, it is possible to raise haemoglobin levels much closer to normal using EPO, without the attendant risks of sensitisation which would occur if transfusions were used in this way. As a consequence, without EPO, patients tolerate low levels of health status and quality of life to minimise the use of transfusions. With EPO, patients awaiting transplant can enjoy a much higher quality of life.

The preferred method for assessing changes in patients' quality of life is the use of self-assessed questionnaires in the pre and post-treatment situations. The Rosser and Kind classification matrix can be used to categorise patients once their responses are known, and because a set of relative values exists for the different health states, moves between states can be quantified in terms of quality-adjusted life years gained (QALYs). (See Gudex and Kind (1988) for full details of the method).

In the absence of a suitable patient group to mount a new trial for this study, reliance has been placed on data collected in other studies. This has been generously provided by Mrs Judith Auer and Dr C G Winearls of the Churchill Hospital, Oxford. Their data was collected using the Nottingham Health Profile rather than the Rosser and Kind matrix so a re-classification has been carried out (see Appendix 6.1).

The following basic assumptions were made (a) no patient before or after EPO treatment would grade him or herself perfectly healthy (ie. without any social disability or distress); and (b) no patient had completely given up employment or housework as a result of dialysis. The reasoning behind these assumptions was that even with fully reversed anaemia a patient on dialysis would experience some disruption to social activities through the need to spend time undergoing dialysis, and also a certain amount of discomfort or

distress. Equally, it was felt that all patients in the group would maintain some level of their pre-illness activities while dependent on transfusions.

The classification of the 24 patients on the Rosser-Kind matrix before EPO treatment is given in Table 6.4 and after EPO treatment in Table 6.5.

Using the weighting system developed by Kind et al (1982), based on healthy valued at one, dead at zero, a relative value can be attached to a year of life spent in each of the categories in the matrix. The weights are given in Appendix 6.2. By aggregating the weighted scores for the 24 patients before and after the use of EPO, a comparison of the mean health state for the group in each situation can be carried out. This is done in Table 6.6 below.

From Table 6.6 it can be seen that the average net change in patient quality of life measured by the Rosser-Kind values is 0.048. However, the patients were initially assessed when they had accumulated the effects of chronic anaemia and may well have underestimated the limitations in their life since it is well known that long experienced symptoms are frequently well tolerated. This could therefore mean that, following treatment these patients would have discovered their previous degree of disability and may well have graded their quality of life at a lower level in retrospect. This would have the effect of increasing the QALY gain.

6.6 COST-EFFECTIVENESS ANALYSIS

6.6.1 Cost per QALY Calculations

The calculation in Section 6.4.5 produced a figure of £4951 as the net additional annual cost of EPO treatment. This produces an average 0.048 of a quality-adjusted life-year per patient. Aggregating across the patient group a net increase of one QALY would be produced by treating 20.8 patients for a year at an additional cost of £103,145.

These cost per QALY figures seem high, so it is appropriate to place them in context. Quality of life for renal patients in the UK has not previously been directly measured using the Kind and Rosser approach. One previous study has, however, calculated relative valuations by transforming data from studies in the USA (Gudex, 1986). The results are presented in Table 6.7.

The range is from 0.820 to 0.970 but the sample of patients in the Bonney study was clearly different from the others, including more seriously ill patients. The figure calculated here for EPO patients places them above most dialysis patients without EPO, and slightly below the average for post-transplant patients. The figure of 0.917 for the pre-EPO patients in the current study reflects the choice of serious anaemia cases for the initial use of EPO.

Given the small sample of patients using EPO and the indirect method of calculating the QALY gains, the order of magnitude of the results is encouragingly consistent with the previous work. However, given the uncertainties involved, and the necessarily arbitrary assumptions which have to be made in a study of this nature, sensitivity analysis on the results is called for.

