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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.

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Abstract

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

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Objectives: 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.
Data sources: Electronic databases were searched from 2000 (1996 in the case of darbepoetin alfa) to September 2004.
Review 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. 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: In total 46 RCTs were included within 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. Haematological response (defined as an improvement by 2 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. Haemoglobin (Hb) change showed a weighted mean difference of 1.63g 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 a red blood cell transfusion (RBCT) by an estimated 18%. Health related quality of life (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 thrombic events, but it is still unclear whether these could be accounted for by chance alone. The results of the previous Cochrane review had suggested a survival advantage for epo (HR 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). 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 a haemoglobin above 12 g dl^{-1} 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. 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 reducing RBCT requirements, and appears to have a positive effect on HRQoL. The incidence of side-effects and effects on survival remains highly uncertain. However, if there is no impact on survival, it seems highly unlikely that epo would be considered a cost-effective use of healthcare resources. The main target for further research should be improving estimates of impact on survival, initially 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, although many trials are in progress, completed but unreported or awaiting mature follow-up. The Birmingham epo model developed as part of this project contains new features that improve its flexibility in exploring different scenarios; further refinement and validation would therefore be of assistance. Finally, further research to resolve uncertainty about other parameters, particularly quality of life, adverse events, and the rate of normalisation, would also be beneficial.

Contents

List of abbreviations

AE	adverse event
ALL	acute lymphocytic leukaemia
AML	acute myeloid leukaemia
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
BNF	British National Formulary
BSI	Brief Symptom Inventory
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CLAS	Cancer Linear Analogue Scale
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
DVT	deep vein thrombosis
ECAS	European Cancer Anaemia Survey
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organisation for Research and Treatment of Cancer
epo	epoetin alfa, epoetin beta or darbepoetin alfa
EQ-5D	EuroQol 5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy
FACT (G, An, F)	Functional Assessment of Cancer Therapy (General, Anaemia, Fatigue)
FDA	Food and Drug Administration
FLI-C	Functional Living Index – Cancer
G-CSF	granulocyte colony-stimulating factor
HaemR	haematological response
Hb	haemoglobin
Hct	haematocrit
HR	hazard ratio
HRQoL	health-related quality of life
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
IL-1	interleukin-1
IL-6	interleukin-6
IPD	individual patient data
ITT	intention-to-treat
LASA	Linear Analogue Self-Assessment scale
MAR	missing at random

continued

List of abbreviations *continued*

MDS	myelodysplastic syndrome
MM	multiple myeloma
MNAR	missing not at random
NA	not applicable
NBS	National Blood Service
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NHP	Nottingham Health Profile
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NSCLC	non-small cell lung cancer
OB	Ortho Biotec
PDI	Psychological Distress Index
PFS	Piper Fatigue Self-Report scale
plat	platinum-based chemotherapy
QALY	quality-adjusted life-year
QoL	quality of life
RBC	red blood cell
RBCT	red blood cell transfusion
RCT	randomised controlled trial
RD	risk difference
rHuEPO	recombinant human erythropoietin
RR	relative risk
SAE	serious adverse event
sc	subcutaneously
SCI	Science Citation Index
SCLC	small cell lung cancer
SD	standard deviation
SE	standard error
SF-36	Short Form 36
SG	standard gamble
SHOT	Serious Hazards of Transfusion
SPC	summary of product characteristics
TR	tumour response
TTO	time trade-off
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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 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 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 thrombic 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, $p = 0.57$; $\chi^2_{(het)} = 37.74$, 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^{-1} 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.

Chapter 1

Aim of the review

The aim of this review was to evaluate by systematic review and economic modelling the effectiveness and cost-effectiveness of epoetin alfa, epoetin beta and darbepoetin alfa (referred to collectively in this report as epo) in anaemia [mean or median haemoglobin (Hb) ≤ 13 g dl^{-1}] associated with cancer, especially that attributable to cancer treatment.

Chapter 2
Background

Description of health problem

Definition of anaemia

Anaemia is defined as a reduction of Hb concentration, red-cell count or packed cell volume to below normal levels. Hb is a component of the blood, contained within red blood cells (RBCs) and responsible for carrying oxygen around the body. The World Health Organization (WHO) states that anaemia should be considered to exist in adults whose haemoglobin levels are lower than 13 g dl^{-1} (males) or 12 g dl^{-1} (females). The National Cancer Institute (NCI) considers normal Hb levels as 12–16 g dl^{-1} (females) and 14–18 g dl^{-1} (males).[1] There is no specific guidance on how to define anaemia with a single value in mixed male and female populations. Anaemia of differing severity is further defined (*Table 1*). There is consensus that levels of Hb below 8 g dl^{-1} and 6.5 g dl^{-1} constitute severe anaemia and life-threatening anaemia, respectively. Further, there is agreement that Hb between 8 and 9.4 g dl^{-1} constitutes moderate anaemia. However, the categorisation of Hb between 9.5 and 10.9 g dl^{-1} into moderate or mild anaemia is inconsistent, as is the possibility that Hb levels above 11 g dl^{-1} may sometimes be normal for the patient. Thus, although there have been attempts to standardise definitions of anaemia, it should be noted that variation continues and that it is important that the exact definition of anaemia being used is stated. It should be noted that the National Institute for Health and Clinical Excellence (NICE) final scope indicates anaemia for the purpose of their appraisal to be <13 g dl^{-1}. The difficulty of anaemia definition is further compounded by the fact that Hb measures are subject to variability. The UK national external quality assessment scheme for haematology shows some minor degree of variation between measured Hb concentrations, typically up to around ± 0.5 g dl^{-1}, but occasionally more, for the same sample at different haematology laboratories that use the same cell counter machines.

Nature of anaemia[2,3]

In adults RBCs are produced in the bone marrow. RBCs have a normal lifespan of about 120 days, so continuous production (erythropoiesis) is required to replace losses. Erythropoietin is a hormone produced mainly by the kidneys, but 10% in the liver, which stimulates the process of RBC production. The normal level of erythropoietin in the plasma is 4–26 IU l^{-1}. This normally increases in response to low levels of oxygen tension within the kidney. As with the measurement of Hb, there is some indication that different manufacturers' kits used at individual laboratories in UK generate different results, although preliminary feedback from a sample exchange programme organised from the Department of Biochemistry at King's College Hospital suggests comparable results for the same test sample with reasonable levels of precision.

A reduction in the quantity and/or quality of RBCs can result from either the defective production of RBC or an increased rate of loss of cells, by either premature destruction or bleeding. A wide range of diseases can lead to these, individually or in combination, including congenital disorders, trauma, autoimmune disease, infection, renal failure and cancer. Anaemia leads to a reduction in

TABLE 1 *Grading systems for anaemia*

Severity	WHO	NCI
Grade 0 (WNL)	≥ 11.0 g dl^{-1}	WNL
Grade 1 (mild)	9.5–10.9 g dl^{-1}	>10.0 g dl^{-1} to WNL
Grade 2 (moderate)	8.0–9.4 g dl^{-1}	8.0–10.0 g dl^{-1}
Grade 3 (serious/severe)	6.5–7.9 g dl^{-1}	6.5–7.9 g dl^{-1}
Grade 4 (life-threatening)	<6.5 g dl^{-1}	<6.5 g dl^{-1}

WNL, within normal limits.

TABLE 2 *Some symptoms of anaemia*

Part of body affected	Compensatory mechanism	Dysfunction[a]
Brain		Fatigue/tiredness, headaches, dizziness, difficulty thinking/concentrating, depressed mood
Eyes		Retinal damage
Heart	Rapid pulse, palpitations	Angina
Lungs	Rapid breathing, breathlessness	In severe cases, worsened breathlessness from pulmonary oedema secondary to heart failure
Kidneys		Water retention
Gut	Loss of appetite	Indigestion, irregular bowel movements, failure to absorb nutrients from food
Muscles/legs		Fatigue, reduced exercise capacity, swelling secondary to water retention (due in turn to kidney and heart failure)
Skin	Pallor, feeling cold	Brittle/broken nails
Reproductive organs		Increased menstrual bleeding, loss of periods, impotence, decreased libido

[a] The clinically important effects are magnified if anaemia develops rapidly or organs are compromised and unable to work at increased capacity, e.g. coronary artery disease for symptoms associated with dysfunction of the heart.

the oxygen-carrying capacity of the blood and so to hypoxia in tissues around the body. In many circumstances the body can compensate for such reduction, primarily by increasing cardiac output, but also by increasing respiration rate, directing blood away from non-vital organs such as the skin, by increasing the ease with which the available Hb gives up its oxygen and increasing the rate of RBC production (unless this is the cause of the anaemia). The efficiency of such compensatory mechanisms to maintain oxygen supply to vital parts of the body, when Hb falls to low levels, is often underestimated.[4] The body will compensate for more chronic anaemias by increasing RBC production and raising the baseline Hb concentration. Given that all organs of the body require oxygen, it is predictable that many symptoms may result. They can be divided into those attributable to the body's attempt to compensate and/or to its failure to function (*Table 2*).

The symptoms arising from dysfunction are much more likely to occur if the anaemia progresses rapidly or the body's ability to compensate is impaired or the body's organs are more susceptible to hypoxia. The latter two are more likely to occur with advancing age. Given the range of symptoms arising once compensatory mechanisms have failed, impact on general quality of life is likely. A problem with the wide-ranging and non-specific nature of symptoms associated with anaemia is that it is sometimes difficult to separate whether symptoms are caused by the anaemia itself or are a direct consequence of the underlying disease.

Treatment of anaemia

Given the variety of causes, consideration of the cause of anaemia is essential. The type of investigations undertaken will vary according to the patient's age and the clinical setting. Blood tests (number, size and colouring of RBCs, amount of iron and ferritin) may provide useful initial indications of the nature of the anaemia and its possible causes. However, further investigations including examination of the bone marrow may be required to elucidate fully the cause and in some cases investigation may be time-consuming and costly.

Investigation is important, because the cause of the anaemia will determine the treatment:

- iron-deficiency anaemia: iron replacement plus identification and treatment of the cause (e.g. surgery to treat bleeding from a bowel tumour)
- vitamin B_{12} deficiency (pernicious anaemia): vitamin B_{12} replacement
- renal failure (damage to kidneys leads to reduced erythropoietin production):

TABLE 3 *Some risks of blood transfusion*

Risk factor	Estimated risk per unit of red cells	Deaths per million units
Viral infection		
Hepatitis A	1 per 1,000,000	0
Hepatitis B	1 per 50,000 to 1 per 170,000	0–0.14
Hepatitis C	1 per 200,000	<0.5
HIV	< 1 per 2,000,000	<0.5
HTLV types I and II	1 per 19,000 to 1 per 80,000	0
Parvovirus B19	1 per 10,000	0
Bacterial contamination	1 per 500,000 to 4,000,000	0.1–0.25
Immune		
Acute haemolytic reactions	1 per 250,000 to 1 per 1,000,000	0.67
Delayed haemolytic reactions	1 per 1,000,000	0.4
TRALI	1 per 200,000 to 1 per 350,000	Not estimated
Transfusion-related graft-versus host disease	1 per 1,000,000 to 1 per 5,000,000	Not estimated

From Hoffbrand *et al*. (2001),[10] augmented by data from Serious Hazards of Transfusion (SHOT) office, Manchester.
HTLV, human T-cell lymphotrophic virus; TRALI, transfusion-related acute long injury.

erythropoietin replacement plus treatment of renal failure
- haemolysis (body attacks its own cells and destroys them): for example, immune suppression with steroids to treat autoimmune haemolysis
- bleeding predisposition due to coagulation or clotting defect: restore missing clotting factors.

However, where the underlying cause is not amenable to specific treatment and the anaemia is severe, or where specific treatment will take some time to take effect and the need to reverse anaemia is urgent, blood transfusions are important.

Blood (red cell) transfusion

It is important to emphasise that there are many types of blood products: red cells, platelets, white cells, fresh frozen plasma, cryoprecipitate and plasma derivatives. It is the first of these that is the relevant support for anaemia.

Red blood cell transfusion (RBCT) is effective in raising Hb levels. One unit of red cells (the red cells processed from one donation) will raise the Hb of most adults by 1 g dl^{-1}. The change takes effect within an hour.[5] The duration of this effect, even if the RBCs have been stored for their maximum of 35 days, is determined by the normal survival time of RBCs, that is, approximately 100 days.[6] On this basis, because each donation will contain a mixture of RBCs, young to old, 50% of the transfused RBCs will disappear by 50 days. Thus, at 30 days the benefit for each unit of transfused RBCs is about 0.6 g dl^{-1}, at 60 days 0.3 g dl^{-1} and at 90 days 0.1 g dl^{-1}. If an adult stops producing RBCs completely, a rule of thumb is that 2 units of RBCs every 2 weeks is sufficient to replace normal loss, and maintain the status quo.[7]

The principle that transfusion, although effective, should only be used appropriately is not a new concern. Guidelines and guidance on when to use transfusions are available[4,8] and although rigorous evidence outside laboratory studies to inform them is scant, it is not completely absent. In particular, the suggestion that the lowering of transfusion thresholds (only recommending transfusions when Hb levels fall to levels lower than had been used in the past) is driven merely by attempts to conserve scarce blood stocks is incorrect. A systematic review of randomised controlled trials (RCTs) by Hill and colleagues[9] suggests that, in the absence of serious cardiac disease, more restrictive transfusion criteria (e.g. 7.0 g dl^{-1}) showed no difference in health outcomes from more liberal thresholds (10 g dl^{-1}). Much of the supporting evidence for this statement comes from one higher quality RCT based in the intensive care setting.

It has been recognised for some time that there is a risk–benefit relationship for RBCT. Many of the risks associated with RBCT listed below have been known for many years, but as can be seen from *Table 3*, pose a very low risk.

These extremely low levels of risk associated with RBCT have recently been confirmed in a major review of all available literature and data in the

context of the Canadian healthcare system.[11] Consistent with these figures, preliminary results from the UK haemovigilance scheme, Serious Hazards of Transfusion (SHOT), identified 1 death per (approximately) 300,000 units of blood supplied over 1996–2003, 23 million units being supplied over this period (SHOT Office, Manchester).[12] However, the SHOT report for 2003 reported again that the most common problems associated with transfusion were errors of administration, with 358 incorrect or inappropriate blood component transfusion incidents reported over a 12-month period. This figure represented an increase of 25% over the previous 12 months. Of these incidents, 16 patients suffered major morbidity, with one possible incident-related death. Unfortunately, concentration on sources of risk or strategies aimed at further decreasing this risk may have been at the expense of clinical studies to define more clearly which groups of patients actually benefit most and to what degree from transfusion.[13]

The issue of increasing cost to improve safety is also raised. The NHS cost to collect and produce a unit of RBCs is stated as having risen from £47 in 1998 to £120 in 2004. These costs are in agreement with other UK cost studies identified in a systematic review by Amin and colleagues,[14] who also confirm that there has been a marked increase in cost of RBCTs over recent years in the USA and Canada as well as the UK. Varney and Guest[15] present a less conservative estimate of the cost of an RBCT (estimated to consist of 2.7 units on average) as £635 in 2000/01. However, they consider the wider costs of transfusion, not just the cost of collecting and processing the RBCs. In their cost estimate 35% of the £635 is attributable to transfusion services, 2% to transfusion-related complications and 65% to hospital stay. They also calculate direct and indirect costs associated with donor's time. However, these are small relative to the NHS costs. Not mentioned in the costing by Varney and Guest[15] are direct and indirect costs to the patient, which patient groups highlight as a major concern in their submissions to NICE on this appraisal. Time taken to attend for cross-matching and time taken to transfuse blood, generally 2 hours per unit, are concerns.

Finally, pressure on numbers of blood donors is an important issue. More restrictive criteria have already had an impact and further precautionary measures to reduce the (potential) risk of variant Creutzfelt–Jacob disease (vCJD) transmission may lead to a loss of 3.2% or 52,000 National Blood Service (NBS) blood donors.[16] However, alternatives to RCBT are emerging in most situations where blood is currently used. Erythropoietin is just one of many methods of conserving blood in different clinical situations, including blood substitutes,[17] autologous transfusion,[18] fibrin sealants,[19] red cell salvage[20] and use of antifibrinolytic agents.[21] Just as important are measures aimed at improving appropriate usage of blood, as described in the Department of Health Better Blood Transfusion initiative (HSC 2002/009).

Whether costs of blood products will continue to rise as rapidly as they have done over the past 10 years is uncertain, but potentially very important. If they do, it will clearly make alternatives to blood, including erythropoietin, relatively cheap in the future provided the costs of these alternatives remain constant.

Nature of anaemia associated with cancer and cancer treatment

Cancer is one important cause of anaemia. Definitions are the same as for anaemia in general and the need to specify the definition being used is as great. However, a special additional problem for measurement, particularly where anaemia is associated with chemotherapy, is that the degree of anaemia will often fluctuate markedly, typically falling to a nadir 2–4 weeks after chemotherapy is given, although this is dependent on many factors, including the nature of the chemotherapy and the number of courses administered. Single measures of Hb may thus overstate or understate the average Hb during the treatment course.

Anaemia associated with cancer is multifactorial and several different mechanisms are often identifiable. An important implication is that single treatments are unlikely to show equal levels of efficacy. The two major components of cancer-associated anaemia, not related to treatment, are:

- Cancer cells directly infiltrate bone marrow and suppress haematopoiesis.
- Cancer cells produce substances, including cytokines, that impair RBC production, decrease RBC survival and cause sequestration of iron. This secondary anaemia, or 'anaemia of chronic disease', is a common problem in which the patient develops a mild anaemia in association with a systemic disease such as malignancy. It is not due to marrow replacement, although this may complicate it.

Other potentially relevant causes of cancer-associated anaemia include:

- Blood loss may occur into or from tumours.
- Tumours may cause damage to kidneys, liver or hormone-producing organs, which in turn causes further anaemia.
- Reduced appetite associated with cancer may cause nutritional deficiencies, especially of iron, vitamin B_{12} and folic acid, which will further impair RBC production.
- Haemolysis, in which the RBCs are broken down. The causes may include immune-mediated antibody destruction, or fragmentation syndromes, which may represent direct or indirect effects by the malignancy.
- Cancer may be associated with changes in coagulation, which aggravate bleeding from tumours.
- Frequent blood sampling for testing can also exacerbate anaemia, particularly in small children.

The contribution of each of these mechanisms will vary depending on the tumour type and stage. Erythropoietin is particularly relevant to the second main mechanism above (secondary anaemia or anaemia of chronic disease). Studies by Miller and colleagues[22] show that levels of erythropoietin, although slightly above normal in cancer-associated anaemia, do not rise to those levels that are observed in iron-deficiency anaemia for the same low Hb. This 'blunting' of the erythropoietin response is thought to be mediated by cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) produced by cancer cells, and is one reason why the use of exogenous erythropoietin was initially investigated.

In addition to any anaemia associated with the cancer itself, a fall in Hb concentration may be associated with treatment of the cancer or coincident administration of other drugs.

Bone-marrow tissue is sensitive to radiation, so haemopoiesis is often impaired when bone marrow is included within the radiotherapy field. Possibly because radiotherapy rarely impacts on all areas of bone marrow simultaneously, Harrison and colleagues[23] observed only moderate increases in the proportion of anaemic patients, defined as <12 g dl^{-1}, before and after radiotherapy (41% versus 54%).

In contrast, chemotherapy may act on all tissues in the body. The effects of chemotherapy will depend on the regimen used. However, virtually all chemotherapy given at sufficient dose for a sufficient period can suppress production of cells by the bone marrow.[24] In general, white blood cell (WBC) and platelet production are affected before RBC production as these cells have a shorter lifespan. Damage to bone-marrow cells is usually temporary and leads to fluctuating anaemia. However, cumulative deterioration may occur over several chemotherapy cycles. In addition to damage to bone marrow, platinum-containing drugs such as cisplatin damage kidney cells producing erythropoietin, which may explain why they are particularly potent myelosuppressants.

Impact of anaemia associated with cancer and cancer treatment

The symptoms of cancer-associated anaemia are no different from anaemia arising from other causes. Anaemia may develop gradually, which gives the body an opportunity to compensate. However, this ability to compensate may be impaired by both the cancer itself and the understandable psychological effects associated with the illness. As mentioned above, the level of cancer treatment-associated anaemia may fluctuate during a cycle of chemotherapy, which may again limit the impact of some compensatory mechanisms.

There are growing claims that the impact of cancer-associated and cancer treatment-associated anaemia, even when developing gradually, may be greater than previously suspected. Strong positive correlations between lowered Hb levels and reductions in various measures of quality of life are cited, such as those reported by Lind and colleagues[25] and Holzner and colleagues.[26] Although such correlations are suggestive, they are open to confounding. Furthermore, when scatterplots of the data are provided, such as in Holzner,[26] the relationship between Hb levels and quality of life look less convincing, which is related to recognised problems with the interpretation of correlation coefficients. Finally, in the study by Lind,[25] which did attempt to control for the confounding factors age, gender and time since diagnosis, only 8% of the variability in quality of life scores was accounted for by Hb, despite Hb being the variable with the strongest association with the various measures of quality of life employed.

Further support for the relationship between anaemia and marked impact on quality of life is also claimed from interventional studies. If erythropoietin were shown to reverse anaemia and improve quality of life in such studies, this would be strong evidence. However, at least one group,

led by Bottomley,[27] has challenged whether these interventional studies actually demonstrate improved quality of life. Re-examining this question is thus an important part of this report, which will in turn inform just how much support the intervention studies lend to the premise that cancer-associated anaemia has a greater impact on quality of life than previously suspected. Should this be demonstrated, attention would be focused on the need actively to treat cancer-associated and cancer treatment-associated anaemia by any means.

Fatigue

One of the major symptoms associated with anaemia in cancer and its treatment, fatigue, has become a particular focus of interest. Cancer-related fatigue is defined by the National Comprehensive Cancer Network as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning".[28] The severity of the fatigue, and the fact that it is not relieved by rest, are key characteristics that distinguish it from the fatigue of everyday life. Several scales have been developed to measure fatigue, such as the Linear Analogue Self-Assessment (LASA) scale, the Piper Fatigue Self-Report (PFS) scale, Functional Assessment of Cancer Therapy (FACT) and the European Organisation for Research and Treatment of Cancer (EORTC).[29] The last two are general quality of life scales with specific subscales or sections devoted to capturing tiredness and fatigue. Care needs to be taken about what period patients are asked to refer to when considering their symptoms (last 4 weeks, last week or today).

Fatigue has been increasingly recognised as a pervasive symptom of cancer, with marked effects on a wide range of functions.[3,4] Volgezang and colleagues[30] report that responses to the question "How often in the past month have you felt fatigue or did you feel fatigue while undergoing treatment" in 419 patients, 49% of whom had received treatment more than 1 year, were as shown in *Table 4*.

Fatigue, as previously mentioned, is also an important symptom of anaemia; the more severe the anaemia, the greater the associated fatigue, as is indicated by the graphs taken from a study by Cella and colleagues[31] reporting responses to the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (F) (*Figure 1*). Although there is considerable overlap of FACIT-F scores there is a clear correlation between Hb level and fatigue.

TABLE 4 *Frequency of fatigue (Volgezang* et al.*[30])*

Frequency of fatigue	% of patients
Every day	32%
On most days	21%
At least once a week	14%
Only a few days each month	11%
Hardly ever	20%
Don't know	2%

The recognition that fatigue has a major impact in cancer, and that it is correlated with cancer-associated anaemia and cancer treatment-associated anaemia, has reinforced the view that reversal of anaemia may be of considerable benefit to patients. However, it is important to recognise that fatigue has many causes other than anaemia.[32] Accounts of cancer-related anaemia sometimes imply that it is synonymous with cancer-related fatigue, and this is not the case. Separation between the two is important because many cases of fatigue are not associated with anaemia and these are unlikely to respond to treatment for it. Furthermore, in those with anaemia, complete reversal of anaemia is unlikely to lead to complete relief of fatigue, as illustrated by a further graph in the study by Cella[31] (*Figure 2*). This shows that individuals with cancer but no anaemia have higher levels of fatigue than the general population.

Frequency of anaemia associated with cancer and cancer treatment

There is a consensus that cancer-associated anaemia is common. Attention has particularly focused on those cancers where chemotherapy is most commonly applied: solid tumours of the breast, lung, ovary and colon/rectum, and haematological malignancies such as leukaemia, non-Hodgkin's lymphoma (NHL), myelodysplasia and multiple myeloma. Myelodysplasia is characterised by marrow failure, and anaemia may be a major feature of the disease. Erythropoietin may be a useful treatment for anaemia in this setting, but has not yet received a licence for use in this indication, and intensive chemotherapy is indicated only in the later stages of the disease. For these reasons it is considered to be outside the scope of the NICE appraisal.

In a large, Europe-wide survey [European Cancer Anaemia Survey (ECAS)] with just under 15,000 cancer patients in 2001,[3] 39% had Hb <12 g dl^{-1} at enrolment, 10% had Hb <10 g dl^{-1} and 1% had Hb <8 g dl^{-1}. The proportions with low Hb at

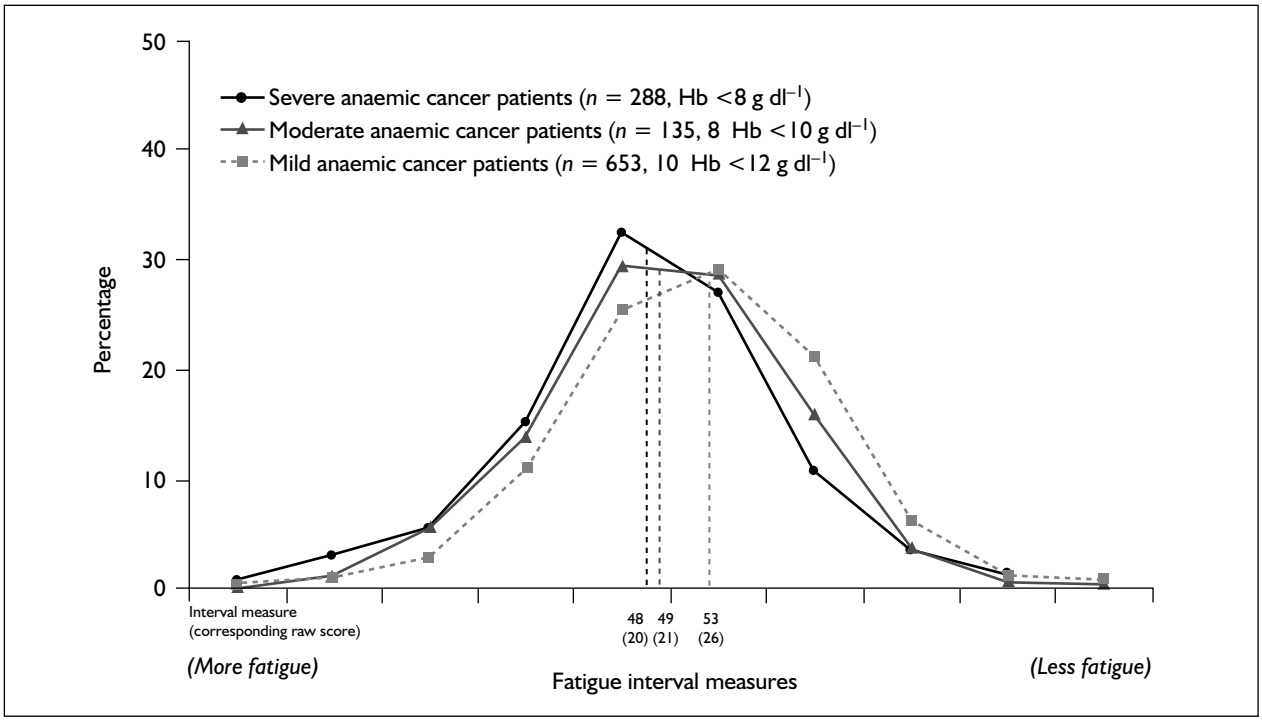

FIGURE 1 *Fatigue and anaemia in cancer patients (modified from Cella* et al.*, 2002.[31] Copyright 1996. American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.). Dotted vertical lines reflect the medians of each group. Means averaged in analysis of variance (ANOVA,* $F_{2291,2} = 18.03$, $p < 0.001$*) were: severe anaemia 7.3, moderate anaemia 49.6 and mild anaemia 52.6.*

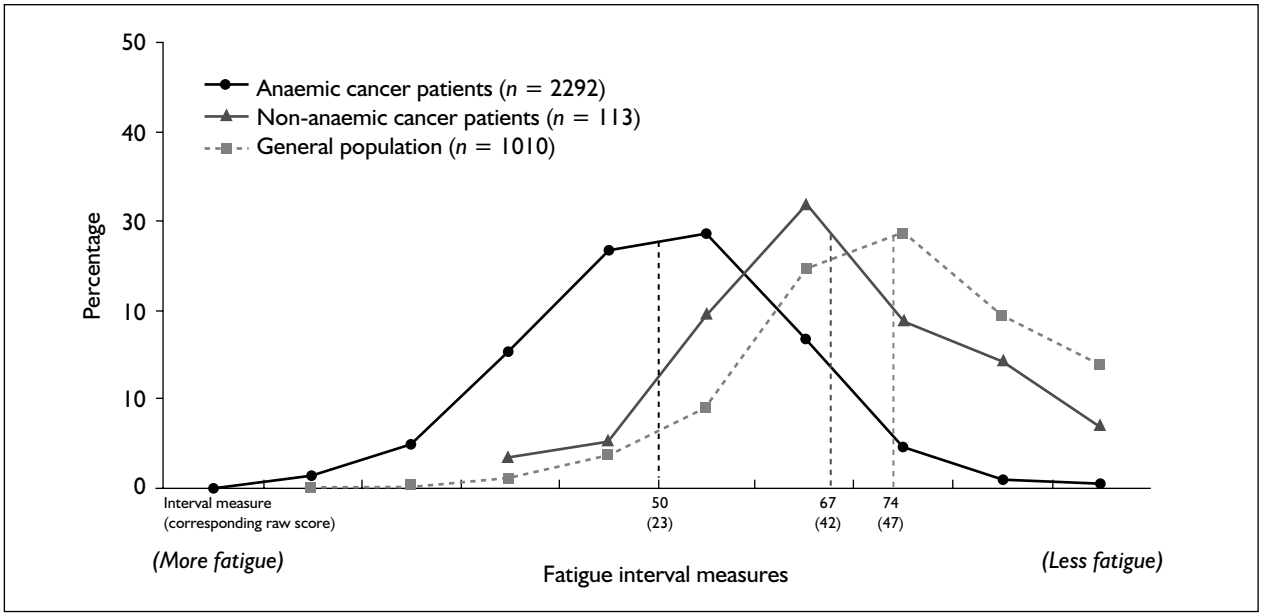

FIGURE 2 *Fatigue in cancer patients and the general population (modified from Cella* et al.*, 2002.[31] Copyright 1996. American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.). Dotted vertical lines reflect the medians of each group. Means averaged in ANOVA,* ($F_{3414,2} = 1087.5$, $p < 0.001$*) were: anaemia cancer patients 50.2, non-anaemia cancer patients 68.4 and general population 74.8.*

enrolment varied according to whether the patients were 'newly diagnosed, without treatment'. 'newly diagnosed, requiring treatment', 'persistent/recurrent' or 'in remission'. The highest rates of anaemia were in the 'persistent recurrent' group (49% with Hb <12 g dl^{-1}) with the lowest rates in 'newly diagnosed without treatment' (31% with Hb <12 g dl^{-1}). The rates were found to vary

TABLE 5 *Prevalence of anaemia by chemotherapy cycle*

Cycle	% Hb < 12 g dl^{-1} at any stage during survey	
	Ludwig and Strasser, 2001[3a]	Tchekmedyian, 2002[33b]
Initial/enrolment	39%	37%
1 39% + 17.9% of 61% =	50%	62%
2 39% + 34.3% of 61% =	60%	73%
3 39% + 42.0% of 61% =	65%	78%
4 39% + 46.7% of 61% =	67%	Not given
5 39% + 46.7% of 61% =	67%	Not given
6 39% + 62.7% of 61% =	77%	Not given

[a] Calculated from the rate of anaemia at enrolment (n = 14,379) plus the incidence rate in those who were not anaemic initially, but began to receive chemotherapy during the course of the survey (n = 2101).
[b] As presented in the study report (n = 350).

with tumour type. Lymphoma/myeloma and gynaecological cancers appear substantially higher, with the ECAS rate being 53% and 49%, respectively, with Hb <12 g dl^{-1}. Breast, head and neck, and urogenital cancers had rates below the average at enrolment (30%, 25% and 29%, respectively).

