The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of different haemoglobin target levels for erythropoietin (EPO) treatment of anaemia in haemodialysis patients. The target levels examined were 9.5 - 10.5 g/dL (reference target), 11 - 12 g/dL, 12 - 12.5 g/dL, and 14 g/dL.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of prevalent haemodialysis patients whose characteristics were representative of typical dialysis centres in the USA in terms of age, gender, race and co-morbidity.

Setting
The setting was a haemodialysis centre. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published from 1990 to 2002. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to assess the expected costs and clinical benefits associated with EPO treatments aimed at reaching the four haemoglobin target levels. Three possible health states were considered. These were alive on haemodialysis, alive with a renal transplant, and dead. The time horizon of the model was lifetime. The cycle length was one year.

Outcomes assessed in the review
The outcomes estimated in the review were:

the annual mortality risk,
the annual number of hospitalisation days,
the annual rate of vascular access failure,
the average annual use of intravenous iron for in-centre haemodialysis patients,
the rate of transplantation,
mortality among renal transplant recipients, and
utility scores.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify all relevant studies reporting clinical data. Randomised clinical trials were used, whenever possible.

Sources searched to identify primary studies
MEDLINE and the Cochrane Library were searched, as were abstracts from major nephrology meetings and the authors’ personal files.

Criteria used to ensure the validity of primary studies
The validity of the primary studies was ensured by the use of randomised clinical trials.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Nine primary studies provided the evidence.

Methods of combining primary studies
The primary estimates appear to have been combined using narrative methods.

Investigation of differences between primary studies
Not stated.

Results of the review
The annual mortality risk for patients in the reference case was 244.4/1,000.

The annual number of hospitalisation days in the reference case was 13.9 days/patient-years.

The annual rate of vascular access failure in the reference case, adjusted for distribution of access types, was 0.074/hemodialysis (with arteriovenous fistula at 25%) and 0.216/haemodialysis (with polytetrafluoroethylene at 75%).

The average annual use of intravenous iron for in-centre haemodialysis patients in the reference case was 1,500 mg/12 months.

The rate of transplantation was 0.054.
The mortality among renal transplant recipients was 0.08 in the first year and 0.038 in the second and subsequent years.

The average utility score for in-centre haemodialysis patients treated to the 11 - 12 g/dL haemoglobin level was 0.621.

The utility score for the 9.5 - 10.5 g/dL target level was 7.4% lower than the score for the target of 11 - 12 g/dL.

The increase in the 12 - 12.5 g/dL and 14 g/dL targets were assessed using two different approaches:

- compared with the 11 - 12 g/dL target, the first approach estimated an increase of 0.43% for the 12 - 12.5 g/dL target and 1.45% for the 14 g/dL target; and
- compared with the 11 - 12 g/dL target, the second approach produced increases of 3.7% (12 - 12.5 g/dL) and 12.3% (14 g/dL), respectively.

The average utility score for patients with functioning renal transplant was 0.816.

No survival difference was estimated for patients treated with either of the higher dose EPO strategies.

The rates of hospitalisations were equivalent between the study arms.

The access failure rates were not affected by haemoglobin target.

**Measure of benefits used in the economic analysis**

The summary benefits measure was the number of quality-adjusted life-years (QALYs) obtained with each treatment strategy. Utility and survival data were derived from the literature. The estimated EPO requirements were also reported. The QALYs were discounted annually at a rate of 3%. The authors stated that there was no evidence that utility scores improve once haemoglobin levels rise above 12.0 g/dL (using physical function scores on the SF-36), but a linear increase was noted for selected dimensions of the HRQOL in certain patients. Therefore, two methods were used to estimate the utilities for the 12 - 12.5 g/dL and 14 g/dL targets, as stated already.

**Direct costs**

Discounting was relevant since the costs were incurred over a long timeframe. An annual rate of 3% was applied. The unit costs were not reported separately from the quantities of resources used. The costs were presented as macro-categories. The health services included in the economic evaluation were EPO and iron treatment, physician services, in-centre haemodialysis, hospital stay, outpatient care, and transplantation. Outpatient care comprised the costs of emergency room visits, day surgery, all diagnostic imaging and laboratory tests, and outpatient medications. The cost/resource boundary of the health care purchaser was adopted. Resource use was estimated using data derived from the literature and some assumptions. The costs came from several sources, such as Medicare rates, average wholesale prices, and a published cost study. The price year was 2001.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not considered in the economic evaluation.

**Currency**

US dollars ($). The costs were first estimated in Canadian dollars (Can$) and then converted to US dollars. At January 2001 the conversion rate was $1 = Can$1.45.
Sensitivity analysis
Sensitivity analyses were carried out to assess the impact of changes in baseline inputs on the estimated cost-effectiveness ratios. Particular attention was given to two variables, the EPO dose and utility weights. Both univariate and multivariate sensitivity analyses were carried out. In general, the ranges of values were derived from the published evidence.

Estimated benefits used in the economic analysis
The estimated incremental QALYs were:

- 0.146 with the 11 - 12 g/dL versus the 9.5 - 10.5 g/dL target;
- 0.009 with the 12 - 12.5 g/dL versus the 11 - 12 g/dL target; and
- 0.020 with the 14 g/dL versus the 12 - 12.5 g/dL target.