Table 6.4 Pre-EPO Treatment
Rosser-Kind Classification

Disability		Distress: None A	Mild B	Moderate C	Severe D	Total
None	I	Healthy	0	0	0	0
Slight social	II	0	4	0	0	4
Severe social Slight physical	III	0	2	2	0	4
Severe physical Light work only	IV	0	0	4	12	16
No paid employment Largely housebound	V	0	0	0	0	0
Chairbound	VI	0	0	0	0	0
Confined to bed	VII	0	0	0	0	0
Unconscious	VIII	0		Not applicable		0
	TOTAL	0	6	6	12	24

Table 6.5 With EPO Treatment
Rosser-Kind Classification

Disability		Distress: None A	Mild B	Moderate C	Severe D	Total
None	I	Healthy	0	0	0	0
Slight social	II	0	12	0	0	12
Severe social Slight physical	III	0	8	0	0	8
Severe physical Light work only	IV	0	0	1	3	4
No paid employment Largely housebound	V	0	0	0	0	0
Chairbound	VI	0	0	0	0	0
Confined to bed	VII	0	0	0	0	0
Unconscious	VIII	0		Not applicable		0
	TOTAL	0	20	1	3	24

Table 6.6 Mean Quality of Life Scores

Before EPO

Rosser Category	Weight	No. of Patients	Group Value
II B	0.986	4	3.944
III B	0.972	2	1.944
III C	0.956	2	1.912
IV C	0.942	4	3.768
IV D	0.870	12	10.440
		24	22.008

Mean patient value = 0.917

After EPO

Rosser Category	Weight	No. of Patients	Group Value
II B	0.986	12	11.832
III B	0.972	8	7.776
IV C	0.942	1	0.942
IV D	0.870	3	2.610
		24	23.160

Mean patient value = 0.965

Table 6.7 Calculations of QALY Values from the Literature

Source	Treatment	QALY
Bonney et al (1978)	Home HD	0.840
Evans et al (1985)	Home HD	0.970
Procci (1980)	Home HD	0.940
Bonney et al	Hospital HD	0.820
Evans et al	Hospital HD	0.950
Bonney et al	After transplant	0.970
Evans et al	After transplant	0.980
Procci	After transplant	0.960
Evans et al	CAPD	0.960

Source: Gudex (1986)

6.6.2 Sensitivity Analysis of Costs

The costs of transfusion in Section 6.4.3 are based on transfusion-dependent patients requiring, on average, 19 units of blood per year. For reasons already outlined the amount of transfusion is kept to the minimum so this figure is thought to be realistic for serious anaemic cases. Clinical opinion indicates that no more than 12 units per year is a desirable limit. If EPO is used to treat patients with less serious anaemia, the number of transfusions replaced would be less, and hence the cost savings lower.

Regarding the EPO dose rate the trend has been to reduce the rate with greater experience of the use of the drug, and particularly to commence treatment with a lower dose rate to reduce the risk of increased hypertension. In future, a reasonable assumption of average dose might be 2 vials per week per patient instead of 3 vials. The time taken to reach the intended Hb level would of course be increased.

Varying the assumptions in this way would produce the range of potential net costs for the use of EPO instead of transfusions shown in Table 6.8.

Table 6.8 Range of Potential Costs

Transfusions per year	EPO Dose per Week	Net Additional Cost per patient
12	3 vials	£5196
19	3 vials	£4951
19	2 vials	£3079

There is also some uncertainty over the exact cost of a unit of blood, which might vary between hospitals, but the size of this variation is relatively small compared to the effect of changes in quantities.

6.6.3 Sensitivity Analysis of Effectiveness

1 Quality of Life

The data on quality of life changes is most subject to uncertainty because of its indirect calculation and the small number of patients. A whole range of adjustments to the assumptions could be made, but the following illustrative procedure has been selected to produce high and low figures to put beside the median values derived from Table 6.6.

High Estimate: in the pre-EPO situation 1 patient is moved downwards from each category to the next one to which patients have been classified;
in the post-EPO situation 1 patient is moved upwards from each category to the next one to which patients have been classified.