A base rate of anaemia prevalence of about 40% agrees with other surveys where the rates of anaemia in patients not receiving chemotherapy are recorded. Tchekmedyian[33] indicates that 37% had Hb <12 g dl^{-1} at baseline in an audit of 350 consecutive cancer chemotherapy patients. Barrett-Lee and colleagues[34] suggest that approximately 17% had Hb <11 g dl^{-1} at the outset of chemotherapy, in an audit involving just solid tumours, of which ovarian cancer had the highest rate (~25%).

Rates of anaemia rise during treatment, especially during chemotherapy. In ECAS,[3] values for 'ever anaemia' (any Hb measurement taken during a period below 12 g dl^{-1}, even if there were some above 12 g dl^{-1}) show that, from enrolment the frequency of patients developing anaemia rose slightly to 40% for those who did not receive cancer treatment at any time during the 6-month period of the survey. In the chemotherapy group this figure rose to 75%. This is cumulative by cycle, as demonstrated in *Table 5*. It should be noted, however, that interpretation of 'ever anaemic' figures is complicated by fluctuation in Hb level during the chemotherapy cycle. How an Hb value in the mild to moderate range is interpreted will depend on a clinical assessment of the time that the Hb is obtained relative to the predicted nadir following chemotherapy (usually 2 weeks, but may differ). For example, Hb of 10.5 g dl^{-1} close to the nadir is likely to be evaluated differently from the same Hb obtained during the recovery phase from chemotherapy.

This pattern of an increasing prevalence of minimum Hb is also seen in the study by Barrett-Lee and colleagues.[34] Here, with a cut-off of <11 g dl^{-1}, the percentage of patients who develop anaemia at any stage rises from 17, to 23, to 30, to 36, to 37 to 38%. The denominators, however, fall with each cycle. The importance of documenting anaemia that starts in later chemotherapy cycles is that it may be less amenable to treatment with erythropoietin, as chemotherapy may have been completed by the time it has begun to have an effect, usually after one or two cycles, if a response is seen (see below). Although most of the increase in anaemia during chemotherapy is likely to be due directly to the effects of chemotherapy, it should be remembered that an important subgroup of patients may be experiencing progressive disease despite treatment, and that this disease progression is the reason for worsening anaemia.

The extent of the rise of anaemia prevalence during treatment appears to vary slightly by tumour type. Ludwig and Strasser[3] found the increases in percentage of anaemia (Hb <12 g dl^{-1}) in those who were not anaemic at enrolment, and who received treatment during the 6 months of the survey, were greatest for lung cancer and gynaecological malignancies (71% and 65%, respectively). The overall figure for chemotherapy for all cancers was 63%.

Similarly, Tchekmedyian[33] identified different increases in percentage of anaemia (Hb <12 g dl^{-1}) over three cycles for some of the chemotherapy

regimens used frequently. Carboplatin plus paclitaxel, cyclophosphamide plus doxorubicin with or without docetaxel, and cyclophosphamide plus fluorouracil seemed to be particularly potent at inducing anaemia. However, no details of the regimens, particularly doses, were given. Groopman and Itri[1] attempted to disentangle the level of anaemia indicated by clinical trials data on various chemotherapy regimens. Problems with definitions and reporting, however, limited the amount that could be concluded specifically, beyond indicating that mild to moderate anaemia was a common consequence of many regimens.

Confounding variables are an important issue when interpreting the results of the surveys used to provide information on prevalence. Some of the most important are:

- age
- mix of cancers
- for each cancer, the mix of severity
- chemotherapy regimes used
- anti-anaemia treatments being used during chemotherapy.

There appear to be some important differences between the surveys in each of these respects, but particularly the last, where:

- Barrett-Lee and colleagues[34] were working in the UK, mainly during 1997, with probable minimal use of exogenous erythropoietin, relying mainly on transfusion
- Ludwig and Strasser[3] collected data across 24 European countries in 2001, and of those who received chemotherapy (n = 8590) 14% received exogenous erythropoietin (alone, or with transfusion, or with iron, or with both transfusion and iron)
- Tchekmedyian,[33] conducted a single-centre audit of consecutive cancer patients in the USA (n = 350) receiving chemotherapy between 2000 and 2002, of whom 55% received exogenous erythropoietin.

Finally, although surveys were identified that provided information on anaemia leading up to and during chemotherapy, no information was identified on how Hb changed following completion of chemotherapy. It seems likely that there will be a period of normalisation after the end of chemotherapy, during which Hb recovers, probably to the prechemotherapy level, possibly to a low normal level, depending on how successful the chemotherapy has been in controlling the cancer.

Relationship between cancer-associated anaemia and survival

Anaemia is well recognised as an adverse prognostic factor for survival in many cancers. Caro and colleagues[35] recently tried to summarise the evidence on any association using a systematic review and meta-analysis. This confirms that anaemia is negatively associated with survival in a wide variety of cancers such as lung, head and neck, myeloma, prostate and lymphoma. Some of this association is due to confounding in that tumours of greater severity/more advanced stage are present to a greater degree in the groups with anaemia than in those without. Thus, adjusted measures of association were smaller. Although the association does remain to some degree in many cancers, this does not imply causality.

Without demonstration of a likely causal relationship, doubt will remain on whether reversal of anaemia will lead to improvements in survival. Ultimately this will only come from RCTs of interventions to reverse anaemia showing survival benefit. The association between survival and anaemia, and theories as to why improved oxygenation could improve the response to anticancer treatment, however, provide support for such trial evidence to be pursued. Further, emerging evidence suggests that correction of anaemia may enhance the ability of radiation to damage cancer cells in solid tumours.[36]

Impact on the NHS

Notwithstanding considerable uncertainties about the amount of morbidity caused by cancer-associated and cancer treatment-associated anaemia, an estimation with conservative assumptions suggests that the impact on the NHS in England and Wales is important.

- The number of people with cancer in any year is around 1,000,000.
- The proportion receiving chemotherapy is 16%.
- 160,000 receive chemotherapy each year.
- The proportion with anaemia (Hb <12 g dl^{-1}) is 77% (anaemia will pre-date the start of chemotherapy in 39%).
- 123,200 have cancer chemotherapy-associated anaemia.
- The average duration of anaemia, based on data from Ludwig and colleagues[37] is 4.5 months or 0.38 years.
- There are 46,400 person-years of cancer treatment-associated anaemia (Hb <12 g dl^{-1}).

The overall impact that this constitutes requires a judgement as to the impairment that Hb <12 g dl^{-1}

represents (including moderate, severe and life-threatening anaemia subsumed within the category). The figure above, from work by Cella and colleagues[31] showing distributions of FACIT-F scores for anaemic cancer patients compared with both cancer patients and the general population, provides some assistance. It should be noted that the calculation above already incorporates any effect of the level of use of exogenous erythropoietin occurring in the Europe-wide survey (ECAS).[37]

Current management of anaemia associated with cancer treatment

An overview of the background literature and the views of the clinicians advising on this report suggested that there is variation concerning the clinical management of cancer treatment-associated anaemia in the England in 2004. The main components of care are described below. While there would be consensus that these are the main alternatives, each used to a greater or lesser extent, there would be variation in the degree to which each component would be pursued, particularly erythropoietin and RBCT. Indeed, it is important to appreciate this variation when interpreting the clinical trials identified in this review; in other words, to ask, "What level of 'normal care' was being practised in the control arm of RCTs?" Minimal transfusion support in the control arm would amplify the effect of erythropoietin on Hb and quality of life, but reduce its effect on transfusion requirements; higher levels of transfusion support would have opposite effects. This makes it important to know whether transfusion practice is applied equally in both the erythropoietin and the control arms of RCTs, and absence of a detailed RBCT protocol and/or blinding will increase the risk of bias.

Investigation of anaemia and treatment of identifiable remediable causes

Although important, the potential complexity of anaemia associated with cancer and the priority given to treatment of the cancer itself may mean that this is pursued to a variable degree.

Conservative, expectant management

All people with cancer will have their Hb measured, particularly if they are receiving treatment. The Hb levels will generally be reassessed with each cycle of chemotherapy, usually just before the next round of chemotherapy is due. Conservative management may rely on general avoidance of severe myelosuppression by delaying or reducing chemotherapy (usually in response to low WBCs and platelets, rather than low Hb) and the knowledge that blood counts will generally return to normal when chemotherapy is completed.

RBCT

Guidelines[8] on transfusion are permissive concerning use of RBCT, with no specific suggestions on appropriate or inappropriate trigger levels (Hb below which transfusion should be given). The British Committee for Standards in Haematology suggests, "red cell transfusions for patients with chronic anaemia should be given at intervals to maintain the haemoglobin just above the lowest concentration that is not associated with symptoms of anaemia …". The difficulty in identifying this level is acknowledged. However, in cancer treatment-associated anaemia most people would be transfused at Hb below 8 g dl^{-1}, and few at Hb above 12 g dl^{-1}. Decisions would be influenced by many factors, including the person's declared level of symptoms, the timing of the Hb level, whether they had benefited from transfusion previously and the patient's preference, taking into account risk and benefit and availability of hospital beds. These views are supported by the survey by Barrett-Lee and colleagues.[34] If pretreatment Hb was <10 g dl^{-1}, the probability of at least one transfusion at some point during the chemotherapy course was about 70%. Overall, 38% developed Hb <11 g dl^{-1} at some stage during six cycles of chemotherapy and 33% (n = 902) received at least one transfusion; 16% (n = 443) received more than one.

The average transfusion quantity in the audit by Barrett-Lee and colleagues[34] was 2.7 units. Twenty-five per cent of transfusions required inpatient admission, with a mean length of stay of 1.5 days. The predicted benefits of a 3-unit transfusion would be an improvement in Hb of 3 g dl^{-1} within 1 day, 2 g dl^{-1} at 30 days and 1 g dl^{-1} at 60 days. This assumes that the rate of destruction of RBCs is not altered. The net predicted effect on Hb would depend on the degree to which RBC production has been impaired by the cancer and/or cancer treatment. If it stopped completely, approximately 1 g dl^{-1} would be lost every 10 days, and the increment in Hb accruing from 3-unit transfusion offset in less than 30 days. There appears to be little information on the impact on patient symptoms that might be expected from any net changes in Hb. Studies such as those by Gleeson and Spencer,[38] albeit in the context of palliative care of cancer, lead to worthwhile improvements in symptoms that

persist for at least 14 days after transfusion. The clinical problems associated with blood transfusion are the general risks as listed above. Using SHOT data for 2003, preliminary estimations indicate that the total risk of serious hazard or major morbidity is approximately one in 100,000 transfusions (SHOT Office, Manchester) (also see *Table 3*). Cost analyses based on cancer patient data[39,40] suggest that minor reactions (e.g. fever, chills and inflammation) requiring symptomatic treatment (antihistamines, cold packs), but not necessitating stopping of the transfusion, may occur at a rate of approximately one in every ten transfusions. However, since 1999, all allogeneic blood components produced in the UK have been subjected to a prestorage leucocyte filtration process and the frequency of minor reactions appears to have been substantially reduced. Patient group submissions to NICE emphasise that time spent receiving the transfusion is likely to be an important negative factor for patients and carers where contact with medical services may already be frequent, especially if remaining survival is limited.

Treatment of the underlying cancer

Although probably not recognised as such, the universal and invariable component of the treatment of any cancer-associated anaemia is the treatment of the cancer itself, whether this be with curative or palliative intent. The success of the underlying treatment is thus likely to have an important effect on cancer-related anaemia. Considering this in detail is greatly complicated by the number of different cancers that may be relevant to this topic. It is also likely that different treatments for individual cancers will interact in varying ways with existing and new ways of managing cancer-related anaemia. A simple example is that the duration of chemotherapy cycles varies, with 3- and 4-week cycles being the two most common alternatives. Assuming that the general practice is to measure Hb before each new cycle of chemotherapy, whether this captures minimum, average or best Hb is likely to vary. Developing a patient pathway for different cancers was part of the development of the in-house economic model, and this in part considers the interaction between the cancer treatment regimen and management strategy for dealing with anaemia (see Appendix 1).

Erythropoietin

Exogenously administered erythropoietin is the new intervention under assessment. It is in addition to, rather than a complete replacement of the existing components of management. Blood transfusion in particular may still be required. Three types of recombinant human erythropoietin are currently available: epoetin alfa (Eprex®, Janssen Cilag), epoetin beta (NeoRecormon®, Roche) and darbepoetin alfa (Aranesp®, Amgen). All, like their endogenous counterpart, act as a mitosis stimulating factor and differentiating hormone, promoting the production of erythrocytes from precursors of the stem cell compartment. Epoetin alfa and epoetin beta are identical in their amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients. Darbepoetin alfa is a hyperglycosylated derivative of epoetin.[24]

It is worth noting that several guidelines concerning the current management of cancer-associated anaemia mention the potential value of erythropoietin.[4,8,41] The authors' clinical advisors confirm that this does not indicate that use of erythropoietin for cancer-associated anaemia is currently part of standard practice in the UK. Information on the degree to which it is used in the UK and other countries will be considered in detail in the next section.

Epoetin licensing indications relevant to UK practice

Treatment in renal failure is the main indication for exogenous erythropoietin, but is not discussed further.

Epoetin alfa is used for the treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).[42] The British National Formulary (BNF)-listed indication is for anaemia in adults receiving cancer chemotherapy.[24]

Epoetin beta is used for the "prevention of anaemia in adult patients with solid tumours and treated with platinum-based chemotherapy prone to induce anaemia (cisplatin ≥ 75 mg/m^2/cycle, carboplatin ≥ 350 mg/m^2/cycle). Also indicated for treatment of anaemia in adult patients with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, who have a relative erythropoietin deficiency and are receiving anti-tumour therapy. Deficiency is defined as an inappropriately low serum

erythropoietin in relation to the degree of anaemia".[43] It is licensed by the European Agency for the Evaluation of Medicinal Products (EMEA) for the prevention and treatment of anaemia in adult patients with solid tumours being treated with platinum-based chemotherapy.[24,44]

Darbepoetin alfa is indicated for patients with non-myeloid malignancies where anaemia is due to the effect of concomitantly administered chemotherapy.[45] The BNF-listed indication is for anaemia in adults with non-myeloid malignancies receiving chemotherapy.

It should be noted that the scope of the NICE appraisal focuses on the "treatment of cancer treatment-induced anaemia".[46] As such, the NICE appraisal is not considering some licensed indications such as the prevention of anaemia. It is also not considering use in cancer-associated anaemia not due to treatment, which is not a currently licensed use for any of the products, although research on effectiveness in this context has been conducted. For further information on the licence indications, see Appendix 2.

Product price

Note that at the time of writing this report the costs of the erythropoietin products appear to be under review and subject to change.

Epoetin alfa is available as Exprex (Janssen-Cilag). The net vial price is £335.20, where a vial = 1 ml (40,000 units). It is also available as a prefilled syringe with net prices of £8.38 =1000 units, £16.76 = 2000 units, £25.14 = 3000 units, £33.52 = 4000 units, £41.90 = 5000 units, £50.28 = 6000 units, £67.04 = 8000 units and £83.80 = 10,000 units.[24]

Epoetin beta is available as NeoRecormon (Roche). The net price for a prefilled syringe is £4.19 = 500 units, £8.38 = 1000 units, £16.76 = 2000 units, £25.14 = 3000 units, £33.52 = 4000 units, £41.90 = 5000 units, £50.28 = 6000 units and £83.80 = 10,000 units. It is also available as a powder for reconstitution at a cost of £419.01 = 50,000-unit vial and £838.01 = 100,000-unit vial (both with solvent). A RecoPen (for subcutaneous use) is also available for use with double-chamber cartridges at a net price of £83.80 = 10,000-unit cartridge, £167.60 = 20,000-unit cartridge and £502.81 = 60,000-unit cartridge.[24]

Darbepoetin alfa is available as Aranesp (Amgen). The net price for a prefilled syringe is £16.76 = 10 µg, £25.14 = 15 µg, £33.52 = 20 µg, £50.28 = 30 µg, £67.04 = 40 µg, £83.80 = 50 µg, £100.56 = 60 µg, £134.08 = 80 µg, £167.60 = 100 µg, £251.40 = 150 µg and £502.80 = 300 µg.[24]

Dosage and cost per treatment course

Calculations were done to give an impression of the cost of treating an average cancer patient, 70 kg in weight, undergoing erythropoietin treatment in the context of a 4-weekly chemotherapy regimen, lasting for six courses, with erythropoietin starting in the second cycle. Although increasing the dose is now recommended if there is no initial response, no increase in dose was assumed in the calculations.

The recommended initial dose of epoetin alfa is 150 units kg^{-1} three times weekly (a once-weekly regimen has recently been approved). This can be increased to 300 units kg^{-1} three times weekly if Hb does not increase by 1 g dl^{-1} after 4 weeks. A dose reduction of 25–50% is required if Hb rises by more than 2 g dl^{-1} per month. If Hb exceeds 14 g dl^{-1} epo should be stopped until Hb falls below 12 g dl^{-1}, at which epoetin alfa can be restarted at 75% of the original dose. The cost of a course of epoetin alfa treatment is £5028.

The recommended dose of epoetin beta is between 450 units kg^{-1} weekly (in three to seven divided doses) increased, if appropriate, to 900 units kg^{-1} weekly (in three to seven divided doses). The cost of a course of epoetin beta treatment is £5028.

The recommended dose of darbepoetin alfa is 2.25 µg kg^{-1} once weekly (can be given once every 3 weeks), with up to double this dose if no response to treatment is observed after 4 weeks. The cost of a course of darbepoetin alfa is £5028.

Additional activities may need to be considered in the wider costs of giving erythropoietin:

- measuring erythropoietin levels, particularly for epoetin beta
- drug administration, particularly for patients out of hospital, unable to give their own subcutaneous injections
- more frequent monitoring of Hb levels
- adjunctive iron supplementation[47]
- treatment of side-effects; see below for the possible nature of these.

Existing evidence

Existing systematic reviews of effectiveness

There has been a number of well-conducted systematic reviews of RCTs. However, the Cochrane review[48] was the most authoritative, independent and rigorous identified in 2004, when the protocol for this report was developed. It considered RCTs assessing the effectiveness of epoetin alfa and beta to the end of 2001; darbepoetin was not considered, because it was not licensed at the time. The Cochrane review builds on another influential systematic review by the Agency for Healthcare Research and Quality.[49] The Cochrane review's conclusions were:

> "There is consistent evidence that the administration of erythropoietin reduces the risk for blood transfusions and the number of units transfused in cancer patients. For patients with baseline haemoglobin below 10 g/dL there is strong evidence that erythropoietin improves haematological response. There is inconclusive evidence whether erythropoietin improves tumour response and overall survival. Research on side effects is inconclusive."

The Cochrane review considered the following adverse events:

- thrombotic events, e.g. deep vein thrombosis (DVT)
- hypertension
- haemorrhage/thrombocytopenia
- rash/irritation/pruritus (itching)
- seizures.

Their assessment was that the evidence was inconclusive. The impact on health-related quality of life (HRQoL) was not considered in detail.[48]

Further RCTs have been reported since the Cochrane review[48] was completed.

One important output of the Cochrane review[48] and other systematic reviews is a well-developed framework for considering the potential factors that may influence the effects of epo from one RCT to the next. These factors include:

- type of anaemia (treatment induced/not)
- Hb at study entry
- tumour type/stage
- age
- use of baseline erythropoietin levels
- quality of investigation of anaemia
- type of erythropoietin
- dose; most particularly, does the trial incorporate dose increase if no response is initially obtained (and what is the definition of no response)?
- iron supplementation (both arms/one arm of RCT; type)
- nature of normal care (thresholds for transfusion)
- time at which outcomes are measured
- quality of RCT (especially allocation concealment).

Of particular interest is the separation of those factors that will operate symmetrically between arms and those that are likely to operate asymmetrically.

Beyond RCTs, several large community trials have also been conducted, which have been widely cited and have been influential in shaping conclusions about effectiveness.[50–52] It should, however, be remembered that these studies are essentially case series assessing pre–post changes in haematological and quality of life outcomes.

Existing economic evaluations

There have been several economic evaluations of the cost-effectiveness, cost–utility and cost–benefit of exogenous erythropoietin. These studies are systematically reviewed as part of this report (see Chapter 5). However, a consistent observation by many observers, including those who are advocates of erythropoietin's clinical effects, is a concern about whether the cost is too high relative to the benefits demonstrated.[53–55] The continuing need for research on cost-effectiveness is highlighted in two key clinical guidelines.[56,57]

Improved targeting of exogenous erythropoietin is an important means by which cost-effectiveness can be improved. However, views are mixed as to whether such targeting is feasible. Ludwig and Fritz[58] suggest a number of predictive factors, such as blunted erythropoietin response and the presence of early changes following the start of exogenous erythropoietin. However, the recent EORTC guidelines[56] found limited evidence, and concluded: "There are no predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice …".

Clinical guidelines

American guidelines from 2002[57] recommend that erythropoietin should be a treatment option for patients with chemotherapy-induced anaemia who have an Hb of less than or equal to 10 g dl^{-1}, with RBCT used as a treatment option depending on the severity of the anaemia and clinical

circumstances. For patients with less severe anaemia (Hb between 12 g dl^{-1} and 10 g dl^{-1}), the decision to use erythropoietin immediately or to wait until Hb levels fall closer to 10 g dl^{-1} should be determined by clinical circumstances, as should the decision to use RBCT. European guidelines from 2004[56] continue to recommend the use of erythropoietin, but with a lower threshold for considering someone sufficiently anaemic to benefit: "In cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90 to 110 g/l based on anaemia-related symptoms."

Current usage

A survey conducted before the publication of the American Society of Clinical Oncology (ASCO) American Society of Hematology (ASH) guidelines found that the use of erythropoietin was higher in the USA than in other countries in Europe, Asia, Africa and the wider Americas.[59] Physicians who reported never using erythropoietin were more likely to practise in countries where the annual per capita healthcare expenditure was low, where a large proportion of healthcare costs was funded from public sources and where there was a national health insurance programme. In addition, infrequent use of erythropoietin was found before the initiation of the first cycle of chemotherapy, and infrequent use of prophylactic erythropoietin in patients who were not anaemic, although 38% of erythropoietin was given to patients with Hb above 10 g dl^{-1}. Using clinical vignettes in the survey, patterns of use were found to be similar among treatment regimens associated with curable versus incurable malignancies.

Specifically in the UK, it is claimed that use of exogenous erythropoietin in anaemic cancer patients is much lower than in other European countries, such as France, Germany, Italy and Spain. Unfortunately, although frequently cited, such as in a letter to the *BMJ*,[60] the source of these data remains unclear. Another article[61] claims to demonstrate marked variation in the percentage of cancer patients with Hb <10 g dl^{-1} being treated with exogenous erythropoietin in 2001/02 between cancer networks in England and Wales. How these data were derived is again not explained, but the national figures of 7% use for England and 10.5% for Wales are consistent with the impressions of the authors' clinical advisors, although it is likely that many departments will use erythropoietin for a smaller proportion of total patients.

Background summary

- Anaemia is a reduction in the number of RBCs circulating in the blood; the consequent reduction in Hb leads to reduced amounts of oxygen reaching the body, leading to a wide range of symptoms.
- Hb levels less than 13 g dl^{-1} are considered anaemic; 12 g dl^{-1} is also commonly used as a cut-off point.
- There is wide agreement that Hb < 6.5 g dl^{-1} represents life-threatening anaemia and Hb 6.5 to 7.9 g dl^{-1} severe anaemia.
- Anaemia associated with cancer and cancer treatment is an important problem, the size of which may not have been appreciated in the past.
- Current management consists of investigating anaemia and treating underlying causes, monitoring, blood transfusions and treating the cancer itself.
- Epoetin alfa, epoetin beta and darbepoetin alfa are exogenously administered erythropoietins that stimulate the bone marrow to increase production of RBCs in exactly the same way as the body's own erythropoietin.
- Systematic reviews of evidence of effectiveness up to the end of 2001 suggest that exogenous erythropoietin is effective in:
  - reducing the numbers requiring RBCT and the amount of RBCs transfused
  - increasing haematological response and Hb levels.
- Uncertainty remains about the effects of exogenous erythropoietin on quality of life and survival.
- There is also uncertainty about side-effects.
- The chief issue holding back the use of exogenous erythropoietin is the perceived high cost relative to the benefits.

Chapter 3

Effectiveness review methods

Assessment of clinical effectiveness

The aim was to review systematically the effectiveness of erythropoietin, with regard to its effectiveness in treating cancer-related anaemia, its effects on the patient regarding underlying malignancy and survival, effectiveness in improving quality of life and the impact of adverse events.

The project was undertaken in accordance with a predefined protocol.[62] There were no major departures from this protocol.

A scoping search was undertaken to identify existing reviews and other background material and to estimate the volume and nature of primary studies. Among this literature a recent well-conducted Cochrane review[48] was identified, which assessed the effectiveness of epoetin alfa and beta up to 2001.

It was agreed that the review commissioned by NICE for the effectiveness part of this HTA would build on the work of the Cochrane review. To this end, the main author from the Cochrane review (Dr Julia Bohlius) worked as a member of the team that produced this review to ensure consistency of review methods. Where the NICE remit differed from the Cochrane review remit, this was acknowledged and the methods were changed in accordance with this. To distinguish between studies included in the Cochrane review and studies identified during this piece of work, studies identified during the Cochrane review will be termed 'Cochrane studies' and studies newly identified during this piece of work commissioned by NICE will be termed 'Birmingham studies'.

Search strategy

As stated above, the Cochrane systematic review formed the basis of this review regarding epoetin alfa and epoetin beta, so the search strategy ran from 2000 onwards for these two drugs. In the case of darbepoetin alfa the search ran from 1996, the year before Phase I trials were initiated on it. Searches ended in September 2004, and studies identified after this date were acknowledged but not included in the analysis. There were no language restrictions (see Appendix 3 for search strategies).

The main purpose of the search was to identify comprehensively completed RCTs of erythropoietin. To this end the following sources were searched:

- bibliographic databases including Cochrane Library (CENTRAL), MEDLINE, EMBASE and the Science Citation Index (SCI)
- research registers of ongoing trials including the National Research Register, Current Controlled Trials metaRegister and ISRCTN database and ClinicalTrials.gov
- citation lists of relevant studies
- contact with experts in the field
- invited industry submissions
- conference proceedings.

Ongoing trials

A search for ongoing trials was also undertaken. Terms for the intervention (erythropoietin, epoetin, darbepoetin) and condition of interest (anaemia/anemia) were used to search the following trials registers: National Research Register 2004 Issue 2, Current Controlled Trials metaRegister, ClinicalTrials.gov, NCI PDQ database and International Cancer Research Portfolio for ongoing trials. Trials that did not relate to cancer-induced or chemotherapy-related anaemia were removed by handsorting. Finally, duplicates, identified via their study identification numbers where possible, were removed, leaving a final list of 29 potentially relevant trials. Searches were carried out on 5 July 2004. Trials that were in progress at the time of writing this report are described in Appendix 7.

Inclusion and exclusion criteria

Study design

Only RCTs were included. Non-randomised trials, in particular quasi-randomised trials, such as where allocation is based on date of birth or day of month, were excluded. Also excluded were RCTs with fewer than ten patients in any study arm.

