

# A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment

J Wilson,<sup>1\*</sup> GL Yao,<sup>2</sup> J Raftery,<sup>2</sup> J Bohlius,<sup>3</sup>  
S Brunskill,<sup>4</sup> J Sandercock,<sup>1</sup> S Bayliss,<sup>1</sup> P Moss,<sup>5</sup>  
S Stanworth<sup>4</sup> and C Hyde<sup>1</sup>

<sup>1</sup> Department of Public Health and Epidemiology,  
University of Birmingham, UK

<sup>2</sup> Health Services Management Centre, University of Birmingham, UK

<sup>3</sup> Cochrane Haematological Malignancies Group,  
Department I Internal Medicine, University of Cologne, Germany

<sup>4</sup> National Blood Service, John Radcliffe Hospital, Oxford, UK

<sup>5</sup> Division of Cancer Studies, University of Birmingham, UK

\* Corresponding author



## Executive summary

Health Technology Assessment 2007; Vol. 11: No. 13

Health Technology Assessment  
NHS R&D HTA Programme  
[www.hta.ac.uk](http://www.hta.ac.uk)





## Executive summary

### Background

Cancer-associated and cancer-treatment-associated anaemia are important problems which have been under appreciated in the past. Management has consisted of investigation of the cause of anaemia, monitoring, blood transfusions and treatment of the underlying cancer. Epoetin alfa, epoetin beta and darbepoetin alfa are three types of exogenous erythropoietin which stimulate the bone marrow to produce red blood cells. They are expensive, with each month of treatment costing around £1000, and patients often requiring 3–6 months of treatment. The cost of alternative treatment, such as red blood cell transfusion (RBCT), is also often underestimated, with the approximate cost per typical transfusion (2 or 3 units), including administration, but not cost to patient and donor, recently being estimated as £635. Increasing scarcity of blood is a further concern.

### Objective

To assess the effectiveness and cost-effectiveness of epoetin alfa, epoetin beta and darbepoetin alfa (referred to collectively in this report as epo) in anaemia associated with cancer, especially that attributable to cancer treatment.

### Methods

Using a recently published Cochrane review as the starting point, a systematic review of recent randomised controlled trials (RCTs) comparing epo with best standard was conducted. MEDLINE, EMBASE, the Cochrane Library and other databases were searched from 2000 (1996 in the case of darbepoetin alfa) to September 2004. Inclusion, quality assessment and data abstraction were undertaken in duplicate. Where possible, meta-analysis was employed.

The economic assessment consisted of a systematic review of past economic evaluations, an assessment of economic models submitted by the manufacturers of the three epo agents and development of a new individual sampling model (the Birmingham epo model).

### Results

#### Effectiveness

A total of 46 RCTs was included in this systematic review, 27 of which had been included in the Cochrane systematic review. All 46 trials compared epo plus supportive care for anaemia (including transfusions) with supportive care for anaemia (including transfusions) alone. Outcomes assessed were anaemia-related outcomes [haematological response, haemoglobin (Hb) change, RBCT requirements], adverse events, health-related quality of life (HRQoL) and malignancy-related outcomes (tumour response, overall survival).

Haematological response (defined as an improvement by  $2 \text{ g dl}^{-1}$ ) had a relative risk of 3.4 [95% confidence interval (CI) 3.0 to 3.8, 22 RCTs] with a response rate for epo of 53%. The trial duration was most commonly 16–20 weeks. There was little statistical heterogeneity in the estimate of haematological response, and there were no important differences between the subgroups examined. Hb change showed a weighted mean difference of  $1.63 \text{ g dl}^{-1}$  (95% CI 1.46 to 1.80) in favour of epo. Treatment with erythropoietin in patients with cancer-induced anaemia reduces the number of patients who receive an RBCT by an estimated 18%.

HRQoL data were analysed using vote counting and qualitative assessment, and a positive effect was observed in favour of an improved HRQoL for patients on epo. Published information on side-effects was of poor quality. New trials provided further evidence of side-effects with epo, particularly thrombotic events, but it is still unclear whether these could be accounted for by chance alone.

The results of the previous Cochrane review suggested a survival advantage for epo, with a hazard ratio (HR) of 0.84 (95% CI 0.69 to 1.02), based on 19 RCTs. The update, based on 28 RCTs, suggests no difference (HR 1.03, 95% CI 0.88 to 1.21) (variance estimate inflated for substantive heterogeneity,  $\chi^2 = 37.75$ , 27 df,  $p = 0.08$ ; HR using standard method 1.03, 95% CI 0.92 to 1.16,  $p = 0.57$ ;  $\chi^2_{\text{(het)}} = 37.74$ , 27 df,  $p = 0.08$ ). Subgroup analysis suggested some

explanations for this heterogeneity, but it is difficult to draw firm conclusions without access to the substantial amounts of missing or unpublished data, or more detailed results from some of the trials with heterogeneous patient populations. The conclusions are, however, broadly in line with those of a Food and Drug Administration (FDA) safety briefing, which recommended that patients with Hb above 12 g dl<sup>-1</sup> should not be treated; the target rate of rise in Hb should not be too great, and further carefully conducted trials are required to determine which subgroups of patients may be harmed by the use of these products, in particular through the stimulation of tumour activity.

### Cost-effectiveness

Five published economic evaluations identified from the literature had inconsistent results, with estimates ranging from a cost per quality-adjusted life-year (QALY) under £10,000 through to epo being less effective and more costly than standard care. The more favourable evaluations assumed a survival advantage for epo. The three company models submitted each relied on assumed survival gains to achieve relatively low cost per QALY, from £13,000 to £28,000, but generated estimates from £84,000 to £159,000 per QALY when no survival gain was assumed. Each of these models relied on Hb levels alone driving utility, and each assumed gradual normalisation of Hb in the standard treatment arm after the end of treatment. The Birmingham epo model followed the company models in regard to the relationship between Hb levels and utility, and also assumed normalisation in the base case. With no survival gain, the incremental cost per QALY was £150,000 falling to £40,000 when the lower, more favourable, confidence interval for survival was used.

### Conclusions

Epo is effective in improving haematological response and RBCT requirements, and appears to have a positive effect on HRQoL. The incidence of

side-effects and effects on survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely that epo would be considered a cost-effective use of healthcare resources.

### Recommendations for research

The following areas are suggested for further research.

- The main target of further research should be to improve estimates of impact on survival. In the first instance this should be through more detailed secondary research, such as the individual patient data meta-analysis started by the Cochrane group.
- Further trials may be required, and have been recommended by the FDA. However, many trials are in progress, completed but unreported or awaiting mature follow-up.
- The Birmingham epo model developed as part of this project has features that are not present in previous models. These features improve its flexibility in exploring different scenarios in the future. Funding is needed to support further refinement and validation of this work.
- Finally, further research to resolve uncertainty about other parameters, particularly quality of life and adverse events, should be pursued in parallel with attempts to improve evidence on survival. The rate of normalisation was also an important parameter in the model for which no published data source was identified, and so further research in this area would be beneficial.

### Publication

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.* A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**(13).

# NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

## Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/51/01. The protocol was agreed in September 2004. The assessment report began editorial review in July 2005 and was accepted for publication in May 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley  
Series Editors: Dr Aileen Clarke, Dr Peter Davidson, Dr Chris Hyde,  
Dr John Powell, Dr Rob Riemsma and Dr Ken Stein  
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2007

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.

Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.