Low estimate: the process is reversed so that pre-EPO patients are moved up and post-EPO patients are moved down.

Full details are given in Appendix 6.2.

This produces high and low estimates of QALY gain per patient per year of 0.058 and 0.039 respectively, as compared to the estimate of 0.048 in Table 6.6.

In the absence of information on the trend in quality of life for patients on EPO treatment or dependent on blood transfusions, comparisons can be made using the annualised figures. Evidence of a relative decline in quality of life for long-term transfusion dependent patients who failed to obtain a successful graft would require a different approach. A difference in survival period for the two groups would require a comparison over time

using discounting techniques for both costs and QALY gains (Gudex and Kind, 1988).

2 Survival

Although there is no hard evidence of differential survival for patients on EPO treatment, as opposed to those dependent on blood transfusions, for the reasons outlined in Section 6.5.1 there is a possibility that life expectancy might be increased. To illustrate the potential impact, estimates have been made of costs per QALY gained, on the assumption that EPO patients survive on average for 11 years, instead of the currently expected 10 years for transfusion dependent patients.

To obtain the estimates, a discounted analysis of costs and QALY gains over an 11 year period is required, full details of which are given in Appendix 6.2. The main differences result from the additional gain of a discounted and quality-adjusted year of life (which is valued much more than the marginal changes in quality experienced in other years), and the addition to costs of an extra full year of EPO treatment, without compensating cost savings from avoided transfusions, as patients not on EPO are assumed to survive for only 10 years. Using the mid-range cost and QALY gain data from Table 6.6, the additional year of survival would reduce the cost per QALY gained from EPO treatment to £44,415. Incorporating some of the other changes in assumptions described in Section 6.6.3 would reduce that figure even further.

6.7 CONCLUSIONS

The foregoing analysis has demonstrated that EPO offers the possibility of measurable gains in quality of life for patients, but that the costs of the treatment are considerably greater than any likely resource savings from the cessation of blood transfusions. The quality of life measure used is a general one, designed to allow comparisons across the whole range of health care interventions many of which prolong as well as improve life for patients. EPO offers improved quality of life only and therefore does not score heavily on a valuation scale which encompasses increased length and quality of life. The situation can be illustrated using cost per QALY gained for basic RRT in comparison with EPO.

Table 6.9 Cost per QALY Gained in RRT (1988 prices)

Kidney Transplant*	£1,724
Haemodialysis*	£11,071
EPO treatment for anaemia in dialysis patients	£103,145

* From Gudex (1986)

Without the basic RRT the patients' life expectancy is short and the consequent gain in life years, regardless of quality, is substantial. EPO is only offering a marginal improvement after the main therapy has been instituted. In terms of resource use the annual cost of EPO treatment of just under £5000 is high compared with the annual cost of haemodialysis of around £15,000 at 1988 prices (and £18,300 at 1990 prices), adapted from Dowie

(1984). The effect of assuming a 10% improvement in life expectancy for EPO patients, is dramatic, reflecting the strong influence of increased length of life in the valuations.

The analysis has been carried out for a limited group of patients, seriously affected by anaemia, who are in the group expected to gain most from EPO treatment. To improve the cost-effectiveness of the use of EPO further selection is indicated. If all patients began in health state IV C on Table 6.4 and improved to health state II B on Table 6.5, the cost per QALY gained would be more than halved. State IV C involves a very limited ability to work and a severe degree of distress resulting from the condition, whereas II B involves slight social disability and only mild distress.

This study has looked at the cost-effectiveness of EPO in the context of other possible uses of health care resources. Alternative approaches are possible including cost-benefit analysis which would look at the productivity gains to society from the use of the drug (see Appendix 6.3). It is important not to mix the approaches. CEA cannot answer the question "should EPO be used?", but can indicate the circumstances in which its use would be most beneficial. The work is preliminary and exploratory rather than definitive. Much better evidence on the impact of EPO on the quality of life and survival rates is needed, as well as clinically agreed dosage rates in specific circumstances, before more definite judgements can be made on the appropriate use of the drug.