Population

Patients had to be diagnosed with malignant disease, using clinical and histological/cytological criteria (any type of malignant disease was

included, irrespective of stage or previous therapy); trials in patients with anaemia resulting from chemotherapy and/or radiotherapy or underlying malignant disease were included. Other causes of anaemia such as haemolysis, iron deficiency and occult bleeding should have been excluded in the participants of the included trials. There were no age restrictions; however, it is recognised that the licences for all three drugs do not cover erythropoietin use in children. Studies where erythropoietin was given in the context of myeloablative chemotherapy ahead of bone marrow or peripheral blood stem cell transplantation, or for short-term preoperative treatment to correct anaemia or to support collection of autologous blood before cancer surgery, were excluded.

Intervention

Interventions with epoetin alfa (Exprex, Ortho Biotec), epoetin beta (NeoRecormon, Roche) or darbepoetin alfa (Nesp Amgen) were studied. Concomitant anaemia therapy such as iron or granulocyte colony-stimulating factor (G-CSF) supplementation was permitted, as was RBCT.

Comparator

In the Cochrane review[48] any comparator was acceptable provided that the only difference between the treatment and control arms was the use of erythropoietin. However, at the NICE consultee meeting on 2 September 2004, after discussion, it was felt that there may be trials in which concomitant supportive anaemia treatments such as G-CSF or iron supplementation had been given to patients receiving erythropoietin, but not to patients in the control arm, which if excluded would cause valuable information to be lost. It was therefore agreed to include these trials, but also to acknowledge that these trials have different comparators to trials where concomitant supportive anaemia treatments are given to patients equally in each arm of the trials.

It was anticipated that comparators would be either placebo or best supportive care. In both, it was anticipated that RBCT would be given when a patient's Hb fell to an unacceptably low level. Ideally, a protocol for when RBCT should be instigated should have been described (i.e. 'transfusion trigger'). The same rules on rescue regarding RBCT should also have been applied in the erythropoietin arm.

Outcomes

Outcomes sought from the studies fell into four categories: anaemia-related outcomes, malignancy-related outcomes, adverse events data and patient-specific outcomes such as quality of life outcomes and patient's preferences.

- Anaemia-related outcomes: haematological response to treatment [defined as a transfusion free increase of Hb of ≥ 2 g dl^{-1} or a haematocrit (Hct) increase of 6%]; mean Hb change; RBCT requirements, including number of patients transfused, number of units transfused per patient and number of units transfused per patient per 4 weeks.
- Cancer-related outcomes: tumour response and overall survival.
- Adverse events: hypertension, rash/irritation, pruritis, mortality, thrombic events, seizure, haemorrhage/thrombocytopenia, fatigue and pure red cell aplasia. (Pure red cell aplasia was included as a specific adverse event after discussion at the NICE committee meeting on 2 September 2004.) A note was made of other adverse events described within the trial reports.
- Quality of life: data on validated quality of life measures was sought, anticipated quality of life measures would include FACT [including FACT-General (G), FACT-Fatigue (F) and FACT-Anaemia (An)]; however, notes were made of any HRQoL measure if reported.
- Patient preference: within the NICE scope it was requested that patient preference data were sought. It was, however, anticipated that accurate information on patient preference would be scant given that RCT data were the source of effectiveness data within this review.

Making inclusion/exclusion decisions

Two reviewers (from JB, SB, JS and JW) independently extracted data from the Birmingham studies using a predesigned data extraction form. For consistency with the Cochrane review[48] the data extraction was based on the original Cochrane data extraction form and data for outcomes of haematological response (HaemR), Hb change and RBCT were identical to those sought by the Cochrane review. For HRQoL and survival outcomes a more detailed extraction form than that used in the Cochrane review was used. Disagreements were resolved by discussion, consulting with a third party where interpretation was difficult. Data from studies with multiple publications were extracted and reported as a single study; in the case of reported discrepancies the most recent publication was used. Data reported here derived from the Cochrane studies were obtained from the Cochrane review[48] unless otherwise stated.

TABLE 6 *Quality assessment*

Treatment allocation	1. Was allocation truly random? Yes: random numbers, coin toss, shuffle, etc. No: for patients number, date of birth, alternate Unclear: if the method not stated 2. Was treatment allocation concealed? Yes: central allocation at trials office/pharmacy, sequentially numbered coded vials, other methods where the trialist allocating treatment could not be aware Inadequate: allocation was alternate, or based on information known to the trialist Unclear: insufficient information given
Similarity of groups	3. Were the patients' characteristics at baseline similar in all groups?
Implementation of masking	4. Was the treatment allocation masked from the participants? (either stated explicitly or an identical placebo used) 5. Was the treatment allocation masked from clinicians?
Completeness of trial	6. Were the numbers of withdrawals, dropouts and lost to follow-up in each group stated? 7. Did the analysis include an ITT or were less than 10% of study arm excluded?

ITT, intention-to-treat.

Two reviewers independently assessed quality for the Birmingham studies judged on the criteria in *Table 6* (taken from the assessment used in the Cochrane review[48]).

For the outcome HRQoL, it is important that Hb values are masked from the patients; this information was noted for the relevant studies.

Methods of analysis/synthesis

A descriptive analysis of included studies was undertaken, and relevant evidence categorised and summarised in tables. Where appropriate, in the absence of substantial clinical and statistical heterogeneity, results from individual studies were quantitatively pooled by meta-analysis (using MetaView 4.1; Cochrane Collaboration). Identified research evidence was interpreted according to the assessment of methodological strengths and weaknesses and the possibility of potential biases. Publication bias for the main outcomes was assessed using funnel plots.

The following subgroup analyses were undertaken:

- study quality: publication type; allocation concealment
- degree of anaemia: Hb at study entry (mean/median <10 g dl^{-1} versus 10–12 g dl^{-1} versus >12 g dl^{-1} as used in the Cochrane review[48])
- underlying malignancies and therapy: tumour type (solid tumours versus haematological versus myelodysplastic syndrome); tumour therapies (platinum-based chemotherapy, non-platinum-based chemotherapy, radiotherapy or no malignancy therapy)
- differences in intervention: erythropoietin agent (epoetin alfa, epoetin beta or darbepoetin alfa); drug doses; use within licensed indications
- concomitant treatments: G-CSF or iron supplementation; transfusion triggers.

The χ^2 test for interaction is presented (test for heterogeneity between groups) and in addition the more exacting F test, which compares the amount of the total heterogeneity falling between groups with that remaining within the groups (essentially a univariate meta-regression). Where there is substantial heterogeneity in the overall data set, high values of F suggest that the characteristic may help to explain that heterogeneity.

The protocol also stated that an exploration of relative erythropoietin deficiency/baseline erythropoietin levels and whether the trial was powered to assess survival outcomes versus trials not powered specifically for this outcome would be undertaken. Owing to time constraints these were not examined.

The general purpose of the subgroup analyses was to form part of a sensitivity analysis to test the robustness of the data and interpretation of results and/or for exploring heterogeneity.

Chapter 4

Effectiveness results

Studies identified

The electronic search yielded 912 titles. Among this number were 131 reviews, of which nine were systematic.

Seventy-six potentially relevant primary studies were excluded on the basis of title and abstract and an additional 20 studies were excluded after scrutiny of the full publication (see Appendix 3). For 38 titles the reviewers could not completely rule out that they did not meet the inclusion criteria, because only vague titles and no abstracts were given. These are listed as unsures (Appendix 3).

From the electronic search therefore 27 relevant new publications were identified, reporting the results of 19 trials. Three trials had multiple publications associated with them;[63–65] a full list can be found in Appendix 4.

Citations of the included studies were also searched by a single reviewer (JW), as were the industry submissions to NICE, November 2004 (JW). This search revealed two additional trials not identified by the electronic search. In addition, the ASH and ASCO websites were searched for abstract publications by a single reviewer (JB), as was the Food and Drug Administration (FDA) report (JB). From searching the ASH/ASCO abstract database 23 potentially relevant trials were identified (*Table 7*). Of these, three were already included in the review,[50,90,91] five were classified as ongoing trials,[72,73,75,81,87] three were included in the review[71,77,78] and two met the inclusion criteria but were identified too late to be incorporated into this review's analysis.[67,83] Nine trials were identified from a report produced by the FDA[92] which investigated safety concerns (*Table 8*). Only two of these were identified elsewhere; one was trial PR00-03-006, which was identified during the search for ongoing trials, and the other was the Vansteenkiste trial.[64]

Ongoing trials

Twenty-nine references to ongoing trials were identified. An addendum describing these trials was submitted to NICE ahead of the first appraisal committee meeting and is included in Appendix 7 of this report.

Included trials

The number of trials found that met the inclusion criteria were:

- Cochrane review: 27 trials were included in the Cochrane review (*Table 9*). Fourteen trials used epoetin alfa, nine epoetin beta, one either epoetin alfa or beta and three an unknown type.
- Update of epoetin alfa and beta searches: 14 new trials were identified, 13 of which were on epoetin alfa and one on epoetin beta (*Table 10*).
- Darbepoetin alfa searches: five trials were identified (*Table 10*).

The Cochrane review[48] included a total of 3287 patients. Altogether there were 4017 patients evaluated in the trials identified by the Birmingham update. Seven trials had fewer than 100 patients and the remaining had over 100, with the largest sample size being 939 from Leyland-Jones.[118] All of the included abstract publications reported trials with a substantial sample size (*Table 10*).

The total number of included trials in this review was therefore 46, with a total of 7304 patients. Nine trials were split into subsets for analysis purposes[90,91,97,104,107,112,113,123,124]

Study design

All included studies were RCTs.

Intervention

Of the total 46 included trials, 27 evaluated epoetin alfa, ten evaluated epoetin beta and five evaluated darbepoetin alfa. There were three trials where it was uncertain as to the brand of erythropoietin used and one trial in which either epoetin alfa or beta was used.

Dose

The current licensed dose for epoetin alfa is 450 IU kg^{-1} per week (given in three divided doses or, as of October 2004, as a once-weekly dose); for epoetin beta the licensed dose is 450 IU kg^{-1} per week (given in three to seven divided doses). The maximum licensed dose for both epoetin alfa and beta is 900 IU kg^{-1} per week. For darbepoetin alfa

TABLE 7 *ASH/ASCO abstract search*

Study	Characteristics	Results	Comments
Arslan, 2002[66] (ASCO)		Shows Hb rise per chemotherapy cycle; patients were started on epo alfa: (1) beginning of chemotherapy, (2) patients whose Hb had decreased by 1 g after start of chemotherapy, and (3) patients who became anaemic at the third cycle. Groups 2 and 3 were then split so that half received epo for all treatments and the other half for 12 weeks	Author contacted, does not fit inclusion criteria
Bassem, 2004 (ASH)		Duplicate of Razzouk[67] (ASCO, 2004), see below for details	
Beggs, 2003[68] (ASCO)	NSCLC: HRQoL, FACT-An and PFS; also looked at IL-6 as a marker for fatigue. Survival data, HRQoL, Hb	n = epo 11 patients, control 10 patients. Hb data not usable, survival epo patients 15.1 months, placebo 6 months, $p = 0.12$	Excluded: only 10 patients in control arm
Bindi, 2004[69] (ASCO)	Darbepoetin, 42 patients, 3 groups, darbepoetin 2.2 μg kg^{-1} per week, rHuEPO 450 IU kg^{-1} per week (3× per week), control. Time evaluated: 0, 4, 8 weeks	Baseline Hb (8 weeks) Darbepoetin: 8.9 g dl^{-1} (10.8 g dl^{-1}) rHuEPO: 9.5 g dl^{-1} (10.9 g dl^{-1}) Control: 10.5 g dl^{-1} (9.7 g dl^{-1}) No SD, therefore not included in meta-analysis	Author contacted, classified as 'pending'
Blayney, 2003[70] (ASH)		Unsure whether there is a control group; not obvious in abstract	Author contacted, classified as 'pending'
Blohmer, 2003[71] (ASCO) Classified as ongoing in Cochrane	Cervical cancer: epo alfa, patients given chemotherapy and radiotherapy, aim of study to look at tumour response in relation to the radiotherapy. Looked at transfusion requirement, Hb increase, relapse-free survival – primary end-point	n = 128 epo, 128 control; epo received iron, control just RBCT. RBCT = intervention. 10% vs 32% ($p = 0.0002$), 42% of intervention. Patients without anaemia through treatment period (cycle 4), control 12%. Mean Hb change: intervention. 12 to 12.2, control 11.9 to 11	Included, data in RBCT Author states that one thrombotic event occurred (personal communication)
Chang, 2002[72] (ASCO)	Epo alfa, breast cancer, chemotherapy. Hb ≤ 12 g dl^{-1}, 40 000 IU once weekly, 16 weeks of treatment. HRQoL	Interim analysis: ongoing trial	Ongoing trial
Charu, 2003[73] (ASH)			Ongoing trial
Crawford, 2003[74] (ASCO)			Excluded, because control patients received epo if Hb <10 g dl^{-1}
Famoyin, 2004[75] (ASCO)			Ongoing trial
Glaspy, 2002[76] (ASH)			Already included in review

continued

TABLE 7 *ASH/ASCO abstract search (cont'd)*

Study	Characteristics	Results	Comments
Henze, 2002[77] (ASCO)	RBCT in children, receiving chemotherapy, ALL (37%), or non-ALL cancers. 600 or 900 IU kg^{-1} per week for 20 weeks. RBCT after 4 weeks to end of study. Days to first transfusion after 4 weeks, volume of transfusion, Hb change, no. units and no. transfusion episodes	$n = 232$ patients. All patients: intervention 62% RBCT, control 69%. ALL patients: intervention 66%, control 89%. Non-ALL patients: intervention 56%, control 60%. All other outcomes significantly better for ALL but not for non-ALL	RBCT included in review
Janinis, 2003[78] (ASCO)	Epo alfa, 30,000 IU per week (3× per week), iron both sides. HRQoL FACT-An. Not licensed dose	327 patients evaluable, tumour response, median Hb baseline 10.5 g dl^{-1}, no transfusion, intervention 9%, control 23% ($p < 0.0001$). Most of the other data are HRQoL	RBCT included in review, other data not included as difficult to tell what they are referring to
Kotasek, 2002[79] (ASCO)			Already included in review
Marinaccio, 2003[80] (ASCO)			Surgery, therefore excluded
O'Shaughnessy, 2002[81] (ASCO)		Unclear; possible interim analysis	Ongoing trial
Razzouk, 2004[67] (Related to Bassem, 2004, ASH)	Children 5–18 years, epo alfa, Hb, HRQoL, mixed	222 patients, (intervention 111, control 111), Hb improvement ($p = 0.012$), no figures given. Transfusion-free figures: epo 36%, control 23%, improvement in HRQoL in age group 5–7 years. Primary end-point was HRQoL	Missed in analysis of RBCT and Hb change, few data reported
Recasens, 2003[82] (ASH)		Unclear whether epo arm received transfusions, therefore include?	No extractable data, full-text publication is expected soon
Savonije, 2004[83] (ASCO)	$n = 315$ (epo 211, control 104), patients on chemotherapy, solid tumour. HRQoL, HaemR	HaemR: intervention 69%, control 31%	Not included in review as thought it was after the review search deadline
Silberstein, 2002[84] (ASCO)		ASCO 2002, belongs to Witzig 2004[85]	Ongoing trial of Witzig which was published outside the search dates, therefore analysis not included in this review
Smith, 2002[86] (ASCO)			Already included in review
Straus, 2002[87] (ASH)			Ongoing trial
Vadhan-Raj, 2004[88] (ASH)	Survival trial, debatable whether it meets inclusion criteria in that patients had 16 weeks of epo followed by surgery, lots of thrombo-embolic events, attributed to epo alfa		Author contacted, classified as 'pending'
Witzig, 2004[85] (see also Silberstein, 2002[84] (ASCO) and Sloan, 2002[89] (ASH)		Published after the Birmingham search	Published after the Birmingham search

ALL, acute lymphocytic leukaemia; NSCLC, non-small cell long cancer; rHuePO, recombinant human erythropoietin.

TABLE 8 *Additional trials identified from the FDA report*[92]

Trial ID	Comment
EPO-CAN-15	SCLC undergoing chemotherapy and radiotherapy, randomised for erythropoietin alfa, belongs to LEGACY trial
EPO-CAN-20	NSCLC undergoing chemotherapy and radiotherapy, randomised for erythropoietin alfa
EPO-GBR-07	Head and neck cancer undergoing radiotherapy, randomised for erythropoietin alfa
GOG-191 PRO1-04-005	Cervical cancer undergoing chemotherapy and radiotherapy, randomised for erythropoietin alfa
NESP 980297	Belongs to Vansteenkiste, 2002[64]
NG-93-004	SCLC undergoing chemotherapy and radiotherapy randomised for erythropoietin alfa
PR00-03-006	Gastric rectal cancer undergoing chemotherapy and radiotherapy, randomised for erythropoietin alfa
PR98-27-008	Mixed cancer population, randomised for erythropoietin alfa
RT0G-99-03	Head and neck cancer undergoing radiotherapy, randomised for erythropoietin alfa

Included study characteristics: descriptions are for all included studies including those identified in the Cochrane review; however, the data regarding the Cochrane studies were obtained from the Cochrane review[48] only and not from the original published papers, with the exception of transfusion triggers.
SCLC, small cell lung cancer.

the licensed dose is 2.25 μg kg^{-1} in a once-weekly dose or 6.75 μg kg^{-1} once every 3 weeks. The maximum dose is 4.5 μg kg^{-1} per week.

Within the included trials, 14 were within the epoetin alfa licensed doses; of those that were not, eight had fixed weekly doses,[75,120,121,125–128,130] one was higher than the licensed dose,[129] two were lower than the recommended dose,[93,95] two publications did not report the dose given[71,118] and two studies were in the unlicensed population of children.[67,77] Most of the trials that gave a fixed dose were identified from the Birmingham studies.

For epoetin beta, six trials were within the licensed dose; of those that were not, two gave fixed doses,[97,108] one gave a dose lower than the licence indication,[104] but this was within a dose-finding study, and one trial[117] gave a dose that is under the current licence indications recommended for autologous blood collection treatment, not anaemic cancer patients.

For darbepoetin alfa, two trials were dose-finding trials[90,122] and therefore included interventions that had doses under and over the current licence recommendation. Smith[91] had doses outside the current licence in relation to the periods that the drug is given (over 4 weeks instead of 3 weeks); this left three trials of darbepoetin alfa with doses within the licence indication.

Duration of erythropoietin treatment and duration of study

The majority of the trials gave erythropoietin therapy over the course of the chemotherapy, with many continuing with erythropoietin therapy for 4 weeks after chemotherapy, which is permissible within the licence indications. As some courses of chemotherapy are of variable duration depending on when the patient received erythropoietin and how they tolerate the chemotherapy, the duration of erythropoietin therapy for individual patients in the trials was variable, leading to some trials reporting the median duration of the erythropoietin therapy. The average time on erythropoietin treatment was 12 weeks, with trial duration clustering around 12–16 weeks.

Concomitant treatments

There were several possible concomitant treatments; these were G-CSF, iron supplementation and RBCT, with some protocols giving recommendations for when transfusions should be given (referred to in this review as transfusion triggers). Only one trial was identified that gave G-CSF;[121] in this trial G-CSF was given with erythropoietin during the first 12 weeks of the trial, and if patients responded they continued to use G-CSF for the remainder of the trial, which was a further 52 weeks.

Three trials were identified in which concomitant iron supplementation was given only to patients

TABLE 9 *Characteristics of included studies: Cochrane review included studies*

Study	*n*	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought
Abels, 1993[93]	124	Epo a	Placebo	Mixed	None	No	HaemR, RBCT
Carabantes, 1999[94]	35	Epo a	Standard	Solid	Chemo: plat	Yes	HaemR, RBCT, HRQoL
Cascinu, 1994[95]	100	Epo a	Placebo	Solid	Chemo: plat	Yes	HaemR, Hb, RBCT, AE
Case, 1993[96]	157	Epo a	Placebo	Mixed	Chemo: non plat	Yes	HaemR, RBCT, HRQoL, AE
Cazzola, 1995[97] c,d	112	Epo b	Standard	Haem	Chemo: non plat	No	HaemR, Hb, RBCT, AE
Coiffier, 2001[65]	262	Epo b	Standard	Mixed	Chemo	No	HaemR, Hb, RBCT, HRQoL
Dammacco, 2001[98]	145	Epo b	Placebo	Haem	Chemo: plat	Yes	HaemR, Hb, RBCT, HRQoL, AE
Del Mastro, 1997[99]	62	Epo (?)	Standard	Solid	Chemo	Unsure	Hb, RBCT, HRQoL, AE
Dunphy, 1999[100]	29	Epo (?)	Standard	Solid	Chemo: plat	Unsure	Hb, RBCT
Henke, 1999[101] a,b,c	50	Epo a or b	Standard	Solid	Radio	No	HaemR, Hb
Henry, 1994[102]	132	Epo a	Standard	Mixed	Chemo: plat	Yes	HaemR, RBCT, HRQoL, AE
Italian Cooperative Study Group, 1998[103]	87	Epo a	Placebo	MDS	None	No	HaemR, Hb, RBCT, AE
Kunikane, 2001[104] a,b	53	Epo b	Placebo	Solid	Chemo: plat	No	Hb, RBCT,
Kurz, 1997[105]	35	Epo a		Solid	Chemo: plat	Yes	HaemR, RBCT
Littlewood, 2001[63a] (see Appendix 4)	375	Epo a	Placebo	Mixed	Chemo: non-plat	Yes	HaemR, Hb, RBCT, HRQoL, AE
Oberhoff, 1998[106]	218	Epo b	Standard	Solid	Chemo: plat	No	HaemR, Hb, RBCT, AE
Österborg, 1996[107] a,b	144	Epo b	Standard	Haem	Chemo: non-plat	No	HaemR, Hb, RBCT, AE
Österborg, 2002[108]	343	Epo b	Placebo	Haem	Chemo: non-plat	Yes	HaemR, Hb, RBCT, AE
Quirt, 1996[109]	54	Epo a	Placebo	Mixed	Chemo	Yes	Hb, RBCT, HRQoL
Rose, 1994[110]	221	Epo a	Placebo	Haem	Chemo	No	HaemR, RBCT, HRQoL
Silvestris, 1995[111]	54	Epo a	Standard	Haem	Chemo	Yes	HaemR, AE
Ten Bokkel, 1998[112] a,b	120	Epo b	Standard	Solid	Chemo: plat	Yes	RBCT, TR, AE
Thatcher, 1999[113] a,b	130	Epo a	Standard	Solid	Chemo: plat	Yes	Hb, RBCT, HRQoL, AE
Thompson, 2000[114]		Epo a	Placebo	MDS	None	No	HaemR, Hb, RBCT
Throuvalas, 2000[115]	55	Epo (?)	Standard	Solid	Chemo: plat + radio	No	Hb, RBCT
Welch, 1995[116]	30	Epo a	Standard	Solid	Chemo: plat	Yes	Hb, RBCT, AE
Wurnig, 1996[117]	30	Epo b	Placebo	Solid	Chemo: mixed	No	Hb, RBCT, AE

AE, adverse event; chemo, chemotherapy; Haem, haematological; MDS, myelodysplastic syndrome; plat, platinum-based chemotherapy; radio, radiotherapy; TR, tumour response.
[a] Although the trial is mixed, the results are reported separately for solid and haematological tumours.

TABLE 10 *Characteristics of included studies: update 2001 to September 2004 (Birmingham)*

Study	*n*	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes
Aravantinos, 2003[119]	47	Epo a	Standard	Solid	Chemo: plat and non-plat	Yes	Hb, Hct, RBCT
Bamias, 2003[120]	144	Epo a	Standard	Solid	Chemo: plat	No	Hb, RBCT (HRQoL in a subset)
Blohmer, 2003[71]	256	Epo a	NR	Solid	Chemo + radio	No	HaemR
Casadevall, 2004[121]	60	Epo a		MDS	NR	No	HaemR, HRQoL, also a cost study
Hedenus, 2002[122] a,b,c	66	Darb a	Placebo	Haem	Chemo	No	HaemR, Hb, RBCT
Hedenus, 2003[123]	349	Darb a	Placebo	Haem	NR	No	HaemR, Hb, RBCT (week 5 to end), AE, HRQoL
Henke, 2003[124]	350	Epo a	Placebo	Solid	Radio	No	HaemR, Hb, AE, tumour
Henze, 2002[77]	232	Epo a	NR	Mixed	Chemo	No: children	HaemR
Huddart, 2002[125]	180	Epo a	Standard	Solid	Chemo: platinum	No	HaemR, Hb, HRQoL (FACT-An)
Iconomou, 2003[126]	112	Epo a	Standard	Solid	Chemo: plat non-plat	No	HaemR, Hb, RBCT, HRQoL
Janinis, 2003[78]	372	Epo a	Standard	Solid	Mixed, plat and non-plat chemo	No	HaemR
Kotasek, 2003[90] a,b,c,d,e,f	217	Darb a	Placebo	Solid	Chemo	No	HaemR, Hb, RBCT, HRQoL
Leyland-Jones, 2003[118]	939	Epo a	Placebo	Solid	NR	No	Survival, AE
Rosen, 2003[127]	90	Epo a	Standard	Solid	Chemo + radio	No	Hb, RBCT
Rosenzweig, 2004[128]	27	Epo a	Standard	Solid	Chemo	No	Hb, HRQoL, AE, survival
Smith, 2003[91] a,b,c	86	Darb a	Placebo	Mixed	None	No	HaemR, Hb, RBCT, AE,
Sweeney,1998[129]	48	Epo a	Standard Iron not given	Solid	Radio	No	HaemR, AE, HRQoL
Thomas, 2002[130]	127	Epo a	Standard	NR	Chemo	No	HaemR, RBCT, HRQoL
Vansteenkiste, 2002[64]	314	Darb a	Placebo	Solid	Chemo: plat	Yes	HaemR, Hb, RBCT, HRQoL, AE, disease progression and survival

darb, darbepoetin; Epo, epoetin; NR, not reported.

TABLE 11 *Malignancies included in trials*

Malignancy	Mixed types	Specific malignancies
Solid tumours	Janinis, 2003;[78a] Araventinos, 2003;[119a] Bamias, 2003;[120a] Huddart, 2002;[125a] Iconomou, 2003;[126a] Sweeney, 1998;[129a] Vansteenkiste, 2002;[64a] Cascinu, 1994;[95] Henke, 1999;[101] Kurz, 1997;[105] Oberhoff, 1998[106]	Henke, 2003[124a] (head/neck); Rosen, 2003[127a] (head/neck); Leyland-Jones, 2003[118a] (met breast); Rosenzweig, 2004[128a] (met breast); Del Mastro, 1997[99] (breast); Carabantes, 1999[94] (lung/ovary); Dunphy, 1999[100] (NSCLC); Kunikane, 2001[104] (NSCLC); Thatcher, 1999[113] (NSCLC); Ten Bokkel, 1998[112] (ovary); Welch, 1995[116] (ovary); Blohmer, 2003[71a] (cervical); Throuvalas, 2000[115] (cervix/bladder); Wurnig, 1996[117] (Ewing's osteosarcoma)
Haematological	Hedenus, 2002;[122a] Hedenus, 2003;[123a] Cazzola, 1995;[97] Dammacco, 2001;[98] Österborg, 1996[107]	Rose, 1994[110] (CLL); Silvestris, 1995[111] (MM)
Mixed solid and haematological	Smith, 2003[91a] Abels, 1993;[93] Case, 1993;[96] Coiffier, 2001;[65] Henry, 1994;[102] Littlewood, 2001;[63] Quirt, 1996;[109]	
MDS	Casadevall, 2004;[121a] Italian Cooperative Study Group, 1998;[103] Thompson, 2000[114]	
NR	Thomas, 2002[130a]	

[a] Birmingham studies.
CLL, chronic lymphocytic leukaemia; met, metastatic; MM, multiple myeloma; NR; not reported.

receiving erythropoietin.[71,127,129] In the rest of the trials iron was given as a fixed dose, or patients were given iron as required, or iron dosing was not reported. Subgroup analysis was undertaken on these variables within the meta-analysis.

More details regarding dose, duration, types of chemotherapy and malignancy types are given in the subgroup analysis for each of the outcomes described.

Population characteristics

Population characteristics of the included trials are summarised in *Tables 11* and *12*; characteristics are described in more detail in Appendix 5. Two trials (both reported in abstract format) were conducted in children.[67,77] Henze[77] did not give an age range, while Razzouk[67] included children from 5 to 18 years of age. Trials with adult populations had an age range of 18–85 years. There was an even spread of gender throughout the trials, with the obvious exception of those trials specifically with patients with gynaecological and breast malignancies; within the breast malignancies all patients were female. There was a variety of malignancies (*Table 11*): 11 trials had patients with a mix of solid tumours, while 14 trials concentrated on specific solid tumour types (head/neck $n = 2$, breast $n = 3$, lung/ovary $n = 1$, NSCLC $n = 3$, ovary $n = 2$, cervical $n = 1$, cervical/bladder $n = 1$ and Ewing's osteosarcoma $n = 1$). There were five trials with a mix of haematological malignancies, with two trials concentrating on specific types (CLL $n = 1$, MM $n = 1$). Seven trials had patients with either solid or haematological tumours, three trials included patients with MDS and one trial did not report the malignancy type. Malignancy treatments consisted of chemotherapy (platinum based and non-platinum based), chemotherapy plus radiotherapy, radiotherapy alone or no specific malignancy treatment.

In 11 trials patients received platinum-based chemotherapy, in five trials patients were on non-platinum-based chemotherapy, in nine trials patients were on chemotherapy but the type was unknown and four trials included patients on either platinum or non-platinum chemotherapy. Three trials involved patients on chemotherapy plus radiotherapy, and in three trials patients were receiving radiotherapy without chemotherapy. In four trials patients were not on malignancy therapies, and three trials did not report malignancy treatments (*Table 12*).