When intravenous EPO was used, the estimated EPO requirements were 3,523 units for the 9.5 - 10.5 g/dL target, 5,078 units for the 11 - 12 g/dL target, 6,097 units for the 12 - 12.5 g/dL target, and 9,341 units for the 14 g/dL target.

The corresponding values when subcutaneous EPO was used were 3,030 units (9.5 - 10.5 g/dL), 4,367 units (11 - 12 g/dL), 5,243 units (12 - 12.5 g/dL), and 8,033 units (14 g/dL), respectively.

Cost results
The total costs associated with the treatment options were not reported.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the alternative treatment strategies.

The estimated incremental cost per QALY (with intravenous EPO use) was $55,295 with 11 - 12 g/dL versus 9.5 - 10.5 g/dL, $613,015 with 12 - 12.5 g/dL versus 11 - 12 g/dL, and $828,215 with 14 g/dL versus 12 - 12.5 g/dL.

The estimated incremental cost per QALY (with subcutaneous EPO use) was $47,877 with 11 - 12 g/dL versus 9.5 - 10.5 g/dL, $529,960 with 12 - 12.5 g/dL versus 11 - 12 g/dL, and $715,028 with 14 g/dL versus 12 - 12.5 g/dL.

Changes in EPO requirements did not affect the results of the base-case analysis.

When the less likely scenario in which utility scores continued to improve in linear fashion with the target haemoglobin was considered, the incremental cost per QALY (with intravenous EPO use) was $71,739 for 12 - 12.5 g/dL compared with 11 - 12 g/dL, and $97,460 for 14 g/dL compared with 12 - 12.5 g/dL.

With subcutaneous EPO use these values were $62,020 and $83,816, respectively.

In general, when model inputs were varied within plausible ranges, the conclusions of the analysis did not change.

Considering only the additional EPO and intravenous iron requirements, the incremental costs per year required to maintain patients with end-stage renal disease at 11.0 - 12.0 g/dL, 12.0 - 12.5 g/dL, and 14.0 g/dL targets compared with 9.5 - 10.5 g/dL were $2,540 (11.0 - 12.0 g/dL), $4,550 (12.0 - 12.5 g/dL), and $9,400 (14.0 g/dL), respectively.

A budget impact analysis showed that, given approximately 210,000 haemodialysis patients in the USA per year, the additional cost implied by each of these guidelines in the USA alone would be $530 million for the 11.0 - 12.0 g/dL target, $955 million for the 12.0 - 12.5 g/dL target, and $2.0 billion for the 14.0 g/dL target.

Authors' conclusions
The use of erythropoietin (EPO) to achieve haemoglobin targets of 11 - 12 g/dL led to an incremental cost per quality-adjusted life-years (QALY) gained of approximately $50,000 to $60,000 in haemodialysis patients. However, the objective of reaching haemoglobin levels in excess of 12 g/dL resulted in prohibitive cost-effectiveness ratios (in general, above $500,000 per QALY). The results of the analysis suggested that higher haemoglobin targets did not reduce hospitalisation costs sufficiently to offset the additional costs of EPO.

**CRD COMMENTARY - Selection of comparators**
The authors provided a justification for the choice of the comparators, which were recommended in different worldwide guidelines for the treatment of haemodialysis patients. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used results from a systematic review, which was carried out to identify all relevant published studies. Clinical trials were the preferred source, which ensured the validity of the estimates used in the model. Limited information on the methods and conduct of the review was provided. The robustness of the estimates used in the model was tested in a sensitivity analysis, in which nearly all model inputs were investigated.

**Validity of estimate of measure of benefit**
The summary benefit measure was appropriate as it detected the impact of the interventions on quality of life and survival. It also has the advantage of being comparable with the benefits of other health care interventions. Discounting was applied, as recommended in the USA. The impact of varying the discount rate was examined in the sensitivity analysis. Different methods were used to determine the utility weights.

**Validity of estimate of costs**
The authors explicitly reported the perspective adopted in the study. As such, it appears that all the categories of costs relevant to that perspective have been included in the analysis. However, a detailed breakdown of the cost items was not provided and information on the unit costs and resource use was unclear. This limits the possibility of replicating the study. The source of the data and the price year were provided, which will assist reflation exercises in other settings. The costs were treated deterministically in the base-case but some key cost inputs were varied in the sensitivity analysis. The authors noted that their results would have changed had the indirect costs been included.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. However, the issue of the generalisability of the study results to other settings was addressed through the extensive sensitivity analyses. This improved the external validity of the analysis. The authors acknowledged some limitations of their study, in particular the relative imprecision of some estimates.

**Implications of the study**
The authors suggested that the cost-effectiveness of EPO should be re-evaluated when new clinical trials, carried out on people without established cardiovascular disease, are available. The results also corroborate actual recommendations of using subcutaneous in place of intravenous EPO. Overall, haemoglobin targets above 12 g/dL should not be recommended.

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Other publications of related interest


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