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Appendix 6.1

Calculation of Quality of Life Changes

1 Data

The data available, from a study conducted by Mrs Judith Aeurs of the Churchill Hospital, Oxford, was classified on the Nottingham Health Profile (Hunt et al, 1980). A method had to be devised to convert this data to the Rosser and Kind classification which was to be used in the study. The NHP consists of a series of 38 questions on different aspects of health and well being, including physical mobility, pain, sleep, energy, social isolation and emotional reactions. The Rosser and Kind classification covers the same aspects using a shorter questionnaire, and classified patients into one of seven disability states and one of four distress states (see Appendix 1.1). The combinations of disability and distress give 28 possible health states plus unconscious and dead.

A summary of the aggregated responses in areas relevant to the Rosser and Kind classification is given in Table A1 (individual patient profiles were not available). The Rosser scale allocates patients to disability categories on the basis of physical mobility and social funtioning, and to distress categories on the basis on the number and intensity of feelings experienced (see questionnaire in Appendix 1.1).

The allocation of the 24 patients to Rosser categories was worked out proportionally, on the basis of estimates of the way in which the Rosser questions would have been answered. The process was of necessity arbitrary in the absence of individual data. The before and after EPO Rosser Classifications are given in Tables 6.4 and 6.5 in the main text.

Appendix 6.1

Table A1: Summary of NHP Data

Problem Area	No. of Patients (24 total)	
	Before EPO	After EPO
Employment	14	6
Looking After Home	18	7
Social Life	15	10
Relationships at Home	11	3
Sex Life	12	7
Hobbies and Interests	16	6
Holidays	18	14
Feeling tired	16	3
Feeling on edge	12	2
Losing temper	12	7
Waking in early hours	13	8

Source: Mrs J Auer, Churchill Hospital, Oxford.

Appendix 6.2

Sensitivity Analysis

1 Quality of Life

Changes in the allocation of patients to Rosser Categories were as follows:

		II B	III B	III C	IV C	IV D
Middle Estimate:	Before EPO	4	2	2	4	12
(Tables 6.4 & 6.5)	After EPO	12	8	0	1	3
Low QALY Estimate:	Before EPO	5	2	2	4	11
	After EPO	11	8	0	1	4
High QALY Estimate:	Before EPO	3	2	2	4	13
	After EPO	3	8	0	1	2

2 Survival

Assuming an increase in life expectancy of 10% for EPO patients an eleven year DCF comparison is required.

Year	Net Cost	Discount Factor	NPV Cost	QALY Gain	NPV Gain
0	4951	1.000	4951	0.048	0.048
1 to 9	4951 p.a.	7.1080	35191	0.048 p.a.	0.341
10	5616	0.6139	3447	0.965	0.5924
			£43589		0.9814

Cost per QALY = £44,415

Appendix 6.3

Productivity Benefits

Although a considerable number of dialysis patients are of working age in the UK, the severely anaemic patients for whom EPO has been used are largely in the older age groups. Younger patients tend to get priority for transplantation, as a longer-term solution to their problems. In individual cases it is quite possible, through the use of EPO, to restore patients to a physical condition which will allow them to undertake longer working hours and harder work. Whether this is a gain to society is another matter.

The use of cost-benefit analysis based on the human capital approach to valuation of benefits has been deliberately avoided here as it attaches a differential value to health benefits according to income and employability. It would imply a different set of priorities in allocating health service resources from that given by maximising health benefits as measured by QALY gains. To add productivity benefits into the CEA equation would be double counting, as the QALY measure explicitly reflects patients' valuation of the ability to work. At a time of high unemployment, the true social benefit from re-employing dialysis patients is likely to be much less than their potential earnings, since other workers are likely to be displaced.

For these reasons, the estimation of "productivity benefits" has not been a major concern of this study.

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