Most of the trials stated as inclusion criteria the level of anaemia that they were willing to accept in patients at baseline. The highest was ≤ 16 g dl^{-1}[127] and the lowest <10 g dl^{-1}.[121] However, the mean/median baseline Hb ranged

TABLE 12 *Malignancy treatments*

Treatment	Trials
Chemo: platinum based	Bamias, 2003;[120a] Huddart, 2002;[125a] Vansteenkiste, 2002;[64a] Carabantes, 1999;[94] Cascinu, 1994;[95] Dammacco, 2001;[98] Dunphy, 1999;[100] Henry, 1994;[102] Kunikane, 2001;[104] Kurz, 1997;[105] Oberhoff, 1998[106]
Chemo: non-platinum based	Case, 1993;[96] Cazzola, 1995;[97] Österborg, 1996;[107] Österborg, 2002;[108] Littlewood, 2001[63]
Chemo: type unknown	Henze, 2002;[77a] Hedenus, 2002;[122a] Kotasek, 2003;[90a] Rosenzwieg, 2004;[128a] Thomas, 2002;[130a] Coffier, 2001;[65] Del Mastro, 1997;[99] Quirt, 1996;[109] Silvestris, 1995[111]
Mixed chemo	Janinis, 2003;[78a] Aravantinos, 2003;[119a] Iconomou, 2003;[126a] Wurnig, 1996[117]
Chemo + radiotherapy	Blohmer, 2003;[71a] Rosen, 2003;[127a] Throuvalas, 2000[115]
Radiotherapy only	Henke, 2003;[124a] Sweeney, 1998;[129a] Henke, 1999[101]
No treatment	Smith, 2003;[91a] Abels, 1993;[93] Italian Cooperative Study Group, 1998;[103] Rose, 1994[110]
NR	Casadevall, 2004;[121a] Hedenus, 2003;[123a] Leyland-Jones, 2003[118a]

[a] Birmingham studies.

from 11.5 to 8.6 g dl^{-1}. Iron deficiency and serum erythropoietin deficiency were reported sporadically across the trials, often in a subset of patients, which is why they were not formally measured in subgroup analysis (see Appendix 5). Iron deficiency was rectified by giving the patients iron supplementation. In most cases oral iron rather than intravenous iron was given, unless patients were unable to tolerate it. Three trials only gave iron to the intervention groups.[71,127,129] The iron levels at baseline in Sweeney[129] for the control group were lower than for the intervention group, which may have had a confounding effect on the results.

Quality of included studies

Quality assessment is presented in *Tables 13* and *14*. Studies were assessed using the checklist described in *Table 6* (p. 19), which for consistency was the same as the one used in the Cochrane review:[48]

- Treatment allocation
  1. Random allocation: in 15 trials identified by Birmingham this was unclear, in contrast to the Cochrane review where this was unclear in only five trials.
  2. Concealment of allocation: this was unclear in 18 trials identified by Birmingham and nine trials included in the Cochrane review.
- Similarity between groups
  3. Baseline characteristics: in 11 trials identified by Birmingham this was unclear, most of these data coming from abstract publications where these details are often not reported. In the Cochrane review it was unclear whether baseline characteristics were balanced in three trials. There were three trials in total where baseline characteristics were not balanced. In Iconomou[126] there was slightly more colorectal cancer in the control group and slightly more lung cancer in the intervention group, in Dunphy[100] gender was not balanced and in Sweeney[129] Hb was lower in the control group at baseline.
- Masking
  4. Treatment allocation masked from patients: in nine trials identified from the Birmingham search this was unclear, leaving six where patients were not blinded to their treatment allocation. In the Cochrane trials, in only one was it unclear whether the patients knew their treatment, and in 11 trials patients knew whether they were receiving epo or not.
  5. Treatment allocation masked from clinicians: again in nine Birmingham trials this was unclear, and in five trials clinicians were not blinded to the patients' treatment. None of the Cochrane trials was unclear, leaving 13 trials where the clinician would have been aware of treatment allocation.
- Completeness of trial
  6. Reporting of loss to follow-up, withdrawals and dropouts: this was unclear in ten Birmingham trials and two trials reported by Cochrane.
  7. ITT analysis or less than 10% lost: in nine Birmingham trials this was unclear; in total three trials reported non-ITT data or had more than 10% loss.

TABLE 13 *Study quality: update 2001 to October 2004 (Birmingham)*

Study	1. Random	2. Concealment allocation	3. Baseline similarity	4. Patients blinded	5. Physicians blinded	6. Losses	7. ITT or >10% dropout
Aravantinos, 2003:[119] Hb, Hct, patients' RBCT	Unclear	Unclear	Yes	No	No	Unclear	Yes
Bamias, 2003:[120] Hb, patients' RBCT (HRQoL in a subset)	Unclear	Unclear	Yes	No	No	Yes	Yes (not for HRQoL)
Beggs, 2003[68]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bindi, 2004[69]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Blohmer, 2003:[71] Hb	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Casadevall, 2004:[121] HaemR, HRQoL, also a cost study	Yes	Yes	Yes	No	Unclear	Yes	Stated ITT, but not undertaken; ITT on the number of patients who received the drug, not the complete group
Hedenus, 2002[122] a,b,c: HaemR, Hb, RBCT	Yes	Unclear	Yes	Yes	Yes	Yes	Depends on outcome
Hedenus, 2003:[123] HaemR, RBCT (week 5 to end), AE, HRQoL (FACT-F)	Yes	Yes	Yes	Yes	Yes	Yes	Analysis used Kaplan–Meier percentages, therefore only % given
Henke, 2003:[124] HaemR, Hb, AE, tumour progression	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Henze, 2002:[77] Hb	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Huddart, 2002:[125] HaemR, HRQoL (FACT-An); abstract	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No group numbers reported, wide confidence intervals in HRQoL? Small group
Iconomou, 2003:[126] HaemR, HRQoL (FACT-An, CLAS)	Yes	Unclear	No[a]	No	No	Yes[b]	[a] Slightly more colorectal cancer in control, slightly more lung cancer in epo group *b* not ITT but less than 10% dropout
Janinis, 2003:[78] HRQoL	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kotasek, 2003[90] a,b,d,e,f: HaemR, Hb, RBCT, HRQoL	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Leyland-Jones, 2003:[118] survival	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear

continued

TABLE 13 *Study quality: update 2001 to October 2004 (Birmingham) (cont'd)*

Study	1. Random	2. Concealment allocation	3. Baseline similarity	4. Patients blinded	5. Physicians blinded	6. Losses	7. ITT or >10% dropout
Rosen, 2003:[127] Hb, patients' RBCT	Unclear	Unclear	Unclear	No	No	Yes	Yes: for Hb responses yes, for tumour response no, for survival unclear
Rosenzweig, 2004:[128] Hb, HRQoL, AE, survival							
Smith, 2003[91] a,b,c: HaemR, Hb, RBCT, AE, (HRQoL but not reported as RCT data)	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Sweeney, 1998:[129] HaemR, AE, HRQoL	Yes	No	No: Hb lower in control	No	No	Yes	Yes
Thomas, 2002:[130] HaemR, RBCT, HRQoL (FACT-An, CLAS); abstract	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vadhan-Raj, 2004:[88] survival	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vansteenkiste, 2002:[64] HaemR, Hb, RBCT (from week 5 and week 1), HRQoL, AE, disease progression and survival	Yes	Unclear	Yes	Yes	Yes	Yes	Yes: not for HRQoL; only 81% of patients analysed

CLAS, Cancer Linear Analogue Scale.

TABLE 14 *Study quality: Cochrane review*

Study	1. Random	2. Concealment allocation	3. Baseline similarity	4. Patients blinded	5. Physicians blinded	6. Losses	7. ITT or >10% dropout
Abels, 1993:[93] HR, RBCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes: dropout information from authors
Carabantes, 1999:[94] HaemR, patients' RBCT, HRQoL; abstract	Unclear	Unclear	Yes	Unclear	No	Yes	Yes
Cascinu, 1994:[95] HaemR, Hb, RBCT, AE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Case, 1993:[96] HaemR, RBCT, HRQoL, AE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cazzola, 1995:[97] HaemR, Hb, RBCT, AE	Yes	Yes	Yes	No	No	Yes	Yes
Coiffier, 2001:[65] HaemR, Hb, RBCT, HRQoL (unpublished data, Boogaerts)	Yes	Unclear	Yes	No	No	Yes	Yes
Dammacco, 2001:[98] HaemR, Hb, RBCT, HRQoL, AE	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Del Mastro, 1997:[99] Hb, RBCT, HRQoL, AE	Yes	Yes	Yes	No	No	Yes	Yes
Dunphy, 1999:[100] Hb, RBCT	Unclear	Unclear	No: gender	No	No	Yes	Yes
Henke, 1999[101] a,b,c HaemR, Hb	Unclear	Unclear	No	No	No	Yes	Yes
Henry, 1994[102] HaemR, RBCT, HRQoL, AE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Italian Cooperative Study Group, 1998:[103] HaemR, Hb, AE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kunikane, 2001[104] a,b: Hb, patients' RBCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kurz, 1997,[105] HaemR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Littlewood, 2001:[63] HaemR, Hb, RBCT, HRQoL, AE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oberhoff, 1998:[106] HaemR, Hb, RBCT, AE	Yes	Yes	Yes	No	No	Yes	Yes
Österborg, 1996[107] a,b,c: HaemR, Hb, RBCT, AE	Yes	Yes	Yes	No	No	Yes	Yes

continued

TABLE 14 *Study quality: Cochrane review (cont'd)*

Study	1. Random	2. Concealment allocation	3. Baseline similarity	4. Patients blinded	5. Physicians blinded	6. Losses	7. ITT or >10% dropout
Quirt, 1996:[109] Hb, patients' RBCT, HRQoL abstract	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes
Rose, 1994:[110] HaemR, patients' RBCT, HRQoL abstract	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Silvestris, 1995:[111] HaemR, AE	Yes	Unclear	Unclear	No	No	Yes	No: not ITT analysis
Ten Bokkel, 1998[112] a,b: patients' RBCT, TR, AE	Yes	Yes	Yes	No	No	Yes	No: not ITT analysis
Thatcher, 1999[113] a,b: Hb, patients' RBCT, HRQoL, AE	Yes	Yes	Yes	No	No	Yes	Yes
Thompson, 2000:[114] HaemR, patients' RBCT	Yes	Yes	Yes	Yes	Yes	Not stated	Yes
Throuvalas, 2000:[115] patients' RBCT	Yes	Yes	Yes	No	No	Not stated	Yes
Welch, 1995[116] Hb, patients' RBCT, AE	Unclear	Unclear	Yes	No	No	Yes	Yes
Wurnig, 1996:[117] Hb, patients' RBCT, AE	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes

Summary

It appears that the trials identified since 2001 are of lower quality than the trials identified by Cochrane[48] before 2001. However, this is probably an artefact in that the Cochrane review authors had written to trial investigators to request missing data, including information on study conduct. Therefore, the data reported here may describe reporting quality rather than the actual quality of the trials. This demonstrates the difficulty of assessing quality of trials from published accounts. Many of the trials where it is unclear are abstract reports. Most of the abstract reports describe large trials (and include one of the largest trials, with 939 patients).[118] This is a concern.

Trial outcomes

Outcomes sought from the trials fell into five categories: anaemia-related outcomes, malignancy-related outcomes, adverse events, HRQoL and patients' preferences. The following results section reports these outcomes separately in the following order:

- anaemia-related outcomes: haematological response; mean Hb change; RBCT requirements
- malignancy-related outcomes: tumour response; overall survival
- adverse events: especially thrombic events (as defined by the trial), hypertension, haemorrhage/thrombocytopenia, rash/irritation/pruritus, seizures and reports of red cell aplasia
- HRQoL outcomes: as measured by HRQoL scales
- patient preference: patients' requests regarding anaemia treatment.

Effectiveness: anaemia-related outcomes

Haematological response, Hb change and transfusion requirements were investigated to assess the effectiveness of erythropoietin on anaemia.

All of the trials included in this review included one or more parameters that measured the effect of erythropoietin on anaemia. In total, 26 trials investigated haematological response, 32 trials investigated Hb change, 33 trials counted the number of patients receiving blood transfusions and 14 trials counted the number of units of blood per patient.

Haematological response

The Cochrane review reported that 15 studies had measured a haematological response (within the definition of "the proportion of participants with an increase in Hb level of 2 g/dL or more or increase in haematocrit of 6 percentage points or more, unrelated to transfusion … analysis restricted to interventional studies with a mean or median baseline Hb ≤ 12 g/dL at study entry"). The Cochrane review also identified an additional study,[95] which used a different definition of haematological response (transfusion-free target-level Hb of 10.0 g dl^{-1} after 9 weeks of treatment), which was excluded from the meta-analysis.

The Birmingham review identified an additional 11 trials that reported a haematological response (*Table 15*). Nine of these were within the Cochrane definition of haematological response.[71,77,78,90,91,122,123,125,126] Two defined haematological response as an increase of 2 g dl^{-1} or more (Cochrane definition) and/or a target level Hb of 12 g dl^{-1} or target Hb of 14 g dl^{-1}.[130] Two studies defined haematological response only as target level Hb,[124,129] both studies defining a haematological response as a target level of ≥ 14 g dl^{-1} for women and ≥ 15 g dl^{-1} for men. One study defined haematological response as either an increase in Hb of 1.5 g dl^{-1} and/or target-level Hb of 11.5 g dl^{-1}.[121]

To be consistent with the Cochrane review, the six Birmingham studies that had used the Cochrane definition of haematological response were included in the meta-analysis. The two Birmingham studies[64,130] that had used the additional criterion of target level incorporated into the definition of haematological response were also included. It was thought that most of the data from Thomas[130] and Vansteenkiste[64] would have been derived from an increase in Hb of 2 g dl^{-1}, as the mean baseline Hb from these studies was at least 2 g dl^{-1} below the target-level Hb.

It was decided not to include those studies in which haematological response was defined only as target-level Hb because the target levels in both these studies were quite high. Given the baseline Hb (Henke:[124] baseline Hb intervention 11.7 (8.5 to 14.4), control 11.8 (6.9 to 14.6); Sweeney:[129] baseline Hb intervention 12.07, control 10.72), it was felt that using these data would not encompass the Cochrane definition sufficiently to make the data comparable. As Casadevall[121] used a different definition, this study was also excluded from the meta-analysis.

TABLE 15 *Haematological response: studies identified since 2001*

Study	Intervention *n/N*	Control *n/N*	Comments
HaemR: as defined in Cochrane review			
Hedenus, 2003[123]	106/176	31/173	Derived using Kaplan–Meier method Intervention: HaemR 60%. Control: HaemR 18%
Hedenus, 2002[122]	(a) 1.0 μg kg^{-1} = 5/11 (b) 2.25 μg kg^{-1} = 12/22 (c) 4.5 μg kg^{-1} = 14/22	1/11	Derived using Kaplan–Meier method (a) 1.0 μg kg^{-1} = 45% (*n* = 11) (b) 2.25 μg kg^{-1} = 55% (*n* = 22) (c) 4.5 μg kg^{-1} = 62% (*n* = 22) Control: 10% (*n* = 11)
Huddart, 2002[125]	16/45	2/45	Only percentages given for HaemR in paper, assumed 45 per group (*n* = 90 for total group given in paper): intervention 36%, control 5% HaemR
Iconomou, 2003[126]	25/57 (44%)	7/55 (13%)	
Kotasek, 2003[90]	(a) 4.5 μg kg^{-1} = 8/32 (b) 6.75 μg kg^{-1} = 8/17 (c) 9.0 μg kg^{-1} = 23/46 (d) 12.0 μg kg^{-1} = 17/28 (e) 13.5 μg kg^{-1} = 20/35 (f) 15 μg kg^{-1} = 20/40	7/51	Derived using Kaplan–Meier method (a) 4.5 μg kg^{-1} = 24% (*n* = 32) (b) 6.75 μg kg^{-1} = 48% (*n* = 17) (c) 9.0 μg kg^{-1} = 50% (*n* = 46) (d) 12.0 μg kg^{-1} = 62% (*n* = 28) (e) 13.5 μg kg^{-1} = 58% (*n* = 35) (f) 15 μg kg^{-1} = 50% (*n* = 40) Control: 14% (*n* = 51)
Smith, 2003[91]	(a) 2.25 μg kg^{-1} = 12/21 (b) 1.69 μg kg^{-1} =10/21 (c) 2.5 μg kg^{-1} = 13/22	1/22	Derived using Kaplan–Meier method (a) 2.25 μg kg^{-1} = 58% (*n* =21) (b) 1.69 μg kg^{-1} = 49% (*n* =21) (c) 2.5 μg kg^{-1} = 60% (*n* =22) Control: 5% (*n*=22)
HaemR as defined by Cochrane and target Hb			
Thomas, 2002[130] **(abstract)**	42/62 (67%)	17/65 (26%)	Target Hb 14 g dl^{-1}
Vansteenkiste, 2002[64]	66%, *n* = 156 103/156	24%, *n* = 158 38/158	Target Hb 12 g dl^{-1} Derived using Kaplan–Meier method
HaemR as defined by target-level Hb only (Hb ≥ 14 g dl^{-1} women, ≥ 15 g dl^{-1} men): not in meta-analysis			
Henke, 2003[124]	148/180 (82%)	26/171 (15%)	
Sweeney, 1998[129]	10/24 (41.6%)	0/24 (0%)	
Other definition of Hb response (Hb ≥ 1.5 g dl^{-1}, stable Hb without RBCT, or target level Hb ≥ 11.5 g dl^{-1}): not in meta-analysis			
Casadevall, 2004[121]	10/24	0/26	

Kaplan–Meier-derived *n* assumed as total number in group at start.

Overall haematological response

Twenty-two studies contributed data to the haematological response meta-analysis (*Figures 3* and *4*). Of these, six contributed more than one point estimate, giving a total of 33 data points. In total, 2151 and 1589 contributed data in the intervention and control arms, respectively. The pooled (fixed effects) relative risk (RR) was 3.40 [95% confidence interval (CI) 3.01 to 3.83] in favour of erythropoietin therapy, with little evidence for statistical heterogeneity (χ^2 = 23.60, 32 df, p = 0.86). The risk difference (RD) was 0.38 (95% CI 0.35 to 0.40, fixed effects).

Publication bias

To test whether publication bias was present in the above sample included in the meta-analysis, a funnel plot was constructed (*Figure 5*). The plot shows that there may be some small negative studies missing, but it was not clearly asymmetrical.

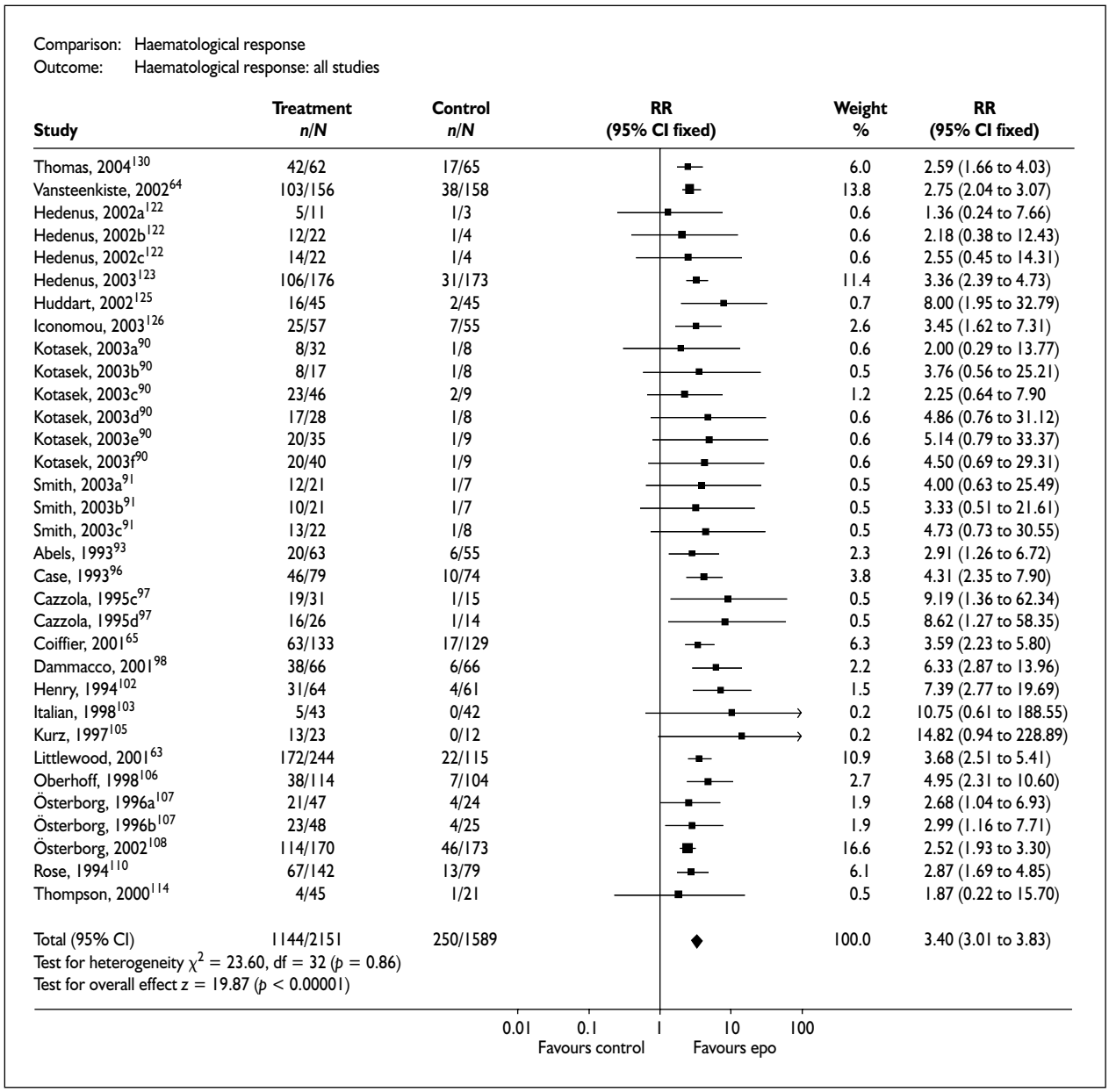

FIGURE 3 *Haematological response*

Subgroup analysis

Subgroup analysis was undertaken on the haematological response data and the results are shown in *Table 16*. Forest plots for these subgroups are available as supplementary material, which can be requested from the authors.

The χ^2 test for interaction is presented (test for heterogeneity between groups) and in addition the more exacting *F* test, which compares the amount of the total heterogeneity falling between groups with that remaining within the groups (essentially a univariate metaregression). Where there is substantial heterogeneity in the overall data set, high values of *F* suggest that the characteristic may help to explain that heterogeneity.

Abstract publications versus full-text publications versus unpublished data from authors (analysis not shown)

Owing to time constraints, this review did not seek missing data from the authors. The Cochrane review,[48] however, did, and obtained further unpublished data for seven studies reporting haematological response outcomes, giving an RR of 3.18 (95% CI 2.61 to 3.88). There were two trials that contributed to the haematological response meta-analysis for which only abstract publications were available.[125,130] These abstracts

Comparison: Haematological response
Outcome: Haematological response: all studies

Study	Treatment *n/N*	Control *n/N*	RD (95% CI fixed)	Weight %	RD (95% CI fixed)
Thomas, 2002[130]	42/62	17/65		3.6	0.42 (0.26 to 0.57)
Vansteenkiste, 2002[64]	103/156	38/158		9.0	0.42 (0.32 to 0.52)
Hedenus, 2002a[122]	5/11	1/3		0.3	0.12 (–0.49 to 0.73)
Hedenus, 2002b[122]	12/22	1/4		0.4	0.30 (–0.18 to 0.77)
Hedenus, 2002c[122]	14/22	1/4		0.4	0.39 (–0.08 to 0.86)
Hedenus, 2003[123]	106/176	31/173		10.0	0.42 (0.33 to 0.52)
Huddart, 2002[125]	16/45	2/45		2.6	0.31 (0.16 to 0.46)
Iconomou, 2003[126]	25/57	7/55		3.2	0.31 (0.16 to 0.47)
Kotasek, 2003a[90]	8/32	1/8		0.7	0.12 (–0.15 to 0.40)
Kotasek, 2003b[90]	8/17	1/8		0.6	0.35 (0.02 to 0.68)
Kotasek, 2003c[90]	23/46	2/9		0.9	0.28 (–0.03 to 0.59)
Kotasek, 2003d[90]	17/28	1/8		0.7	0.48 (0.19 to 0.77)
Kotasek, 2003e[90]	20/35	1/9		0.8	0.46 (0.20 to 0.72)
Kotasek, 2003f[90]	20/40	1/9		0.8	0.39 (0.13 to 0.65)
Smith, 2003a[91]	12/21	1/7		0.6	0.43 (0.09 to 0.76)
Smith, 2003b[91]	10/21	1/7		0.6	0.33 (0.00 to 0.67)
Smith, 2003c[91]	13/22	1/8		0.7	0.47 (0.16 to 0.77)
Abels, 1993[93]	20/63	6/55		3.4	0.21 (0.07 to 0.35)
Case, 1993[96]	46/79	10/74		4.4	0.45 (0.31 to 0.58)
Cazzola, 1995c[97]	19/31	1/15		1.2	0.55 (0.33 to 0.76)
Cazzola, 1995d[97]	16/26	1/14		1.0	0.54 (0.31 to 0.77)
Coiffier, 2001[65]	63/133	17/129		7.5	0.34 (0.24 to 0.44)
Dammacco, 2001[98]	38/66	6/66		3.8	0.48 (0.35 to 0.62)
Henry, 1994[102]	31/64	4/61		3.6	0.42 (0.28 to 0.56)
Italian, 1998[103]	5/43	0/42		2.4	0.12 (0.01 to 0.22)
Kurz, 1997[105]	13/23	0/12		0.9	0.57 (0.34 to 0.79)
Littlewood, 2001[63]	172/244	22/115		8.9	0.51 (0.42 to 0.61)
Oberhoff, 1998[106]	38/114	7/104		6.2	0.27 (0.17 to 0.37)
Österborg, 1996a[107]	21/47	4/24		1.8	0.28 (0.07 to 0.49)
Österborg, 1996b[107]	23/48	4/25		1.9	0.32 (0.12 to 0.52)
Österborg, 2002[108]	114/170	46/173		9.8	0.40 (0.31 to 0.50)
Rose, 1994[110]	67/142	13/79		5.8	0.31 (0.19 to 0.42)
Thompson, 2000[114]	4/45	1/21		1.6	0.04 (–0.08 to 0.16)
Total (95% CI)	1144/2151	250/1589		100.0	0.38 (0.35 to 0.40)

Test for heterogeneity $\chi^2 = 95.15$, df = 32 ($p < 0.00001$)
Test for overall effect $z = 26.92$ ($p < 0.00001$)

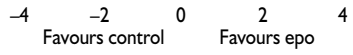

FIGURE 4 *Haematological response (risk difference)*

were identified from the Industry submission to NICE by Ortho Biotec (Technology appraisal of erythropoietins for the management of cancer-related anaemia; November 2004). For studies where the data were from peer-reviewed publications the RR was 3.56 (95% CI 3.03 to 4.19, fixed effects); for the two studies only from abstract publication the RR was 3.17 (95% CI 2.06 to 4.88, fixed effects). Therefore, little difference in effect was identified between publication types.

Allocation concealment
Without good concealment of allocation, the randomisation can be compromised, leading to selection bias at baseline. Allocation concealment was assessed as being adequate or unclear. Twelve trials had adequate allocation concealment and in ten trials it was unclear. There was no difference in haematological response between the trials that reported allocation concealment and those that did not.

Licence indications (analysis not shown)
The licences vary slightly among the three erythropoietin products (see Appendix 2). *Tables 7* and *8* describe whether the study interventions were within the licence indications, principally whether the dose, disease, malignancy therapy were within the licence indication, and for epoetin beta, if haematological patients were in the study

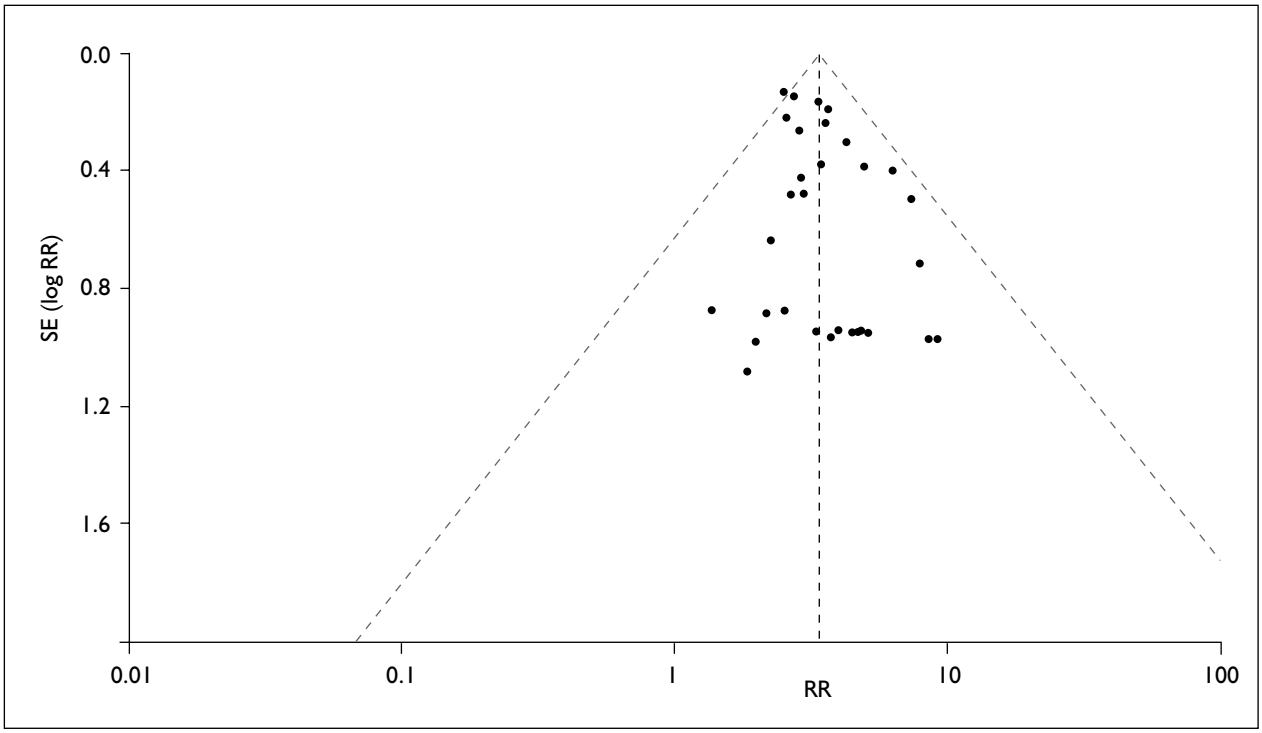

FIGURE 5 *Haematological response: funnel plot*

population whether they also had erythropoietin deficiency at baseline. As all of the studies describe mean Hb levels of less than 13 g dl^{-1} (with the majority describing Hb levels of 11 g dl^{-1}), all of the included studies that measured haematological response fall within the licence indications in this respect.

Of the 22 studies that contributed to the meta-analysis, eight fell within the licence indications, nine fell outside licence conditions, and two dose-finding studies incorporated doses that were too low[90,122] or too high[90] to fall within the licences. The reasons for studies not meeting licence indications were related to dose (some studies prescribe fixed doses rather than doses based on body weight[97,106,108,125,126,130] or doses lower than licence,[90,93,122] dose frequency[91] or malignancy treatment (patients not receiving concomitant chemotherapy[91,114,123]). Some studies had more than one licence violation. In one study it was difficult to evaluate whether patients with solid tumours were receiving platinum-based chemotherapy, a licence requirement for patients receiving epoetin beta.

There was no evidence of a difference in results for trials conducted within or outside the licence.

Agent

Three types of erythropoietin are available: epoetin alfa, epoetin beta and darbepoetin alfa. Of the 22 studies that contributed to the meta-analysis, 12 used epoetin alfa, five used epoetin beta and five used darbepoetin alfa.

There is no evidence that haematological response varies according to which agent is used.

Dose

Subgroup analysis for dose was analysed as: per licence indication, higher than licence indication, lower than licence indication, and fixed dose rather than weight-based dosing (also not within licence). Fifteen studies gave doses within licence indications, one study gave a dose higher than licensed dose, four studies gave lower than licensed dose and six studies gave fixed rather then weight-based doses. The study that gave a higher than licensed dose was part of a dose-finding study,[90] and three of the four studies that gave lower doses were also dose-finding studies[90,91,122]

There was no evidence of any variation in effectiveness with dose. However, as the high- and low-dose studies are very small, no firm conclusions can be drawn. Interpretation of the

TABLE 16 *Subgroup analysis: haematological response*

		Trials	RR	CI	$\chi^2_{(het)}$	df	*p*
Baseline Hb							
<10 g dl^{-1}		27	3.53	(3.06 to 4.06)	19.34	26	
10–12 g dl^{-1}		5	2.84	(2.25 to 3.59)	0.79	4	
>12 g dl^{-1}		0	–	–		–	
NR		1	3.40	(3.01 to 3.83)	–	–	
		Total within-group heterogeneity			20.13	30	
		Total between-group heterogeneity			3.47	2	**0.18**
		***F* (between:within)**			2.59	2,30	**0.09**
	Total	33			23.60	32	
Allocation concealment							
Adequate		15	3.41	(92.88 to 4.05)	12.85	14	
Unclear		18	3.38	(2.85 to 4.01)	10.74	17	
		Total within-group heterogeneity			23.59	31	
		Total between-group heterogeneity			0.01	1	**0.92**
		***F* (between:within)**			0.01	1,31	**0.91**
	Total	33			23.60	32	
Masking							
Double blind		10	3.47	(2.90 to 4.16)	13.16	9	
Unblinded		6	4.02	(2.87 to 5.63)	2.90	5	
		Total within-group heterogeneity			16.06	14	
		Total between-group heterogeneity			0.85	1	**0.36**
		***F* (between:within)**			0.74	1,14	**0.40**
	Total	16			16.91	15	
Agent							
Epoetin alfa		12	3.84	(3.14 to 4.70)	11.04	11	
Epoetin beta		7	3.20	(2.58 to 3.97)	6.85	6	
Darbepoetin alfa		14	3.08	(2.50 to 3.80)	3.31	13	
		Total within-group heterogeneity			21.20	30	
		Total between-group heterogeneity			2.40	2	**0.30**
		***F* (between:within)**			1.70	2,30	**0.20**
	Total	33			23.60	32	
Dose							
Within licence indication		20	3.35	(2.93 to 3.84)	15.61	19	
Higher than licence indication		1	4.50	(0.69 to 29.30)	–	0	
Lower than licence indication		4	2.62	(1.35 to 5.05)	0.75	3	
Fixed dose per week (not IU kg^{-1})		8	3.75	(2.78 to 5.05)	6.61	7	
		Total within-group heterogeneity			22.97	29	
		Total between-group heterogeneity			0.63	3	**0.89**
		***F* (between:within)**			0.27	3,29	**0.85**
	Total	33			23.60	32	
Different malignancies							
Solid tumours		12	3.40	(2.72 to 4.24)	6.64	11	
Haematological malignancies		12	3.27	(2.75 to 3.89)	11.19	11	
MDS		2	4.27	(0.86 to 21.19)	0.98	1	
Mixed		7	4.07	(2.99 to 5.55)	2.40	6	
Malignancy NR		1	2.59	(1.66 to 4.03)	–	–	
		Total within-group heterogeneity			21.21	29	
		Total between-group heterogeneity			3.17	4	**0.53**
		***F* (between:within)**			1.08	4,29	**0.38**
	Total	34			24.38	33	

continued

TABLE 16 *Subgroup analysis: haematological response (cont'd)*

	Trials	RR	CI	$\chi^2_{(het)}$	df	*p*
Different therapies						
Chemotherapy with platinum	6	4.04	(3.13 to 5.21)	11.13	5	
Chemotherapy without platinum	8	3.21	(2.66 to 3.87)	6.99	7	
Chemotherapy plus radiotherapy	0	–	–	–	–	
Radiotherapy alone	0	–	–	–	–	
No therapy	6	3.50	(1.89 to 6.47)	1.23	5	
Unclear	13	3.21	(2.60 to 3.97)	3.55	12	
	Total within-group heterogeneity			22.90	29	
	Total between-group heterogeneity			0.70	3	**0.87**
	***F* (between:within)**			0.30	3,29	**0.83**
Total	33			23.60	32	
Duration of study						
6–9 weeks	5	5.71	(3.24 to 10.04)	3.35	4	
12–16 weeks	23	3.25	(2.83 to 3.73)	13.82	22	
>20 weeks	3	3.46	(2.48 to 4.83)	0.47	2	
NR	2	3.17	(2.06 to 4.88)	2.46	1	
	Total within-group heterogeneity			20.10	29	
	Total between-group heterogeneity			3.50	3	**0.32**
	***F* (between:within)**			1.68	3,29	**0.19**
Total	33			23.60	32	
Iron supplementation						
Fixed	3	3.83	(2.72 to 5.38)	1.03	2	
As necessary	15	3.57	(3.04 to 4.19)	15.06	14	
No explicit statement	15	2.90	(2.33 to 3.60)	4.65	14	
	Total within-group heterogeneity			20.74	30	
	Total between-group heterogeneity			2.86	2	**0.24**
	***F* (between:within)**			2.07	2,30	**0.14**
Total	33			23.60	32	
Transfusion trigger						
Hb ≤8 g dl^{-1} l	4	3.25	(2.12 to 4.99)	1.42	3	
Hb ≤8 gdl^{-1} or prn	12	3.23	(2.78 to 3.76)	10.02	11	
prn only	2	3.25	(2.26 to 4.67)	1.84	1	
NR	15	3.97	(3.02 to 5.23)	8.58	14	
	Total within-group heterogeneity			21.86	29	
	Total between group heterogeneity			1.74	3	**0.63**
	***F* (between:within)**			0.77	3,29	**0.52**
Total	33			23.60	32	

fixed dose is complicated by the unknown distribution of patients' weights.

Malignancy type

For the meta-analysis malignancy types were grouped into solid tumours, haematological tumours, MDS and mixed, which consisted of studies that included patients with both solid and haematological tumours. Of the trials reporting haematological response outcomes, only one,[130] an abstract publication, did not report the type of malignancy of the included patients. Of the others, all but one,[125] again an abstract publication, reported malignancies down to disease level, with one study[64] giving details of stages of disease. All but one of the solid tumour studies had a range of tumours, mostly breast, lung, gastrointestinal, gynaecological and prostate. Vansteenkiste[64] looked specifically at lung cancer, both NSCLC and SCLC. The haematological malignancies reported were Hodgkin's disease, NHL, CLL and MM.

There was no evidence that haematological response varies by tumour site.

Treatment of malignancy
To investigate whether the type of therapy that patients were receiving for their malignant disease had any influence on haematological response, the following subgroups were investigated: platinum-based chemotherapy, chemotherapy not based on platinum, radiotherapy, patients not on any antimalignancy treatment, and a further category for studies where it was unclear which therapy patients were on. None of the trials included in the meta-analysis involved patients receiving radiotherapy; however, two trials not included in the meta-analysis because they defined haematological response by target-level Hb were undertaken on patients receiving radiotherapy as the main malignancy treatment. There were six studies in which patients received platinum-based chemotherapy, five studies involving patients receiving non-platinum-based chemotherapy and four small trials investigating patients not receiving antimalignancy treatments. In six trials it was unclear as to the type of antimalignancy therapy that patients were receiving.

There was no evidence that haematological response varies by type of therapy.

Duration of study
The majority of studies (n = 14) had a duration of between 12 and 16 weeks, only four studies had a duration of 6–9 weeks and only two studies had a duration of over 20 weeks.

There was no evidence that results varied by the duration of the study.

Iron supplementation
Of the 22 studies included in the meta-analysis, 15 recorded that iron supplementation was given; three of these studies[63,105,126] gave fixed levels of iron, whereas the remaining studies gave iron as necessary. Seven studies (accounting for 30.7% of the weight) gave no explicit statement regarding iron supplementation.

There was no evidence that haematological response varies by trial policy on iron supplementation.

G-CSF supplementation
None of the trials included in the meta-analysis gave G-CSF supplementation.

Transfusion trigger
In all of the trials all patients had the chance to receive an RBCT. The following transfusion triggers were reported in the trials: Hb ≤ 8 g dl^{-1}, Hb ≤8 g dl^{-1} or prn, prn only or not reported. There was no evidence that haematological response varied with transfusion trigger.

Summary: haematological response
Treatment with erythropoietin in patients with cancer-induced anaemia is effective in producing a haematological response as defined as an Hb rise of at least 2 g dl^{-1}. Fifty-three per cent of patients who received epo had a haematological response, in contrast to 15.7% of control patients. The subgroup analysis highlighted the under-reporting of factors such as concomitant anaemia treatments and adjuvant chemotherapy in this area of research and also highlighted the difficulty in assessing this group of trials, as there may have been confounding factors cancelling each other out.

Hb change

Of the additional 22 Birmingham trials identified, 12 had measured a change in Hb (*Table 17*), with five measuring a change from baseline contributing data to the meta-analysis. Of the remaining six studies, Hedenus[123] reported Hb change from week 5, not from baseline (week 1) of the trial, Aravantinos[119] reported Hb levels for every cycle of chemotherapy up to cycle 5, Sweeney[129] reported weekly Hb levels for the 7 weeks of therapy given, Henke[124] reported Hb levels at weeks 4 and 9, and Casadevall[121] reported Hb levels at baseline and week 12. Data reported in this way were not suitable for meta-analysis. In addition, Sweeney[129] gave iron supplementation only in the intervention arm and Casadevall[121] gave G-CSF supplementation again only to the intervention group, and there is a strong possibility that confounding has occurred in these trials.

The Cochrane review[48] included six studies of Hb change in the meta-analysis. Owing to excessive heterogeneity (test for heterogeneity χ^2 229.21, df 9, $p < 0.00001$) the Cochrane review did not pool the results from the six trials, but calculated Hb change separately for each of the studies and found a weighted mean difference (WMD) ranging from 0.34[97] (95% CI 0.07 to 0.61) to 3.30[101] (95% CI 1.13 to 5.47) in favour of epo. As stated in the methods, the present review built on the work of Cochrane; data were taken from the Cochrane publication and not data extracted from the primary publication. However, when this analysis was repeated with the data from the additional Birmingham studies, excessive heterogeneity was again present. At the time at which this review went to peer review (2 February 2005) this was still

TABLE 17 *Change in Hb*

Study ID	Mean/median change in Hb: Intervention	Mean/median change in Hb: Control	*p*	Hb values as reported in the paper
Aravantinos, 2003[119]	NR	NR		Intervention: Hb cycle 1: 9.8 ± 0.5; cycle 2: 9.32 ± 0.8; cycle 3: 10.66 ± 1.3; cycle 4: 11.47 ± 1.67; cycle 5: 12.11 ± 1.39 Control: Hb cycle 1: 9.32 ± 0.8; cycle 2: 10.2 ± 1.01; cycle 3: 10.07 ± 1.32; cycle 4: 10.31 ± 1.56; cycle 5: 10.55 ± 1.83 $n = 24$ intervention, $n = 23$ control
Bamias, 2003[120]	0.57 ± 0.25 ($n = 72$)	–0.49 ± 0.16 ($n = 72$)	0.001	
Boogaerts, 2003[131]				Intervention: median Hb change 2.1 (range –3 to 8) ($n = 133$) Control: median Hb change 0.9 (range –3 to 6) ($n = 129$) $p \leq 0.001$ (at 12 weeks)
Casadevall, 2004[121]	NR	NR		Data on Hb levels is given only for 'responders '. Not ITT (total *n* for trial is 30 per group). Intervention = 9.1 g dl^{-1} ± 1.8 at baseline; 10.4 ± 1.3 g dl^{-1} at 12 weeks, 10 responders. Control = 8.6 g dl^{-1} ± 1.1 at baseline; 8.8 g dl^{-1} ± 1.2 g dl^{-1} at 12 weeks; 24 patients. Mean change not given. G-CSF on intervention arm, therefore not included in meta-analysis
Hedenus, 2003[123]	1.80 (SE 0.20) ($n = 174$)[a]	0.19 (SE 0.10) ($n = 170$)[a]	<0.001	[a] ITT, change from baseline using the last available Hb value not within 28 days of transfusion
	2.66 (SE 0.20) ($n = 94$)[b]	0.69 SE 0.14 ($n = 86$)[b]	<0.001	[b] Completers, i.e. patients with Hb values at week 13 not within 28 days of transfusion
Hedenus, 2002[122]			NR	Measured from week 5 (day 29) to week 13 (day 85) SD NR; mean Hb change 1.0 μg kg^{-1} = 1.56 (–0.13, 3.250) ($n = 11$) 2.25 μg kg^{-1} = 1.64 (1.68, 3.24) ($n = 22$) 4.5 μg kg^{-1} = 2.46 (1.68, 3.24) ($n = 22$) Control: 1.0 (0.55, 1.45) ($n = 11$) Not included in meta-analysis as not measured from baseline
Henke, 2003[124]	NR	NR		Intervention: median Hb baseline: 11.7 (range 8.5–14.4); week 4: 14.8 (SD 1.8); week 9: 15.4 (SD 1.7) ($n = 180$) Control: median Hb baseline: 11.8 (range 6.9–14.6); week 4: 12.4 (SD 1.3); week 9: 12.9 (SD 1.9) ($n = 171$)
Huddart, 2002[125]	*n* not available	*n* not available		Intervention: mean max increase 2.6 g dl^{-1} (95% CI 1.99 to 3.12) Control: mean max. increase 1.2 g dl^{-1} (95% CI 0.77 to 1.63); abstract published, *n* unknown, reported as 90 overall

continued

TABLE 17 *Change in Hb (cont'd)*

Study ID	Mean/median change in Hb: Intervention	Mean/median change in Hb: Control	*p*	Hb values as reported in the paper
Iconomou, 2003[126]	1.7 (SD 1.6) week 12 *n* =57/61	0.3 (SD 1.4) week 12 *n* = 55/61	Diff. 1.4, $p < 0.001$	Intervention: mean Hb baseline: 10.1 (SD 0.5); week 12: 11.8 (SD 1.8) Control: mean Hb baseline: 10.1 (SD 1.4); week 12: 10.4 (SD 1.4). 12 weeks = end of epo therapy
Kotasek, 2003[90]	4.5 μg kg^{-1} = 5.4 (SE 2.2) (*n* = 32) 6.75 μg kg^{-1} = 8.6 (SE 3.8) (*n* = 17) 9.0 μg kg^{-1} = 9.0 (SE 2.4) (*n* = 46) 12.0 μg kg^{-1} = 14.5 (SE 2.4) (*n* = 28) 13.5 μg kg^{-1} = 16.3 (SE 3.8) (*n* = 35) 15 μg kg^{-1} = 12.1 (SE 3.0) (*n* = 40)	–2.0 (SE 2.0) (*n* = 51)	no *p*-values given	Change in Hb = end of treatment phase for each patient minus the baseline; if a patient had RBCT then the last pretransfusion Hb value was substituted A second analysis, 'change in Hb from baseline after 12 weeks', was also analysed but is not ITT. Only changes in Hb to end of treatment phase are reported here
Smith, 2003[91]	2.25 μg kg^{-1} per week = 1.18 (SD 2.0) (*n* = 21) 1.69 μg kg^{-1} per week = 1.22 9 (SD 1.64) (*n* = 21) 2.5 μg kg^{-1} per week = 1.70 (SD 1.91) (*n* = 22)	0.00 (SD 0.93) (*n* = 22)		
Sweeney, 1998[129]	NR	NR	NR	Reported as (1) mean changes in weekly Hb levels; (2) weekly mean change in Hb level subtracted from the previous weeks mean level; (3) Hb of pre/post radiotherapy: intervention pre-radiotherapy: Hb = 12.07, post-radiotherapy Hb = 13.62; control pre-radiotherapy Hb = 10.72, post-radiotherapy Hb = 11.01; $p = 0.22$ pre-radiotherapy, and $p = 0.0012$ post-radiotherapy Iron only given in the intervention group Max. 7-week epo treatment
Thomas, 2002[130]	Mean change from baseline[c] 1.9 g dl^{-1} (SD 1.74) (*n* = 62)	Mean change from baseline[c] 0.39 g dl^{-1} (SD 1.38) (*n* = 65)		Abstract publication, included study in Ortho Biotec submission [c] At 12 weeks

SD, standard deviation; SE, standard error.

under investigation. Since then, it was found that the standard deviation (SD) imputed for Littlewood[63] was an error and this was replaced by an SD reported in a subsequent publication, which reported more detailed trial results. In addition, it was felt that Cazzola[97] should not be included as it reported a weekly rate rather than Hb change over the duration of the trial. This only makes a minor change to the summary estimate. With the error, the pooled estimate of WMD was 1.68 (95% CI 1.64 to 1.79) with $\chi^2 = 241.41$, df 21, $p = 0.00001$. The reworked meta-analysis is shown in *Figure 6*, where the WMD is 1.63 (95% CI 1.46 to 1.80) with test for heterogeneity $\chi^2 = 23.74$, df 19, $p = 0.21$.

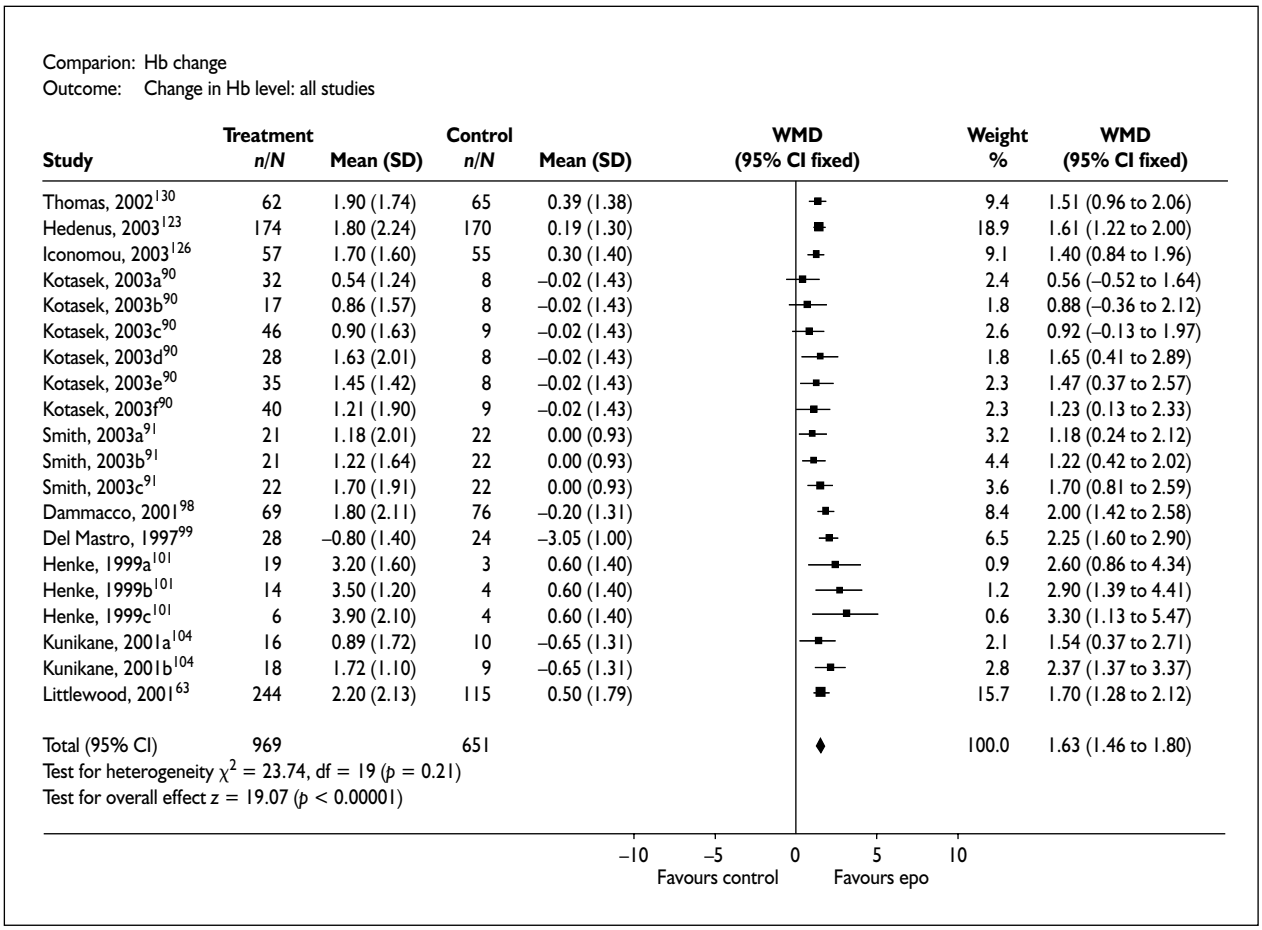

FIGURE 6 *Change in Hb level: all studies*

Overall Hb change

Ten trials contributed data to this meta-analysis (*Figure 6*). Of these, four contributed more than one point estimate, owing to dose subgroups giving a total of 20 data points. In total, 969 and 651 patients contributed data in the intervention and control arms, respectively. Hb change was in favour of erythropoietin treatment, with a WMD of Hb between the intervention and control arms of 1.63 g dl^{-1} (95% CI 1.46 to 1.80).

Publication bias funnel plot

A funnel plot for all included studies reporting Hb change was drawn (*Figure 7*). The funnel plot is reasonably symmetrical.

Subgroup analysis

Subgroup analysis was undertaken on the Hb change data, and results are shown in *Table 18*. Forest plots for these subgroups are available as supplementary material, which can be requested from the authors. To test for between-group and within-group heterogeneity, the χ^2 test for interaction and F test were applied.

There is some evidence from the subgroup analysis that the moderate heterogeneity in the overall results may be explained by concomitant treatment or epo agent used, or possibly by the duration of the study, which shows a weaker effect, but these data should be treated with caution as they only include a fairly small subset of trials, with most of the information being contributed by a single large trial,[63] and there is some evidence of publication bias for this outcome. Furthermore, for most of the analyses the majority of trials fall into a single category, and so the results are particularly prone to chance effects.

Summary: Hb change

The overall WMD between intervention and control groups found a difference in Hb of 1.63 g dl^{-1}, with the test for heterogeneity χ^2 23.74, df 19, p = 0.21. Subgroup analysis found that this effect was reasonably consistent across subgroups.

Transfusion requirements

The risk of RBCT was measured by counting the number of patients who received RBCTs during

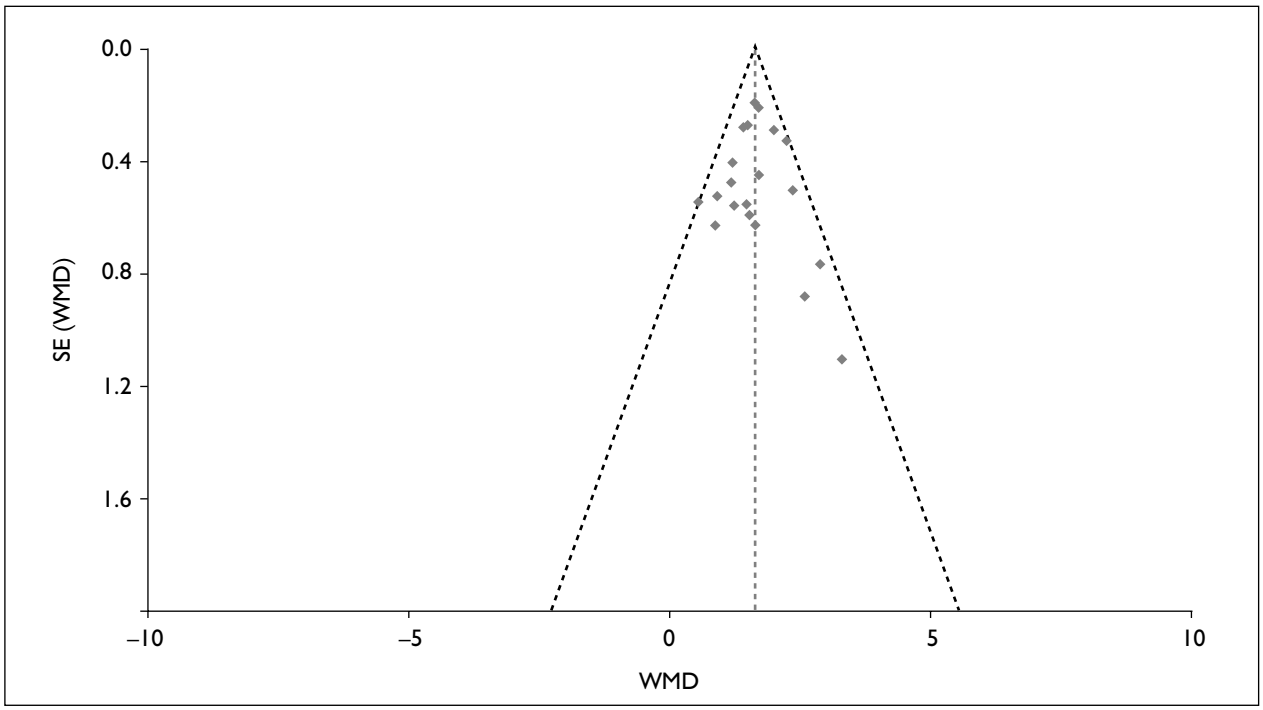

FIGURE 7 *Publication bias funnel plot*

TABLE 18 *Subgroup analysis: change in Hb*

	Trials	WMD	CI	$\chi^2_{(het)}$	df	*p*
Baseline Hb						
<10 g dl^{-1}	10	1.56	(1.34 to 1.79)	6.81	9	
10–12 g dl^{-1}	8	1.72	(1.42 to 2.01)	11.89	7	
>12 g dl^{-1}	3	2.15	(1.66 to 2.65)	1.32	2	
	Total within-group heterogeneity			20.02	18	
	Total between-group heterogeneity			4.58	2	**0.10**
	***F* (between:within)**			2.06	2,18	**0.16**
Total	21			24.60	20	
Different malignancies						
Solid tumours	16	1.57	(1.33 to 1.82)	21.67	15	
Haematological malignancies	2	1.73	(1.41 to 2.05)	1.21	1	
Mixed	1	1.70	(1.28 to 2.120	–	–	
Malignancy NR	1	1.51	(0.96 to 2.06)	–	–	
	Total within-group heterogeneity			22.88	16	
	Total between-group heterogeneity			0.86	3	**0.84**
	***F* (between:within)**			0.20	3,16	**0.89**
Total	20			23.74	19	
Different therapies						
Chemotherapy with platinum	3	2.01	(1.55 to 2.47)	1.12	2	
Chemotherapy without platinum	2	1.86	(1.51 to 2.22)	1.91	1	
Radiotherapy	3	2.89	(1.88 to 3.89)	0.24	2	
No therapy	9	1.36	(0.86 to 1.87)	5.33	8	
Unclear	3	1.42	(1.18 to 1.66)	0.82	2	
	Total within-group heterogeneity			9.42	15	
	Total between-group heterogeneity			14.32	4	**0.01**
	***F* (between:within)**			5.70	4,15	**0.01**
Total	20			23.74	19	

continued

TABLE 18 *Subgroup analysis: change in Hb (cont'd)*

	Trials	WMD	CI	$\chi^2_{(het)}$	df	*p*
Iron supplementation						
Fixed	5	1.72	(1.40 to 2.04)	6.65	4	
As necessary	6	1.72	(1.47 to 1.97)	6.48	5	
No explicit statement	9	1.40	(1.08 to 1.72)	7.93	8	
Total within-group heterogeneity				21.06	17	
Total between-group heterogeneity				2.68	2	**0.26**
***F* (between:within)**				1.08	2,17	**0.36**
Total	20			23.74	19	
Duration of study						
6–9 weeks	5	2.33	(1.73 to 2.94)	3.17	4	
12–16 weeks	13	1.55	(1.34 to 1.76)	14.52	12	
>20 weeks	2	1.63	(1.29 to 1.96)	0.29	1	
Total within-group heterogeneity				17.98	17	
Total between-group heterogeneity				5.76	2	**0.06**
***F* (between:within)**				2.72	2,17	**0.09**
Total	20			23.74	19	
Agent						
Epoetin alfa	3	1.57	(1.28 to 1.85)	0.77	2	
Epoetin beta	3	2.01	(1.55 to 2.47)	1.12	2	
Darbepoetin alfa	10	1.39	(1.14 to 1.65)	6.04	9	
Either epoetin alfa or beta	3	2.89	(1.88 to 3.89)	0.24	2	
Unsure	1	2.25	(1.60 to 2.90)	–	–	
Total within-group heterogeneity				8.17	15	
Total between-group heterogeneity				15.57	4	**0.00**
***F* (between:within)**				7.15	4,15	**0.00**
Total	20			23.74	19	
Allocation concealment						
Adequate	7	1.74	(1.47 to 2.01)	6.99	6	
Unclear	13	1.56	(1.35 to 1.78)	15.78	12	
Total within-group heterogeneity				22.77	18	
Total between-group heterogeneity				0.97	1	**0.32**
***F* (between:within)**				0.77	1,18	0.39
Total	20			23.74	19	

the trial. In total, 39 trials explored this outcome; 25 were described by Cochrane and the Birmingham searches identified a further ten trials. Of the Birmingham trials, four[71,78,125,130] are conference abstract publications only. An additional publication by Boogaerts[131] reports data that are already included in the Cochrane review (obtained by the Cochrane authors as additional unpublished data; see Coiffier[65]); however, Boogaerts also reports the number of patients receiving RBCTs excluding the first 4 weeks of the trial. There is a total of 53 data points for the meta-analysis (*Figure 8*) as several of the trials have more than one intervention arm.

The RR for all trials reporting data on the number of patients receiving a transfusion was 0.63, (95% CI 0.58 to 0.67, fixed effects). Test for heterogeneity was $\chi^2 = 4.75$, df 48, $p = 0.0001$, with the test for overall effect $z = -13.08$, $p < 0.0001$ (*Figure 8*). This heterogeneity was much higher than that reported by Cochrane[48] (RR 0.67, 95% CI 0.62 to 0.73, fixed effects): test for heterogeneity $\chi^2 = 57.76$, df 29, $p = 0.0012$, test for overall effect = –9.73, $p < 0.0001$. The risk difference (*Figure 9*) was –0.19 (95% CI –0.21 to –0.16, fixed effects).

The funnel plot shows marked asymmetry, but the pattern is not consistent with publication bias (*Figure 10*).

Subgroup analysis

Subgroup analysis was undertaken on the number of RBCT data (*Table 19*). Forest plots for these subgroups are available as supplementary material, which can be requested from the authors.

Comparison: Participants receiving RBCT
Outcome: Participants receiving RBCT

Study	Treatment *n/N*	Control *n/N*	RR (95% CI fixed)	Weight %	RR (95% CI fixed)
Thomas, 2002[130]	7/62	31/63		2.8	0.24 (0.11 to 0.50)
Vansteenkiste, 2002[64]	40/148	77/149		7.0	0.52 (0.38 to 0.71)
Aravantinos 2003[119]	9/24	23/23		2.2	0.37 (0.22 to 0.63)
Bamias, 2003[120]	11/72	24/72		2.2	0.46 (0.24 to 0.86)
Hedenus, 2002a[122]	3/11	1/3		0.1	0.82 (0.13 to 5.30)
Hedenus, 2002b[122]	6/22	2/4		0.3	0.55 (0.17 to 1.80)
Hedenus, 2002c[122]	3/22	2/4		0.3	0.27 (0.06 to 1/15)
Hedenus, 2003[123]	52/167	79/165		7.3	0.65 (0.49 to 0.86)
Iconomou, 2003[126]	9/61	16/61		1.5	0.56 (0.27 to 1.17)
Kotasek, 2003a[90]	8/30	3/8		0.4	0.71 (0.24 to 2.08)
Kotasek, 2003b[90]	5/17	3/8		0.4	0.78 (0.25 to 2.50)
Kotasek, 2003c[90]	12/41	4/9		0.6	0.66 (0.28 to 1.57)
Kotasek, 2003d[90]	9/35	4/8		0.6	0.51 (0.21 to 1.26)
Kotasek, 2003e[90]	7/27	3/9		0.4	0.78 (0.25 to 2.39)
Kotasek, 2003f[90]	7/38	4/9		0.6	0.41 (0.15 to 1.12)
Rosen, 2003[127]	19/47	24/43		2.3	0.72 (0.47 to 1.12)
Smith, 2003a[91]	16/20	6/6		0.8	0.80 (0.64 to 1.10)
Smith, 2003b[91]	6/20	7/7		1.0	0.30 (0.15 to 0.59)
Smith, 2003c[91]	10/20	7/7		1.0	0.50 (0.32 to 0.78)
Abels, 1993[93]	21/63	21/55		2.1	0.87 (0.54 to 1.42)
Carabantes, 1999[94]	4/20	13/15		1.4	0.23 (0.09 to 0.57)
Cascinu, 1994[95]	10/50	28/50		2.6	0.36 (0.19 to 0.65)
Case, 1993[96]	32/79	36/74		3.4	0.83 (0.58 to 1.19)
Cazzola, 1995c[97]	6/31	4/15		0.5	0.73 (0.24 to 2.19)
Cazzola, 1995d[97]	4/26	4/14		0.5	0.54 (0.16 to 1.83)
Coiffier, 2001[65]	43/133	67/129		6.2	0.62 (0.46 to 0.84)
Dammacco, 2001[98]	19/69	36/76		3.1	0.58 (0.37 to 0.91)
Del Mastro, 1997[99]	0/31	2/31		0.2	0.20 (0.01 to 1.85)
Dunphy, 1999[100]	2/13	5/14		0.4	0.43 (0.10 to 1.85)
Henry, 1994[102]	34/64	42/61		3.9	0.77 (0.58 to 1.03)
Italian, 1998[103]	28/43	35/42		3.2	0.78 (0.60 to 1.01)
Kunikane, 2001a[104]	1/16	0/9		0.1	1.76 (0.08 to 39.33)
Kunikane, 2001b[104]	2/18	0/10		0.1	2.89 (0.15 to 54.99)
Kurz, 1997[105]	5/23	8/12		1.0	0.33 (0.14 to 0.78)
Littlewood, 2001[63]	62/251	49/124		6.0	0.63 (0.46 to 0.85)
Oberhoff, 1998[106]	32/114	44/104		4.2	0.66 (0.46 to 0.96)
Österborg, 1996a[107]	33/37	19/24		2.3	0.89 (0.67 to 1.17)
Österborg, 1996b[107]	39/48	20/25		2.4	1.02 (0.80 to 1.29)
Österborg, 2002[108]	65/169	90/173		8.1	0.74 (0.58 to 0.94)
Quirt, 1996[109]	4/27	8/27		0.7	0.50 (0.17 to 1.47)
Rose, 1994[110]	65/142	47/179		5.5	0.77 (0.60 to 0.99)
Ten Bokkel, 1998a[112]	2/45	7/17		0.9	0.11 (0.02 to 0.47)
Ten Bokkel, 1998b[112]	6/42	6/16		0.8	0.38 (0.14 to 1.01)
Thatcher, 1999a[113]	19/42	13/22		1.6	0.77 (0.47 to 1.24)
Thatcher, 1999b[113]	9/44	13/22		1.6	0.35 (0.18 to 0.68)
Thompson, 2000[114]	34/45	19/21		2.4	0.84 (0.67 to 1.04)
Throuvalas, 2000[115]	2/28	10/26		1.0	0.19 (0.04 to 0.77)
Welch, 1995[116]	4/15	8/15		0.7	0.50 (0.19 to 1.31)
Wurnig, 1996[117]	8/15	14/14		1.3	0.53 (0.33 to 0.86)
Total (95% CI)	834/2637	988/1976		100.0	0.63 (0.58 to 0.67)

Test for heterogeneity $\chi^2 = 94.75$, df = 48 ($p = 0.0001$)
Test for overall effect $z = 13.08$ ($p < 0.00001$)

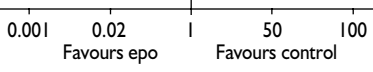

FIGURE 8 *Transfusion requirements (relative risk)*

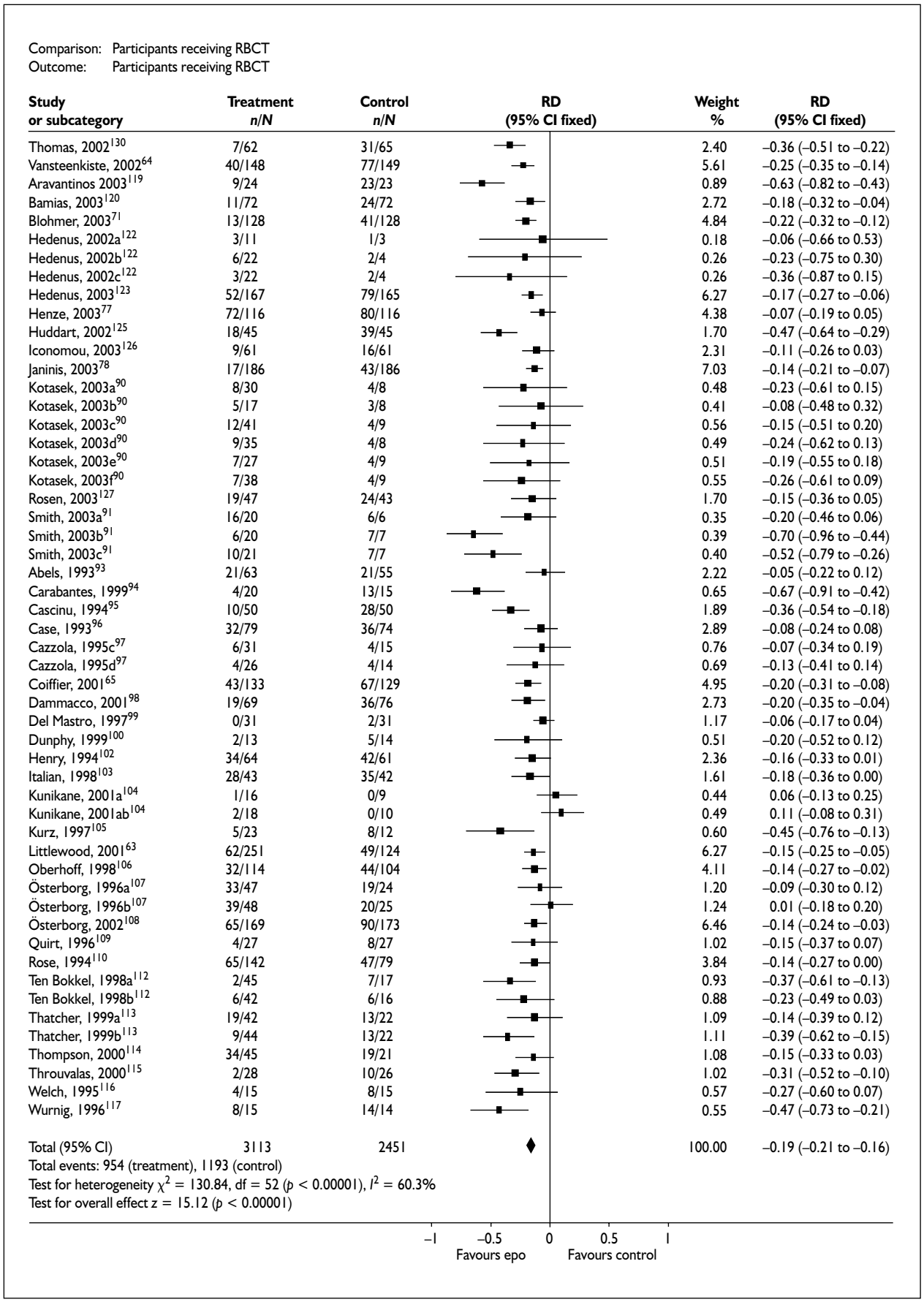

FIGURE 9 *Transfusion requirements (risk difference)*

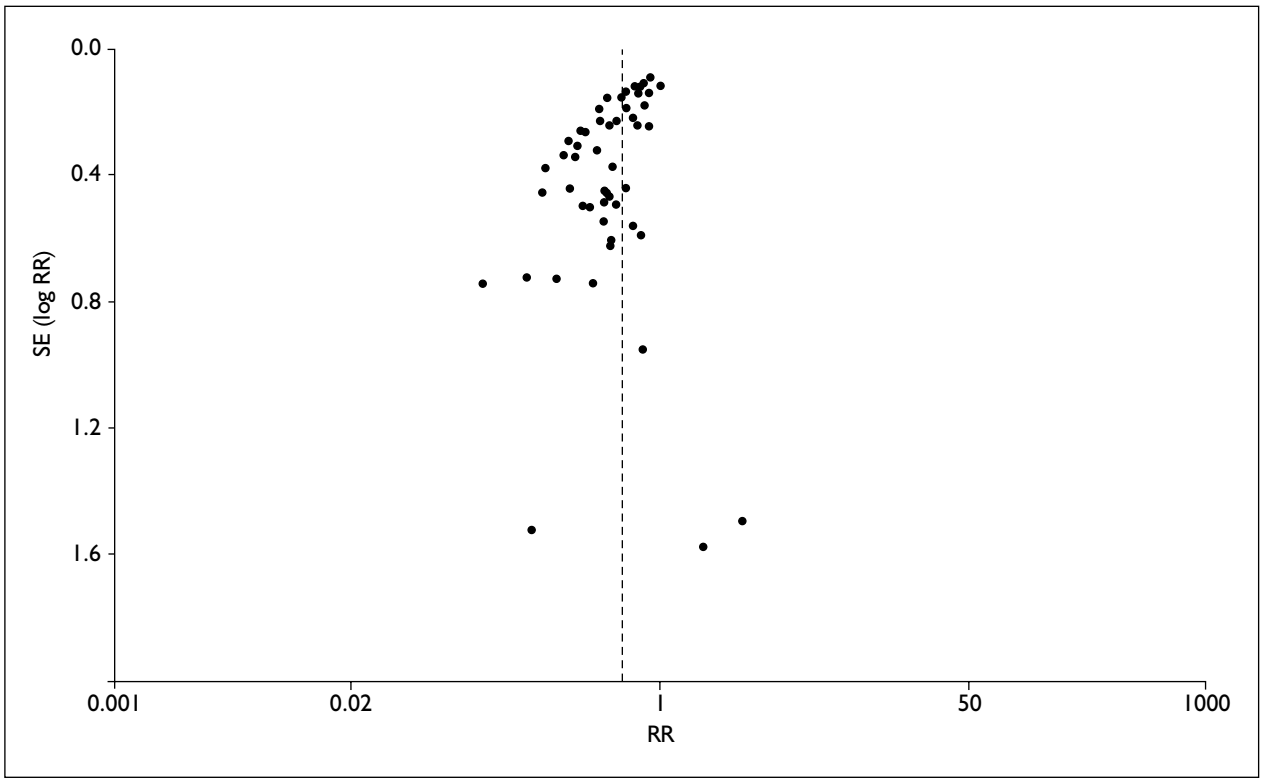

FIGURE 10 *RBCT: funnel plot*

To test for between-group and within-group heterogeneity the χ^2 test for interaction and *F* test were applied.

There is fairly substantial heterogeneity in this outcome, which appears to be principally explained by type of malignancy and type of therapy, both of which produce highly significant metaregressions, with the relative risk of blood transfusion appearing to be substantially lower for those with solid tumours or receiving platinum-based chemotherapy or chemoradiation (there were no trials reporting this outcome for radiotherapy alone). These observations are supported by the non-significant trends by baseline Hb and policy on iron supplementation.

These results are reasonably secure, given the large proportion of trials contributing data to this analysis and the consistency between the results.

Summary: RBCT

Treatment with erythropoietin in patients with cancer-induced anaemia reduces the number of patients who receive RBCT by an estimated 18%. There was, however, statistically significant heterogeneity between the trials. Patients with solid tumours and patients who were on platinum-based chemotherapy are also less likely to receive RBCT if on erythropoietin than patients with other tumour types and on other tumour therapies. Iron supplementation also appears to reduce the numbers of patients receiving RBCTs.

Mean number of RBC units transfused per patient

Only one Birmingham study, by Vansteenkiste[64] reported data that could be included in the meta-analysis. This was a large trial, which accounts for 20.9% of the weight. The patients in Vansteenkiste had solid tumour malignancies and were being treated with platinum-based chemotherapy. The trial intervention was darbepoetin against placebo. All of the data included by the Cochrane review[48] that contributed to this meta-analysis were in the form of unpublished data obtained by the study authors.

The addition of Vansteenkiste[64] made only a very slight difference to the Cochrane[48] estimate of WMD –1.00 (95% CI –1.31 to –0.70, fixed effects) to WMD –1.05 (95% CI –1.32 to –0.78), test for heterogeneity $\chi^2 = 8.96$, df 16, $p = 0.91$ (*Figure 11*).

Summary: RBCT per patient

The results suggest that there is only a slight difference between the number of RBC units that

TABLE 19 *Subgroup analysis: RBCT*

		Trials	RR	CI	$\chi^2_{(het)}$	df	*p*
Baseline Hb							
<10 g dl^{-1}		29	0.69	(0.64 to 0.74)	39.41	28	
10–12 g dl^{-1}		14	0.43	(0.36 to 0.51)	43.58	13	
>12 g dl^{-1}		7	0.56	(0.40 to 0.80)	5.90	6	
NR		3	0.65	(0.55 to 0.77)	21.82	2	
		Total within-group heterogeneity			110.71	49	
		Total between-group heterogeneity			12.51	3	**0.01**
		***F* (between:within)**			1.85	3,49	**0.15**
	Total	53			123.22	52	
Different malignancies							
Solid tumours		30	0.48	(0.43 to 0.54)	30.92	29	
Haematological malignancies		12	0.72	(0.64 to 0.80)	15.11	11	
MDS		2	0.80	(0.68 to 0.96)	0.16	1	
Mixed		10	0.70	(0.63 to 0.79)	28.36	9	
		Total within-group heterogeneity			74.55	50	
		Total between-group heterogeneity			48.67	2	**0.00**
		***F* (between:within)**			16.32	2,50	**0.00**
	Total	54			123.22	52	
Different therapies							
Chemotherapy with platinum		19	0.52	(0.46 to 0.59)	28.23	18	
Chemotherapy without platinum		9	0.76	(0.67 to 0.85)	9.86	8	
Chemotherapy plus radiotherapy		2	0.47	(0.32 to 0.67)	5.54	1	
No therapy		6	0.74	(0.64 to 0.86)	12.98	5	
Unclear		17	0.60	(0.53 to 0.68)	31.01	16	
		Total within-group heterogeneity			87.62	48	
		Total between-group heterogeneity			35.60	4	**0.00**
		***F* (between:within)**			4.88	4,48	**0.00**
	Total	53			123.22	52	
Iron supplementation							
Fixed		6	0.50	(0.40 to 0.62)	5.06	5	
As necessary		25	0.66	(0.61 to 0.73)	35.03	24	
No explicit statement		20	0.62	(0.56 to 0.69)	66.97	19	
In intervention arm only		53	0.47	(0.33 to 0.67)	5.54	1	
		Total within-group heterogeneity			112.60	49	
		Total between-group heterogeneity			10.62	3	**0.01**
		***F* (between:within)**			1.54	3,49	**0.22**
	Total	53			123.22	52	
Duration of study							
6–9 weeks		9	0.63	(0.50 to 0.78)	12.54	8	
12–16 weeks		28	0.63	(0.58 to 0.68)	43.99	27	
>20 weeks		15	0.63	(0.56 to 0.70)	61.08	14	
NR		1	0.40	(0.23 to 0.67)	–	–	
		Total within-group heterogeneity			117.61	49	
		Total between-group heterogeneity			5.61	3	**0.13**
		***F* (between:within)**			0.78	3,49	**0.51**
	Total	53			123.22	52	
Dose							
Within licence indication		30	0.64	(0.59 to 0.69)	47.81	29	
Higher than licence indication		2	0.50	(0.32 to 0.77)	0.22	1	
Lower than licence indication		5	0.60	(0.43 to 0.84)	5.75	4	
Fixed dose per week (not IU/kg)		12	0.57	(0.49 to 0.66)	45.66	11	

continued

TABLE 19 *Subgroup analysis: RBCT (cont'd)*

	Trials	RR	CI	$\chi^2_{(het)}$	df	*p*
Given every 4 weeks	2	0.39	(0.26 to 0.57)	1.36	1	
Unclear	2	0.70	(0.58 to 0.85)	14.10	1	
Total within-group heterogeneity				114.90	47	
Total between-group heterogeneity				8.32	5	**0.14**
***F* (between:within)**				0.68	5,47	**0.64**
Total	53			123.22	52	
Agent						
Epoetin alfa	23	0.61	(0.56 to 0.67)	72.47	22	
Epoetin beta	13	0.69	(0.61 to 0.78)	24.73	12	
Darbepoetin alfa	14	0.57	(0.49 to 0.67)	16.60	13	
Unclear	3	0.25	(0.10 to 0.66)	0.72	2	
Total within-group heterogeneity				114.52	49	
Total between-group heterogeneity				8.70	3	**0.03**
***F* (between:within)**				1.24	3,49	**0.31**
Total	53			123.22	52	
Allocation concealment						
Adequate	24	0.68	(0.62 to 0.75)	48.13	23	
Unclear	29	0.57	(0.52 to 0.63)	64.11	28	
Total within-group heterogeneity				112.24	51	
Total between-group heterogeneity				10.98	1	**0.00**
***F* (between:within)**				4.99	1,51	**0.03**
Total	53			123.22	52	

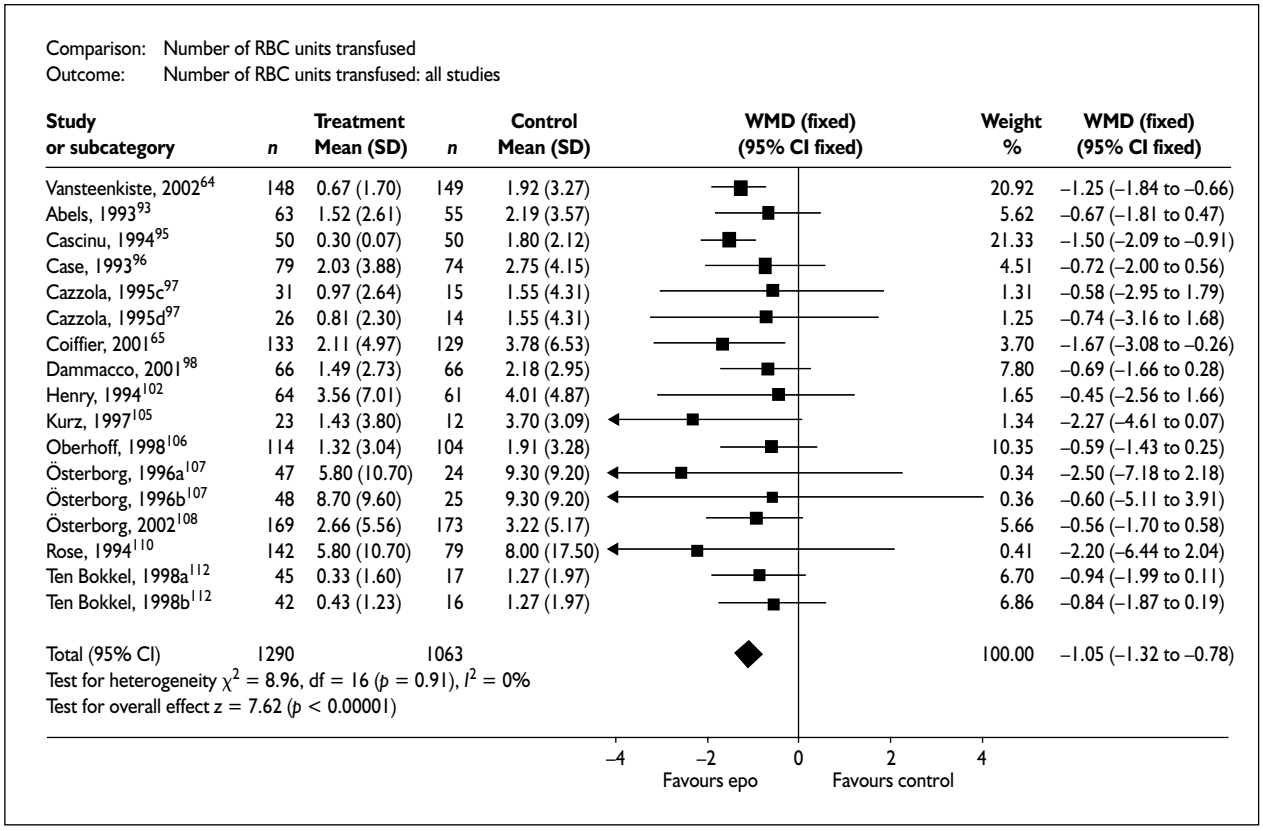

FIGURE 11 *Number of RBCs transfused*

TABLE 20 *Cochrane results versus Birmingham update results*

Anaemia-related outcome	Cochrane review	Birmingham
HaemR	RR 3.60 95% CI 3.07 to 4.23 $\chi^2_{(het)}$ 16.91, df 15 ($p = 0.32$) 14 trials, $n = 2347$	RR 3.40 95% CI 3.01 to 3.83 (fixed) $\chi^2_{(het)}$ 23.60, df 32 ($p = 0.86$) 21 trials, $n = 3740$
Hb change from baseline to end of study	WMD 1.66 95% CI 1.65 to 1.73 $\chi^2_{(het)}$ 220.21, df 9 ($p < 0.00001$) 6 trials, $n = 755$	WMD 1.63 95% CI 1.46 to 1.80 $\chi^2_{(het)}$ 23.74, df 19 ($p = 0.21$) 10 trials, $n = 1620$
No. of patients receiving RBCT	RR 0.67 95% CI 0.62 to 0.73 $\chi^2_{(het)}$ 57.76, df 29 ($p = 0.0012$) 25 trials, $n = 3069$	RR 0.63 95% CI 0.58 to 0.67 (fixed) $\chi^2_{(het)}$ 94.75, df 48 ($p = 0.001$) 35 trials, $n = 5564$
No. of RBCTs per patient	WMD –1.00 95% CI –1.31 to –0.70 $\chi^2_{(het)}$ 8.43, df 15 ($p = 0.91$) 13 trials, $n = 2056$	WMD –1.05 95% CI –1.32 to –0.78 $\chi^2_{(het)}$ 8.96, df 16 ($p = 0.91$) 14 trials, $n = 2353$

intervention and control patients receive. Only one trial in the Birmingham update reported this outcome.

Anaemia-related outcomes: overall summary

Of the anaemia-related outcomes the most robust data (with the least statistical heterogeneity) came from the outcome of haematological response (*Table 20*). This outcome measure had a clear definition of an increase in Hb of 2 g dl^{-1} or more which was unrelated to transfusion. The analysis showed that patients on epo were three times more likely to experience a 2 g dl^{-1} increase in Hb than patients in the control group; however, a small number of patients in the control group (15.7%) experienced a haematological response.

The haematological response analysis does not count Hb increases that are less than 2 g dl^{-1} and misses patients who are able to maintain their Hb or patients who are maintaining an Hb level despite being on anaemia-inducing chemotherapy. Hb change therefore had the potential to identify lower increases and stable Hb. Unfortunately, there were fewer trials reporting this outcome; all the trials reported an increase in Hb in favour of epo and the overall WMD Hb increase was 1.63 g dl^{-1}. Unlike haematological response, which had the caveat that patients had to be transfusion free for a month before assessment, Hb change was not restricted to patients who were transfusion free, therefore the results may have been confounded by transfusion in some of the patients (with the potential further confounding of transfusion triggers[9]).

The number of patients receiving RBCTs was the third outcome assessed to investigate the effects of epo on anaemia. Data were reported for the whole of the trial period; the RR of receiving a blood transfusion was 0.63 in favour of epo, equating to 30.6% of patients in the epo arms receiving blood transfusion in comparison to 48.7% in the control groups. The number of transfusions per patient was also investigated. Only 14 trials reported this outcome, and many of these data were received by the Cochrane review through further questions to the trial authors. There was little difference between epo and control groups regarding the amount of blood transfused.

Effectiveness: malignancy-related outcomes

Two outcomes assessed the effect of erythropoietin on patients' underlying malignancy. These were tumour response and overall survival.

Tumour response

The Cochrane review[48] identified seven studies that had measured a complete tumour response (*Table 21*). The pooled result suggested an improvement in favour of epo, with an RR of 1.36 (95% CI 1.07 to 1.72 fixed effects model). The Birmingham search identified only one further study that reported tumour response data; Bamias[120] used epoetin beta on patients with solid

TABLE 21 *Trials assessing effects on tumour response/progression of disease*

Study	Results for use in meta-analysis			Tumour response definition	Results as reported in paper, which could not be used in meta-analysis	Comments
	Intervention	Control	*p*			
Tumour response						
Bamias, 2003[120]	30/53	27/57		WHO criteria[132] For patients with ovarian cancer tumour response was defined as no evidence of radiological disease and normal CA 125 after cytoreductive surgery and chemotherapy	Intervention *n* = 53/72 evaluable (74% of those randomised) Tumour response = 30/53 (56%) Control *n* = 57/72 evaluable (79% of those randomised) Tumour response = 27/57 (47.4%)	No SD or *p*-values reported
Disease progression						
Henke, 2003[124]				Primary end-point was locoregional tumour progression or death, whichever came first. Also assessed was time to locoregional tumour progression and survival. Tumour progression was assumed when tumour size increased by >25%	208/351 (59%) of the ITT population experienced locoregional tumour progression or died during the follow up: 92/171 (53%) in placebo and 116/180 (64%) in intervention group. 79 and 64 patients, respectively, were censored. However, the stage-adjusted and stratum-adjusted RR for locoregional progression-free survival was 1.62 for intervention (95% CI 1.22 to 2.14, $p = 0.0008$). For locoregional progression only RR = 1.69 (95% CI 1.16 to 2.47, $p = 0.007$)	Population was those undergoing radiotherapy; this study had a primary outcome of progression-free survival, therefore was powered to detect it
Leyland-Jones, 2003[118]			NR	NR	"The observed difference in number of early deaths was mainly due to an increase in incidence of disease progression in the epoetin alfa group compared with placebo (6% vs 3%) [n = 28 vs 14 patients if assume 1:1 randomisation] as well as an increase in the incidence of thrombotic and vascular events in the epoetin alfa group (1% vs 0.2%)"	Trial enrolled 939 patients, given 12 months of epo treatment and was terminated early by the independent data monitoring committee. 12-month survival was analysed. "Almost all imbalance in mortality occurred within the first 4 months and was attributed to disease progression"

continued

TABLE 21 *Trials assessing effects on tumour response/progression of disease (cont'd)*

Study	Results for use in meta-analysis			Tumour response definition	Results as reported in paper, which could not be used in meta-analysis	Comments
	Intervention	Control	*p*			
Rosenzweig, 2004[128]			NR	NR	Intervention: disease progression = 2/14 Control: disease progression = 3/13	Trial ended early due to thrombotic events
Progression-free survival						
Rosen, 2003[127]				NR	Median progression-free survival not attained Progression-free survival. Intervention (*n* at start 47): 12 months = 75%, 24 months = 70%, 36 months = 68%, 48 months = 68% Control (*n* at start 43): 12 months = 70%, 24 months = 60%, 36 months = 58%, 48 months = 55%. *p* = 0.35	Kaplan–Meier progression-free survival
Vansteenkiste, 2002[64]			NR	NR	Median duration of progression-free survival: Intervention = 22 weeks (95% CI = 18 to 31 weeks) 129/156 (83%) Control = 20 weeks (95% CI 17 to 23 weeks) 141/158 (89%)	Tumour response reported as progression-free survival. Information from 2002 publication data on progression-free survival current to August 2001, average follow-up of 1 year
Awaiting follow-up						
Hedenus, 2003[123]			NR	NR	NR	Information about tumour progression is continuing to be collected during a long-term follow-up period

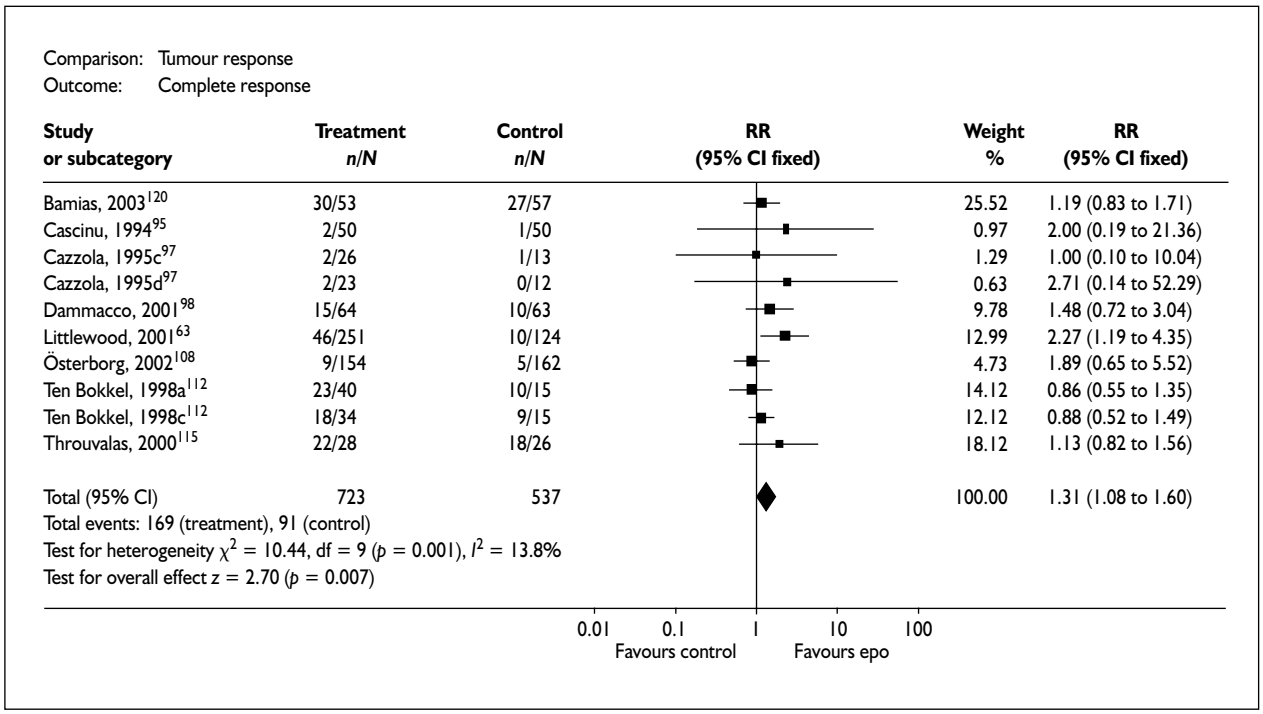

FIGURE 12 *Tumour response*

tumours, receiving platinum-based chemotherapy. When this was added to the Cochrane data the RR reduced to 1.31 (95% CI 1.08 to 1.60) (*Figure 12*).

Five additional trials identified by the Birmingham searches assessed tumour growth by looking at disease progression[118,124,128] and progression-free survival.[64,127] There were concerns regarding the number of deaths in both Leyland-Jones[118] and Rosenzweig.[128] In Henke,[124] progression-free survival was higher in the control group, but when adjusted for disease stage and stratum the progression-free survival came out in favour of erythropoietin.

This is a difficult area of assessment, especially in a heterogeneous mix of tumour types, and these results should be treated with caution. The results of the survival analysis are presented below, followed a discussion of relevant comments from an FDA safety briefing.

Survival analysis

Methods

This section is supplementary to the general methods for the systematic review (Chapter 3).

Data were extracted on the number of deaths in each arm, reported hazard ratio (HR) and associated confidence interval and log-rank p-value. Length of follow-up and presentation of Kaplan–Meier survival curves were also noted.

Where available, results based on individual patient data (IPD) from the Cochrane review were used for meta-analysis. Where data were only obtainable from a publication the methods published by Parmar and colleagues[133] were used where possible to obtain estimates of the log-hazard ratio and its variance.

Where a hazard ratio and an associated confidence interval (or p-value) were reported, these were used to obtain estimates of the log-hazard ratio and its variance. Where no hazard ratio was reported, other less direct methods proposed by Parmar[133] were attempted. Where none of these published methods could be used, a simple estimate of the expected number of deaths (E) on each arm was obtained by reference to the observed number of deaths (O) and the randomisation ratio. For example, if two-thirds of the patients randomised were on one arm of the trial, then the expected number of deaths on that arm would be two-thirds of the total number of deaths observed.

This 'simple' method is based on similar techniques proposed in Parmar,[133] but it is not yet known how well it performs. Therefore, results obtained from IPD or from trials where survival

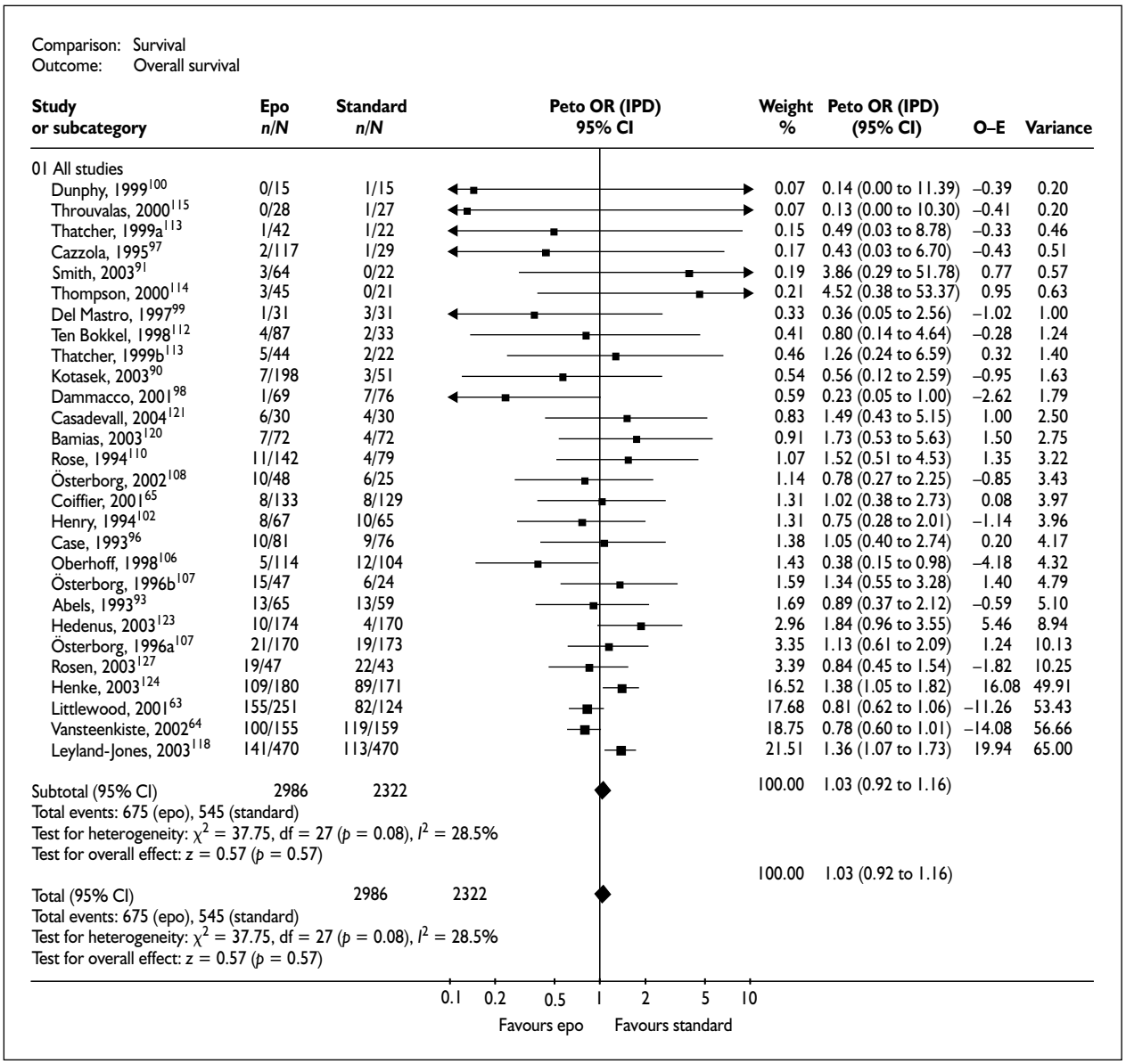

FIGURE 13 *Survival results. Note that the boxes on the plots do not appear at the correct size. Approximately 75% of the information is contributed by just the four largest trials. OR, odds ratio*

results were well reported were compared with the results obtained from the same trials using the 'simple' method, to allow some check on reliability (in the context of this review only).

Results

Survival data were available from a total of 28 trials, 19 of which had been included in the previous Cochrane review.[48] No survival data were obtainable from 13 trials, two of which had been included in the previous Cochrane review; three of these trials reported explicitly that no deaths had been observed.

The results from the previous Cochrane review were a hazard ratio of 0.84 in favour of epo (95% CI 0.69 to 1.02, $p = 0.08$) for the combined unadjusted survival data. There was little heterogeneity, with a $\chi^2_{(het)}$ of 13.71 on 18 df ($p = 0.75$).

With the new data from the nine additional studies included, the updated result is a hazard ratio of 1.03 (95% CI 0.92 to 1.16, $p = 0.57$) in favour of placebo/standard treatment, with a $\chi^2_{(het)}$ of 37.74 on 27 df ($p = 0.08$) (*Figure 13*).

The marked change in the results is due to the fairly extreme results favouring no treatment/placebo in the newer studies, six out of nine reporting somewhat more deaths on the epo arm, although updated survival data obtained

from the FDA[92] for the Vansteenkiste trial[64] (which reported immature survival data at publication) show a very positive result in favour of epo. The combined results for these nine newer trials are a hazard ratio of 1.15 (95% CI 1.00 to 1.32, $p = 0.048$) in favour of placebo/no treatment, with a $\chi^2_{(het)}$ of 17.33 on 8 df ($p = 0.027$).

The 'random effects' model is not easy to apply to this type of data, but a simple alternative is simply to inflate the variance of the pooled 'fixed effects' estimate to reflect heterogeneity. This is achieved by multiplying the variance of the pooled estimate from the traditional 'fixed effects' model and multiplying this by (χ^2_{het} /df) to obtain a more reasonable summary of the uncertainty in the estimate in the presence of substantial heterogeneity. Using this method, the same estimate of the hazard ratio, 1.03, is obtained, but with a wider confidence interval of 0.88 to 1.21 ($p = 0.68$).

Note that the trials in *Figure 13* have been ordered by their weight in the pooled analysis, as this is not adequately reflected by the box sizes in the plot; the extremes are too great for the software to plot boxes proportional to weight. Unlike other end-points, the contribution of a trial to a pooled survival analysis is essentially dependent on the number of deaths observed rather than the number of patients recruited. In this set of data around 75% of the information is contributed by just four large trials.

Comparison of methods for obtaining summary survival results

In general the 'simple' approach, which was the only method available for 15 of the 28 trials, seemed to perform well when compared with the gold-standard results available for 12 of the trials (*Figure 14*). Unsurprisingly, the only trials with any substantive heterogeneity between the results were the four large trials that had observed substantial survival differences. In this set of trials, the simple method seems to give slightly less extreme results than the gold standard in trials that observed a survival difference. This is probably due to the apparently non-proportional hazards seen in many of these trials, which would give larger estimates than the assumptions underlying the simple method.

Encouragingly, the method does not appear systematically to overestimate or underestimate results compared with the gold standard. The pooled result for the 12 trials was 1.03 (95% CI 0.91 to 1.16, $p = 0.68$) for the gold-standard method, and 1.04 (95% CI 0.92 to 1.18, $p = 0.52$) for the simple approach.

Subgroup analysis

Subgroup analysis was undertaken (*Table 22*). Forest plots for these subgroups are available as supplementary material, which can be requested from the authors. To test for between-group and within-group heterogeneity the χ^2 test for interaction and F test were applied.

These subgroup results are discussed below.

Discussion of effects of epo on underlying malignancies

Despite the lack of concordance between the results from the earlier studies, as reported in the Cochrane review, and the newer studies identified for this review, the heterogeneity overall appears reasonably consistent with chance ($p = 0.08$). However, there is considerable clinical heterogeneity (site of cancer, setting, dose, comparator, etc.), which should not be dismissed. Following the very positive results of the Littlewood trial[63] (which contributed over half of the total survival information to the Cochrane review[48]), the survival data from the Henke[124] and Leyland-Jones[118] trials were greeted with some surprise and dismay. The updated results of the Vansteenkiste trial (obtained from the FDA[92]), however, appear to confirm the earlier Littlewood[63] results. These four trials contribute almost 75% of the total information available, with the other 21 trials contributing between 0.05% and 3.5% each, and so the marked, qualitative, disagreement in the results of these four trials cannot easily be dismissed.

Hypotheses have been proposed to explain the differing results from these trials (as far as the authors are aware, the mature survival results from the Vansteenkiste trial have not yet been widely disseminated). It has been suggested that survival outcomes might be site-specific, with epo perhaps increasing the effectiveness of treatment in some cancers owing to improved oxygen supply making the tumour more vulnerable to cytotoxic treatment,[36] while stimulating tumour growth in other cancers, possibly owing to the presence of erythropoietin receptors. Others have suggested that the dose of epo and/or the level of Hb at which treatment is given may be relevant, pointing to the apparent excess of cardiac deaths seen in a number of studies. Finally, there have been suggestions that imbalances in patient characteristics may have affected the results of some trials.

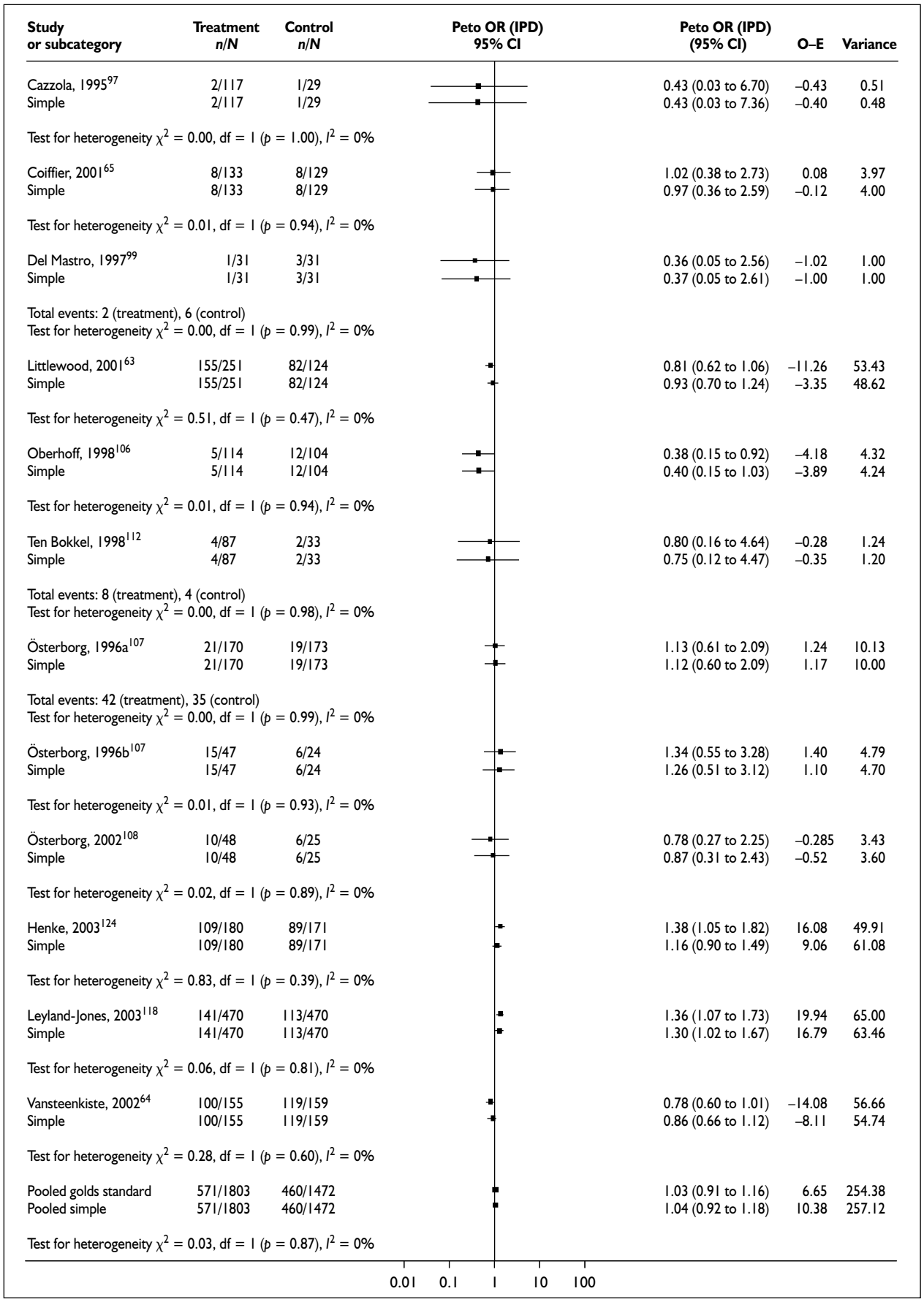

FIGURE 14 *Comparison of 'gold standard' with 'simple' method.* [a] *Birmingham study.*

TABLE 22 *Subgroup analysis: survival*

		Trials	HR	CI	$\chi^2_{(het)}$	df	*p*
Baseline Hb							
<10 g dl^{-1}		17	0.91	(0.76 to 1.08)	17.20	16	
10–12 g dl^{-1}		6	1.03	(0.86 to 1.24)	11.33	5	
>12 g dl^{-1}		5	1.31	(1.04 to 1.66)	3.19	4	
		Total within-group heterogeneity			31.72	25	
		Total between-group heterogeneity			5.78	2	**0.06**
		***F* (between:within)**			2.28	2,25	**0.12**
	Total	28			37.50	27	
Different malignancies							
Solid tumours		13	1.08	(0.94 to 1.24)	22.49	12	
Haematological malignancies		7	1.18	(0.84 to 1.67)	7.93	6	
MDS		2	1.86	(0.62 to 5.65)	0.62	1	
Mixed		6	0.85	(0.67 to 1.07)	1.82	5	
		Total within-group heterogeneity			32.86	24	
		Total between-group heterogeneity			4.64	3	**0.20**
		***F* (between:within)**			1.13	3,24	**0.36**
	Total	15			37.50	27	
Different therapies							
Chemotherapy with platinum		10	0.74	(0.59 to 0.94)	8.10	9	
Chemotherapy without platinum		8	0.89	(0.72 to 1.110	4.03	7	
Type of chemotherapy not specified		1	1.36	(1.07 to 1.73)	–	–	
Chemotherapy plus radiotherapy		1	0.84	(0.45 to 1.54)	–	0	
Radiotherapy alone		1	1.38	(1.05 to 1.82)	–	0	
No therapy		3	1.20	(0.55 to 2.61)	2.34	2	
Unclear		4	1.39	(0.86 to 2.23)	2.46	3	
		Total within-group heterogeneity			16.93	21	
		Total between-group heterogeneity			20.57	6	**0.00**
		***F* (between:within)**			2.12	6,21	**0.01**
	Total	8			37.50	27	
Duration of study							
6–9 weeks		4	0.74	(0.33 to 1.64)	1.48	3	
12–16 weeks[a]		12	0.95	(0.69 to 1.31)	16.30	11	
>20 weeks[a]		12	1.05	(0.93 to 1.19)	18.92	11	
		Total within-group heterogeneity			36.70	25	
		Total between-group heterogeneity			0.80	2	**0.67**
		***F* (between:within)**			0.27	2,25	**0.76**
	Total	28			37.50	27	
Dose							
Within licence indication		17	1.05	(0.93 to 1.18)	28.47	16	
Higher than licence indication[b]		0	–	–	–	–1	
Lower than licence indication		1	1.69	(0.37 to 2.12)	–	0	
Mixed doses		1	0.54	(0.12 to 2.59)	–	0	
Fixed dose per week (not IU kg^{-1})		8	0.95	(0.69 to 1.32)	7.27	7	
Given every 4 weeks		1	3.86	(0.29 to 51.78)	–	0	
		Total within-group heterogeneity			35.74	22	
		Total between-group heterogeneity			1.76	5	**0.88**
		***F* (between:within)**			0.22	5,22	**0.95**
	Total	10			37.50	27	

continued

TABLE 22 *Subgroup analysis: survival (cont'd)*

	Trials	HR	CI	$\chi^2_{(het)}$	df	*p*
Agent						
Epoetin alfa	12	1.07	(0.91 to 1.25)	12.08	11	
Epoetin beta	9	1.14	(0.92 to 1.42)	12.90	8	
Darbepoetin alfa	4	0.88	(0.69 to 1.11)	7.29	3	
Unsure	3	0.27	(0.05 to 1.43)	0.28	2	
	Total within-group heterogeneity			32.55	24	
	Total between-group heterogeneity			4.95	3	**0.18**
	***F* (between:within)**			1.22	3,24	**0.33**
Total	25			37.50	27	
Allocation concealment						
Adequate	15	0.85	(0.70 to 1.04)	8.72	14	
Unclear	13	1.13	(0.99 to 1.30)	23.52	12	
	Total within-group heterogeneity			32.24	26	
	Total between-group heterogeneity			5.26	1	**0.02**
	***F* (between:within)**			4.24	1,26	**0.05**
Total	28			37.50	27	

[a] Vansteenkiste[64] included in >20-week follow-up for this analysis as survival data based on mature update submitted to the FDA.[92]

[b] Mixed doses for Kotasek[90] not split by arm as too few events observed.

All three of these key hypotheses have some support in the data reported above. In subgroup analysis, Henke[124] found that patients with advanced disease or cancer of the hypopharynx seemed to fare worse on epo. However, although Littlewood[63] reported positive results both overall and in the subgroup of patients with solid tumours (which included patients with metastatic breast cancer), the Leyland-Jones trial[118] in patients with metastatic breast cancer was stopped early because of an excess of deaths on epo. Similarly, while Vansteenkiste reported positive survival benefits in patients with lung cancer, an FDA safety briefing[92] reports two unpublished trials in lung cancer that were terminated early owing to an excess of thromboembolic events and, for one trial, excess mortality on the epo arm. The available aggregate data are thus contradictory. IPD meta-analysis would allow a more detailed subgroup analysis of specific malignancies (e.g. breast cancer, lung cancer, head and neck cancer), to investigate these observations further.

The Henke trial[124] also offers some indirect evidence concerning possible increased risk in healthier patients, finding excess deaths in patients who had a higher baseline Hb, while the Leyland-Jones trial,[118] which was stopped early because of an excess of deaths on epo, was conducted in an explicitly preventive setting, recruiting patients with Hb above 12 g dl^{-1} with treatment aimed at maintaining this level throughout platinum-based chemotherapy. In this context, it is interesting to recall the apparent trend over time in the survival outcomes of the older and newer trials which, if real, may be due in part to changes in practice, including dose, scheduling, patient selection and timing of the intervention.

The excess deaths on epo in both Henke[124] and Leyland-Jones[118] were observed relatively early on in the trials. The excess deaths in the Leyland-Jones trial[118] (using chemotherapy for metastatic breast cancer) were seen in the "first 4 months", somewhat earlier than in the Henke trial (using radiotherapy for head and neck cancer), where the divergence appears to start around month 3 before the curves become parallel again at around month 8. This difference in the pattern of survival seen in these trials may be due to a number of factors, such as the site and type of cancer (in this case, breast cancer versus head and neck cancer), treatment modality (chemotherapy versus radiotherapy), the nature of any imbalances in patient characteristics or simple chance. However, it is worth noting that Henke recruited patients with somewhat lower Hb at baseline (10–12 g dl^{-1}), which may explain a delay in observing excess deaths compared with the Leyland-Jones trial, if Hb levels were indeed contributing to excess mortality through increased cardiovascular risk.

This hypothesis is given weak support by the subgroup analysis by baseline Hb levels, with results slightly favouring epo at low baseline Hb levels, favouring neither at moderate levels and favouring no treatment at high levels. A simple test for interaction suggests that this effect may be real, with a p-value of 0.06. The more exacting F test, comparing the total heterogeneity between groups split by baseline Hb with the heterogeneity remaining within these groups (effectively a metaregression on baseline Hb), gives a p-value of 0.12.

The subgroup analysis of survival results by concomitant anticancer treatment offers some evidence that survival outcomes may depend on the type of anticancer treatment given ($\chi^2_{(\text{interaction})} = 16.93$, 6 df, $p = 0.01$; $F = 4.25$, 6,21 df, $p = 0.002$).

This observation is consistent with the hypothesis that high Hb levels may contribute to increased mortality, as platinum-based chemotherapy depletes RBCs and so would maintain Hb at low levels throughout the treatment cycles, negating any risk from maintaining Hb at excessive levels with epo.

The suggestion of benefit (as opposed to the absence of harm) in terms of survival observed with platinum-based chemotherapy could be due to a number of factors, including chance. There is insufficient evidence available either to determine whether there are real survival benefits associated with epo given in conjunction with platinum-based chemotherapy, or to speculate as to the reasons why this benefit might accrue. Although the results for this subgroup suggest a survival benefit associated with epo, there is some asymmetry in the funnel plot and it would be unwise to draw any firm conclusions without obtaining data from all of the relevant trials. In particular, at least two of the trials noted in the FDA safety briefing[92] which were stopped early owing to safety concerns used platinum-based chemotherapy in all patients, one in lung cancer and one in cervical cancer.

Although it is tempting to draw firm conclusions, it is important to note that the analysis presented here is dominated by only four large trials, with one (Leyland-Jones[118]) alone in the 'chemotherapy not specified' group; it is not clear that platinum was prohibited from this trial as chemotherapy was given according to local standard practice, and may have included some platinum-based as well as non-platinum regimens; otherwise, it would belong in the same group as the Littlewood[63] trial, which reported very different survival outcomes. Although there are clear differences between the two trials in terms of the types of patients recruited (especially tumour type and baseline Hb), the Leyland-Jones trial was set up explicitly to explore (and extend) the hypothesis generated by the Littlewood trial, as explained in an FDA briefing document:[92]

> "The Breast Cancer Erythropoietin Trial (BEST), designed by Johnson & Johnson, was conducted to extend and possibly confirm the results of an earlier trial (Study EPO-INT-10). EPO-INT-10 was a randomized, placebo-controlled trial that had enrolled 375 subjects. The patients had either solid or non-myeloid hematologic malignancies and hemoglobin levels of either 10.5 g/dL or between 10.5 and 12.0 g/dL after a hemoglobin decrease of at least 1.5 g/dL per cycle since starting chemotherapy. Patients received study drug for 12 to 24 weeks. No specific target hemoglobin was given, however, the dose of EPREX was to be held if the hemoglobin was greater than 15 g dl^{-1}, and restarted at 12 g/dL. The trial was not powered for survival, but there was a trend in overall survival favoring the EPREX arm (log rank test $p = 0.13$; Cox regression analysis hazards ratio of 1.309 ($p = 0.052$)) … An additional basis for initiation of EPO-INT-76 was the supposition that use of an erythropoietin to increase hemoglobin levels might improve survival given the literature suggesting a link between low hemoglobin levels (as a marker for tumor hypoxia), poorer response to treatment (both radiation and chemotherapy), and worsening survival.
>
> Study EPO-INT-76 was designed to test the hypothesis that maintaining hemoglobin in the range of 12 to 14 g/dL via the administration of EPREX would improve survival and quality of life in patients with metastatic breast cancer receiving chemotherapy."

Finally, commentary on both the Henke[124] and Leyland-Jones[118] trials has noted some imbalances in baseline characteristics, suggesting that the epo arms in both trials had a slightly greater proportion of patients with poor prognostic factors. Adjusted analyses attempting to account for these imbalances give somewhat less extreme results in both trials, although they both still favour placebo. However, adjusted analyses are of limited value in these circumstances.[134]

Imbalances such as these may arise by chance, or alternatively, they may arise as a result of some breakdown in randomisation. For example, the Henke trial[124] used sealed packages kept at each of the 23 centres, which can be insecure, particularly when the packaging, appearance and characteristics of the two treatments are not always

entirely indistinguishable. The imbalance in the numbers randomised (171 versus 180) appears quite large, even for a trial with as many centres as this (23).

The possibility that insecure randomisation could be responsible for the differences seen in some trials is supported to some extent by subgroup analysis ($\chi^2_{(\text{interaction})} = 5.26$, 1 df, $p = 0.02$; $F = 4.24$, 1,26 df, $p = 0.05$). However, this analysis should be treated with caution, as three of the four large trials are included in the 'unclear' group; Henke[124] is the only one of these three where there are reasonable concerns over the quality of concealment based on the information supplied in the publication (as opposed to a lack of information in the publication). However, the imbalances in patient characteristics in the Henke trial do not appear as large, or as worrying, as some commentators have suggested, while the baseline imbalances noted in the Leyland-Jones[118] trial were found after a retrospective data collection exercise to investigate the reasons why the survival outcomes were unexpectedly negative; any data set will yield 'explanations' (some more welcome than others) if interrogated hard enough. The 'good news' of other trials, such as Littlewood[63] and Vansteenkiste,[64] should be subjected to a similar degree of scrutiny before drawing any conclusions. Further details of the randomisation and quality of follow-up for all of the key survival trials may help to confirm or allay concerns that bias, possibly unintentional, may have affected the outcomes.

Finally, it is important to note that two of the trials mentioned in the FDA safety briefing[92] used a similar design to the Henke[124] trial (radiotherapy in head and neck cancer). One was stopped early because of poor recruitment, and no adverse safety effects were noted. The other was stopped early owing to publication of the Henke trial, leading to an unplanned interim analysis which showed a non-significant trend against epo in safety and tumour control outcomes. Mature survival data from these and other trials will be useful in examining these issues further.

There are very limited data in the public domain with which to examine these hypotheses, with mature survival data only being available for four large trials. The results reported above suggest that caution should be exercised in using (or continuing to use) epo in patients with relatively high Hb levels, but the evidence presented above is far from conclusive and there are substantial quantities of missing/unpublished data relating to this question. Some of these additional, unpublished, data are referred to in an FDA briefing document by the Oncologic Drugs Advisory Committee dated 4 May.[92] This includes details of a number of trials that were terminated early owing to an excess of thromboembolic events and/or increased tumour activity and/or excess mortality. Some of these trials remain unpublished and so are not yet available for inclusion in this review. The key conclusions of the FDA briefing are reproduced below.

The authors concur with the FDA's conclusions and recommendations (see below). However, they would also add that some of the trials in this review remain on follow-up and will report more mature survival data in the future, particularly the large trial by Hedenus,[123] which has only reported very early data so far. In addition, there is a large number of ongoing or recently completed trials, some of which should report within the next few months. The hypotheses that have been proposed to explain the patterns of tumour response and survival observed can be examined in detail with better information about the design and conduct of all of these trials and, ideally, IPD on key patient characteristics to allow a reliable investigation, through IPD meta-analysis, of subgroup effects in these and any future trials.

FDA conclusions regarding safety and Hb levels

> "It is clear from this data that both the rate of rise in hemoglobin and a target hemoglobin of greater than 12.0 g/dL may contribute to an increased risk of cardiovascular/thrombotic events in patients with chronic renal failure on dialysis. The data from major efficacy study that supported the supplemental approval for Aranesp for treatment of the anemia of cancer chemotherapy demonstrated a rapid rate of rise in hemoglobin (more than 0.5 g/dL/week) was associated with an increased incidence of hypertension, vascular thrombosis, ischemia and infarction.
>
> The Agency considers studies conducted using target hemoglobin levels of greater than 12 g/dL to be potentially unsafe; studies employing such strategies should be conducted under IND [Investigational New Drug Application]. In addition, such studies should be specifically designed to detect an impact on survival as well as the impact on thrombotic event rates. With regard to clinical practice, clinicians should adhere to the dose adjustments governing the rate of rise of hemoglobin that have been incorporated into the Aranesp and Procrit/Epogen package inserts."

FDA conclusions regarding risk of tumour promotion

> "There is now a body of literature consisting of studies in cell lines and in animal models that

supports the possibility that erythropoietin may have a role to play in the growth of certain tumors. There are also other studies that suggest that erythropoietin has no such role. The question of whether EPO does or does not function as a growth factor for tumors (and/or vasculature) now has more immediacy, because of the results of the clinical studies outlined in this document.

Four multicenter, randomized, placebo controlled clinical trials have been conducted thus far, the N93-004 (Procrit), NESP 980297 (Aranesp), EPO-INT-76 (EPREX), and the Henke (epoetin beta) study, which were designed to measure tumor outcomes or survival in homogenous populations of tumors. In two of the four studies, which also happen to be the two largest studies, there was evidence of a tumor promotion effect in the arm that received recombinant erythropoietin. In EPO-INT-76, there was also a detrimental effect on 12-month survival. While aspects of both of these studies have been criticized, the size of the two trials that showed evidence of tumor promotion (929 subjects in the EPO-INT-76 trial, 351 in the Henke trial), the size and design (randomized, placebo-controlled) of both trials and the consistency in results provide data that in the opinion of the FDA, warrant further investigation.

The basis for the adverse effects of erythropoietin on malignancy/tumor stimulation is uncertain, however, it seems reasonable that an effect could be mediated through binding to erythropoietin receptors on both tumor and vascular cells. The three studies were performed in three different primary tumor types: small cell carcinoma of the lung, metastatic breast cancer, and carcinoma of the head and neck. A tumor promotion effect was seen in the breast cancer and head and neck studies, but not in the small cell lung cancer study. This may indicate heterogeneity of malignancies, such as differences in erythropoietin receptor distributions between types of malignant tumors.

Future studies that investigate the effect of erythropoietic growth factors on tumor promotion should incorporate the following features into their design:

- Homogenous primary tumor.
- Homogenous chemotherapy and/or radiation regimens.
- Randomized, placebo-controlled.
- Data collection that will allow the systematic acquisition of information of tumor response, time to progression, and survival.
- Target hemoglobin values of no greater than 12.0 g/dL, with prespecified rules for dose adjustment.
- Prespecified definitions for cardiovascular and thrombovascular events.
- A Data Safety Monitoring Board with a charter that states criteria for halting the study in the event of a prespecified number of cardiovascular or thrombotic adverse events occurs.
- Collection of data regarding the erythropoietin receptor status of primary tumor sites.
- Studies on tumor populations with high, low, and intermediate quantities of erythropoietin receptors."

Adverse events

Altogether, 13 of the Birmingham trials reported adverse events and a summary can be found in *Table 23*. To be consistent with Cochrane[48] the review sought data on the following adverse events: thrombic events, hypertension, haemorrhage/thrombocytopenia, rash/irritation/pruritus, seizures and reports of red cell aplasia.

Only thrombic events and hypertension were reported in the Birmingham trials and where these were reported no definitions were given. Three trials reported hypertension: Bamias[120] found hypertension in two patients receiving erythropoietin, Rosenzweig[128] found hypertension in one patient receiving erythropoietin, and Sweeney[129] reported no hypertensive events in either trial arm. There were three trials reporting thrombic events;[118,123,128] Rosenzweig[128] was stopped early because four out of 14 patients had a thrombic event at the beginning of the trial. In both Leyland-Jones[118] and Rosenzweig[128] the authors tried to assess the reasons why there was a perceived increased incidence of thrombic events. The trial reports advise caution in interpreting the thrombic events reported in the trials, Leyland-Jones 2003[118] states that there were design issues making analysis difficult and Rosenzweig[128] concludes that there may be a possible risk of increased thrombic events in the population in which they occurred (i.e. metastatic breast cancer), but because of the low sample size conclusions are difficult.

Adverse events data are notoriously difficult to interpret in RCTs,[135] and in this review are made even more difficult to interpret because of the heterogeneity of the populations being investigated (i.e. all cancers). If the events are crudely counted, Henke,[124] Iconomou[126] and Rosenzweig[128] report more events for the intervention groups, whereas Hedenus,[122] Kotasek[90] and Smith[91] report more events for the control groups.

None of the trials report red cell aplasia. This rare event has been recently reported[136] at an

TABLE 23 *Adverse events*

Study	No. of events overall		Adverse events reported	
	Intervention	Control	Intervention	Control
Bamias, 2003[120]	2 episodes/72 patients (3%)	0 episodes/72 patients	Increased BP, 2/72 (2.7%)	Increased BP, 0/72
Casadevall, 2004[121]	7 episodes/30 patients (23%)	7 episodes/30 patients (23%)	Mortality 6/30 (20%) Progression to AML 1/30 (3%)	Mortality 6/30 (20%) Progression to AML 1/30 (3%)
Hedenus, 2002[122] **(all doses)** (% given in publication, therefore numbers approximated)	93 events/55 patients (169%)	39 episodes/11 patients (354%)	Nausea 15/55 (27%) Fatigue 14/55 (26%) Fever 12/55 (21%) Peripheral oedema 11/55 (19%) Abdominal pain 9/55 (16%) Back pain 9/55 (16%) Vomiting 9/55 (16%) Constipation 8/55 (15%) Diarrhoea 8/55 (15%) Dyspnoea 8/55 (15%) Upper respiratory tract infection 8/55 (15%)	Nausea 5/11 (46%) Fatigue 5/11 (46%) Fever 5/11 (46%) Peripheral oedema 2/11 (19%) Abdominal pain 3/11 (27%) Back pain 4/11 (36%) Vomiting 6/11 (56%) Constipation 4/11 (36%) Diarrhoea 2/11 (18%) Dyspnoea 2/11 (18%) Upper respiratory tract infection 4/11 (36%)
Hedenus, 2003[123]	68 episodes/175 patients (39%)	62 episodes/169 patients (37%)	Mortality 10/175 Fatigue (no definition given) 58/175 (33%)	Mortality 4/169 Fatigue (no definition given) 58/169 (34%)
Henke, 2003[124]	255 episodes/180 patients (142%)	208 episodes/171 patients (122%)	Mortality 109/180 (61%) General 54/180 (30%) Infections 38/180 (21%) Disorders of blood/lymphatic 23/180 (13%) Respiratory/thoracic 11/180 (6%) Vascular: BP, VT, PE, CVA 20/180 (11%)	Mortality 89/171 (52%) General 43/171 (25%) Infections 34/171 (20%) Disorders of blood/lymphatic 14/171 (8%) Respiratory/thoracic 19/171 (11%) Vascular 9/171 (5%)
Iconomou, 2003[126]	12 episodes/61 patients (20%)	4 episodes/61 patients (6.5%)	Mortality 4 deaths reported overall Mild injection pain 3/61 (5%) Moderate injection pain 1/61 (1.6%) Oedema at injection site 4/61 (6.5%)	Mortality: 4 deaths reported overall (6.5%) Injection sites NA

continued

TABLE 23 *Adverse events (cont'd)*

Study	No. of events overall		Adverse events reported	
	Intervention	**Control**	**Intervention**	**Control**
Kotasek, 2003[90]	319 episodes/198 patients (161%)	98 episodes /51 patients (192%)	Mortality 7/198 (3.5%) Nausea 72/198 (36%) Fatigue 63/198 (32%) Vomiting 44/198 (22%) Constipation 42/198 (21%) Diarrhoea 42/198 (21%) Dyspnoea 38/198 (19%) Abdominal pain 7/198 (3.5%) Peripheral oedema 30/198 (15%) Skeletal pain 18	Mortality 3/51(5.8%) Nausea 17/51(33%) Fatigue 20/51 (39%) Vomiting 10/51 (19.6%) Constipation 9/51 (17.6%) Diarrhoea 10/51 (19.6%) Dyspnoea 9/51 (17.6%) Abdominal pain 7/51 (13.7%) Peripheral oedema 4/51 (7.8%) Skeletal pain 0
Leyland-Jones, 2003[118]	No. of patients in study NR	No. of patients in study NR	Disease progression after 4 months 6% TVEs after 4 months 1%	Disease progression after 4 months 3% TVEs after 4 months 0.2%
Rosenzweig, 2004[128]	7 episodes/14 patients (50%)	2 episodes/13 patients (15%)	Thrombic events 4/14 (28.5%) (DVT $n = 1$, DVT + DVT $n = 2$, brachial vein thrombosis associated with infection in mediport $n = 1$) Hypertension = 1/14 (11%) (DVT confirmed by Doppler) Disease progression 2/14 (14.2%)	Thrombic events NR Disease progression 2/13 (15%)
Rosen, 2003[127]	24 episodes/47 patients (51%)	33 episodes/43 patients (78%)	Grade 2/3 Hb toxicity 24/47 (51%)	Grade 2/3 Hb toxicity 33/43 (76.7%)
Smith, 2003[91]	73 episodes/64 patients (114%)	40 episodes/22 patients (181%)	AE for all patients in study 64 Fatigue 11/64 (17%) Dyspnoea 10/64 16% Nausea 10/64 (16%) Asthenia 8/64 (13%) Depression 8/64 (13%) Vomiting 8/64 (13%) Peripheral oedema 7/64 (11%) Limb pain 7/64 (11%) Headache 4/64(6%)	AE for all patients in study 22 Fatigue 6/22 (27%) Dyspnoea 0 Nausea 4/22 (18%) Asthenia 7/22 (32%) Depression 7/22 (32%) Vomiting 4/22(18%) Peripheral oedema 4/22(18%) Limb pain 4/22(18%) Headache 4/22(18%)

continued

TABLE 23 *Adverse events (cont'd)*

Study	No. of events overall		Adverse events reported	
	Intervention	**Control**	**Intervention**	**Control**
Sweeney, 1998[129]	4 episodes/24 patients (17%)	2 episodes/24 patients (8%)	Mortality 0 in 7 weeks of treatment Hypertension 0/24 Pruritis 1/24 (4%) Herpes zoster 1/24 (4%) Dyspepsia 2/24 (8%) (related to iron)	Mortality 0 in 7 weeks of treatment Hypertension 0/24 Pruritis 0/24 Herpes zoster 2/24 (8%) Dyspepsia 0/24
Vansteenkiste, 2002[64]	254 episodes/156 patients (163%)	257 episodes/158 patients (163%)	Mortality 22/156 Thrombic event 7/156 (4.5%) Fatigue 31/156 (20%) Dyspnoea 28/156 (18%) Asthenia 36/156 (23%) Fever 27/156 (17%) Anorexia 25/156 (16%) Constipation 27/156 (17%) Chest pain, non-cardiac 17/156 (11%) Cough 17/156 (11%) Disease progression 17/156 (11%)	Mortality 19/158 Thrombic event 5/158 (3%) Fatigue 38/158 (24%) Dyspnoea 38/158 (24%) Asthenia 28/158 (18%) Fever 27/158 (17%) Anorexia 27/158 (17%) Constipation 22/158 (14%) Chest pain, non-cardiac 24/158 (15%) Cough 24/158 (15%) Disease progression 24/158 (15%)

AML, acute myeloid leukaemia; BP, blood pressure; CVA, cerebral vascular accident; NA, not applicable; PE, pulmonary embolism; TVE, thrombic and vascular events; DVT, deep vein thrombosis.

estimated "exposure incidence of 18 cases per 100,000 patient years for the Exprex formulation without human serum albumin, 6 per 100,000 patient years for the Exprex formulation with human serum albumin, 1 case per 100,000 patient years for NeoRecormon and 0.2 case per 100,00 patient years for Epogen", with most of the incidents occurring in renal patients. This rare event therefore would be unlikely to show up in the trial population studied in this review.

Quality of life

HRQoL has become a key clinical outcome. Alongside measures of clinical, chemical and mortality status, the assessment of quality of life presents a patient's evaluation of the impact of their disease or treatment on their everyday life.

Methods

A search specifically targeted at HRQoL was conducted in MEDLINE from 1966 to September 2004. Two reviewers (SB, JW) identified potential studies from title and, where available, abstract. Inclusion criteria were the same as those for the main review. Data were tabulated and analysed qualitatively. A vote-counting method was used to summarise the data. This classifies studies as showing a positive or negative or neutral effect. It does not take into account the effect size and therefore conclusions regarding the size of benefit/disbenefit cannot be calculated. However, vote counting has the advantage that all of the available data can be summarised, which is an advantage particularly in this type of outcome where different scales have been used to assess HRQoL. By vote counting, the actual trial result regarding HRQoL is used as a categorical statistic, an assumption is made that the different HRQoL measures are comparable, but the details regarding the process of this data collection are ignored.

Previous HRQoL systematic reviews

Five systematic reviews appraising epo treatment for anaemia in patients with cancer included an assessment of quality of life.[27,48,137–139] Two reviews[137,138] suggest a general improvement in quality of life for patients treated with epo. Concern with the amount and quality of available evidence precluded three reviews from drawing any conclusions.[27,48,139]

Only two of the five reviews included controlled clinical studies;[48,139] the remaining reviews included a mix of data from randomised and non-randomised trials,[137] and controlled clinical trials and community-based, single-arm trials.[27,138] The included RCTs differed across the reviews, with only two RCTs being common to all.[63,113] Reasons for this include the dates when the literature was searched for each review (range 1980 to 2002) and the variation in the focus of each review resulting in a range of treatment comparator arms (placebo, no treatment, dose of erythropoietin). In Ross,[138] patients with anaemia related to renal disease were also included. Differences in assessment and interpretation are also due to the large number of scales available to measure HRQoL (see Appendix 6).

These issues are discussed within the five reviews; however, while concerns with the content and methodological diversity in the measurement of quality of life precluded three reviews from undertaking any meaningful meta-analysis,[27,48,139] two reviews meta-analysed available data.[137,138]

The aspects (domains) of quality of life measured by each tool vary. The five reviews chose to interpret and analyse findings from included studies in different ways. One review analysed mean change in quality of life by the domains of quality of life measured in the various scales, assuming that the domain 'energy/fatigue' on one scale equates to 'energy/fatigue' on another scale.[138] A second review analysed data within each quality of life scale, presenting mean change scores for each scale: CLAS, FACT, (Eastern Cooperative Oncology Group (ECOG) and Short Form 36 (SF-36).[137] One review focused the summary of data on the tool used by the majority of the studies in their review (11 of 13): the visual analogue scale (VAS).[27] Two reviews summarised and commented on the findings of each included study; where possible summaries were grouped by quality of life scale used.[48,138]

Two reviews[137,138] were supported by pharmaceutical companies associated with epoetin (RW Johnson Pharmaceutical Research Institute, New Jersey; Amgen Inc., California). Unpublished clinical data were included in the review by Jones.[137]

Results

The quality of life search identified 20 trials, of which 11 had been reported by the Cochrane review. There were two trial updates; Boogaerts[131] reported an update of quality of life data in the trial originally reported by Coiffier,[65] and two papers reanalysed data from the trial originally reported by Littlewood.[140,141] Abels 1993[93] incorporates the results of trials described by Henry[102] and Case.[96]

TABLE 24 *HRQoL instruments used in the trials*

Quality of life measure	Cochrane trials	Birmingham trials
FACT-G (1987)	Österborg, 2002;[108] Littlewood, 2001[63]	Casadevall, 2004;[121] Janinis, 2003[78]
FACT-An (1987 – date of copyright)	Österborg, 2002;[108] Littlewood, 2001[63]	Casadevall, 2004;[121] Thomas, 2002;[130] Janinis, 2003;[78] Boogaerts, 2003;[131] (see also Coiffier, 2001[65]); Huddart, 2002,[125]
FACT-F (1987)	Österborg, 2002;[108] Littlewood, 2001[63]	Casadevall, 2004;[121] Boogaerts, 2003[131] (see also Coiffier, 2001[65]); Hedenus, 2003;[123] Janinis, 2003;[78] Iconomou, 2003;[126] Vansteenkiste, 2002[64]
SF-36 (1993)	Littlewood, 2001[63] (see also Fallowfield, 2002[140])	Boogaerts, 2003[131] (see also Coiffier, 2001)[65]
NHP (1984)	Dammacco, 2001;[98] Carabantes, 1999[94]	
FLI-C (1984)	Quirt, 1996[109]	
LASA (CLAS) (1976)	Dammacco, 2001;[98] Littlewood, 2001;[63] Abels, 1993[93] (see also Henry, 1994;[102] Case, 1993[96])	Iconomou, 2003;[126] Thomas, 2002[130]
VAS	Thatcher, 1999;[113] Welch, 1995[116]	Sweeney, 1998[129] Boogaerts, 2003[131]
PDI (date?)	Del Mastro, 1997[99]	
Other	Kurz, 1997;[105] Rose, 1994[110]	

FLI-C, Functional Living Index; NPH, Nottingham Health Profile; PDI, Psychological Distress Index.

As can be seen in *Table 24*, some trials reported more than one quality of life scale.

General description

All of the trials except for Abels[93] and Rose[110] that were published before 2000 (which includes most of the trials reported by Cochrane) had a sample size of less than 100 and used VAS,[93,116,129] NHP[94] PDI[99] or other unvalidated questionnaires.[105,110,111,113] Of the trials that were published after 2000 all but Casadevall[121] and Huddart[125] had sample sizes over 100. All of these trials except for Dammacco,[98] which used the NHP and LASA, used the FACT scale to assess HRQoL. LASA was also used in four other trials.[63,93,126,130]. SF-36 was only used in two trials.[63,131]

The total number of patients evaluated was 3185.

Quality of included studies

The quality of included studies was assessed using the checklist reported in *Table 6* (p. 19) and is summarised in *Table 25*). This scale assessed treatment allocation (i.e. the randomisation process and concealment of allocation), baseline characteristics (i.e. whether groups were similar at baseline), implementation of blinding (whether patients and physicians were blinded to treatment) and completeness of the trial.

The method of randomisation was unclear in six trials, four of which were abstract publications. Only seven trials had adequate concealment of allocation, Sweeney[129] had inadequate concealment of allocation and in 11 trials it was unclear. Most trials were balanced at baseline, two were not balanced (Iconomou[126] had slightly more patients with lung cancer in the epo group and slightly more colorectal cancer patients in the control group, and Sweeney 1998[129] had a lower Hb level in the control group) and in four trials this was unclear.

Eight trials were placebo controlled and therefore assumed to have patients and physicians blind to treatment. In seven trials patients were not blinded to treatment allocation and in four it was unclear. In eight trials physicians were not blinded to treatment and in three it was unclear. In 14 trials losses to follow-up were accounted for and in five it was unclear.

Finally, eight trials either included an ITT analysis or had less than 10% exclusions, in a further eight trials more than 10% of patients were not included in the final assessment and in three trials it was unclear. In summary, therefore, most studies described the methods of randomisation and were balanced at baseline.

TABLE 25 *Quality of studies*

	1. Random	2. Concealment allocation	3. Baseline similarity	4. Patients blinded	5. Physicians blinded	6. Losses	7. ITT or >10% dropout	Comments
Birmingham trials								
Casadevall, 2004[121]	Yes	Yes	Yes	No	No	Yes	No	
Hedenus, 2003[123]	Yes	Yes	Yes	Yes	Yes	Yes	No	At 12 weeks >10% withdrawals
Huddart, 2002[125]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No group numbers given
Iconomou, 2003[126]	Yes	Unclear	No	No	No[a]	Yes	Yes: <10% dropout	[a] Psychologist blinded
Janinis, 2003[78]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Sweeney, 1998[129]	Yes	No	No	No	No	Unclear	No: >10% dropouts	
Thomas, 2002[130]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Vansteenkiste, 2002[64]	Yes	Unclear	Yes	yes	Yes	Yes	No: 81% of patients analysed	
Cochrane trials								
Abels, 1993[93] (includes Case, 1993[96] and Henry, 1995[142]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Carabantes, 1999[94]	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	
Coiffier, 2001;[65] unpublished data, Boogaerts	Yes	Unclear	Yes	No	No	Yes	No: >10% dropout	
Dammacco, 2001[98]	Yes	Unclear	Yes	Yes	Yes	Yes	No: > 10% dropout for placebo group	
Del Mastro, 1997[99]	Yes	Yes	Yes	No	No	Yes	Yes	
Kurz, 1997[105]	Yes	Yes	Yes	Yes	Yes	Yes	No: unclear whether ITT	
Littlewood, 2001[63]	Yes	Yes	Yes	Yes	Yes	Yes	No	
Quirt, 1996[109]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	
Rose, 1994[110]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	
Thatcher, 1999[113]	Yes	Yes	Yes	No	No	Yes	Yes	
Welch, 1995[116]	Unclear	Unclear	Yes	No	No	Yes	Yes	
Total *n* = 19	Yes = 13 Unclear = 6	Yes = 7 No = 1 Unclear = 9	Yes =13 No = 2 Unclear = 3	Yes = 7 No = 7 Unclear = 4	Yes = 8 No = 8 Unclear = 3	Yes = 14 No = 5	Yes = 8 No = 8 Unclear = 3	
% good quality	73%	36%	68%	42%	42%	42%	73%	42%

Over half of the studies assessed did not blind patients or physicians to treatment and over half did not include an ITT analysis or lost more than 10% of patient final evaluations. Blinding of patients to their treatment is probably the most likely quality parameter to affect HRQoL scores, as patients may be prone to the placebo effect.

Vote count

The results of the vote counting are summarised in *Table 26*.

FACT

FACT-G (Generic): four trials used this scale (see *Table 24*). Casadevall[121] did not report the results of this analysis, and Janinis[78] reported an increase in HRQoL in favour of epoetin alfa, but not at a statistically significant level. Österborg[108] and Littlewood[63] found a statistically significant increase in favour of erythropoietin, Österborg stressed that this did not occur until week 12.

FACT-F (Fatigue): eight trials used this scale (see *Table 24*). Casadevall[121] found no difference between the control and intervention group. Three trials found a statistically significant difference.[63,123,126] Four trials found that there was a difference in favour of erythropoietin in HRQoL as measured by FACT-F, but this did not reach statistical significance.[64,78,108,131]

FACT-An (Anaemia): seven trials used this scale (see *Table 24*); again, Casadevall[121] found no difference between control and intervention. This trial involved a population of patients that are outside the licence indications (patients had MDS), and G-CSF was given only to the intervention group. Five trials had a statistically significant increase in HRQoL as measured by this scale.[63,108,125,130,131] Only one trial[78] had a non-statistically significant increase in the FACT-An score in favour of epoetin alfa.

SF-36

This generic measure was used by two trials. Boogaerts[131] found a statistically significant increase in favour of epoetin beta; however, there was a greater than 10% dropout in the HRQoL analysis. Littlewood[63] found a non-statistically significant increase in favour of epoetin alfa.

NHP

Two trials used this as an outcome measure. Dammacco[98] found a statistically significant result for the domains of emotional reactions and social isolation in favour of epoetin alfa, but a negative result for the domain of sleep; that is, patients on epoetin alfa did not sleep as well as the control group. The other trial[94] using this scale was a trial of 35 patients, and no difference was found between intervention and control.

LASA

This scale is a generic VAS, but was designed for use in cancer patients. No one trial used the LASA in its entirety. All trials measured three domains: energy levels, ability to perform daily activities and overall HRQoL.

All five trials that used this scale had over 100 patients. Three of the trials had statistically significant results in favour of erythropoietin.[63,126,130] Dammacco[98] had a statistically non-significant result in favour of epoetin alfa for energy levels, and a statistically non-significant result in favour of epoetin alfa for overall HRQoL. Abels[93] had non-significant changes in favour of erythropoietin.

Although three trials[113,116,129] did not refer to the VAS that they used as a LASA, these three trials measured the same domains: energy levels, ability to perform daily activities and overall HRQoL, as the five trials noted above. Sweeney[129] had non-significant changes in favour of erythropoietin, while Thatcher[113] and Welch[116] reported no difference observed between intervention and control. The findings for these eight trials are grouped in the same column in *Table 26*.

One trial used a VAS to assess global HRQoL state.[131] The remaining scale used was the PDI (used by Del Mastro[99]). Only Boogaerts[131] had a statistically significant result in favour of erythropoietin.

The remaining trials used non-validated questionnaires,[105,109,110] and all but Rose found no difference between the groups. Rose[110] had a statistically significant result for questions relating to energy levels in favour of epoetin alfa.

Birmingham trials: individual trial description

Casadevall, 2004[121]

Trial/population characteristics. This was a trial of 60 patients (30 in each group), which investigated the effectiveness of epoetin alfa, the control being standard care in patients with MDS. This trial was complicated by the administration of G-CSF to the intervention group only, which may have been a confounding factor on the trial outcomes. In the first 12 weeks of the trial, patients who were given epoetin alfa were also given G-CSF;

TABLE 26 *Direction of effect on quality of life*

Trial (date order)	FACT-G	FACT-F	FACT-An	SF-36	NHP	FLI-C	LASA/VAS	BSI	HUI	PDI	Other	Comments
Casadevall, 2004[121]	NR	↔	↔									Possible confounding
Thomas, 2002[130]			✓[a]				✓[a]					[a] Abstract publication; difficult to assess the robustness of these results
Janinis, 2003[78]	☑	☑	☑									Abstract; little detail given
Boogaerts, 2003[131] (Coiffier trial 2001)[65]		☑	✓	✓							✓	Patients and physicians not blinded to treatment. More than 10% dropouts
Hedenus, 2003[123]		✓										
Iconomou, 2003[126]		✓					✓					
Österborg, 2002[108]	✓	☑	✓									At 12 weeks
Vansteenkiste, 2002[64]		☑										
Huddart, 2002[125]			✓									
Dammacco, 2001[98]					✓[b] ✕[c]		✓[d] ☑[e]					[b] For emotional reactions, social isolation; [c] sleep, [d] for energy level, daily activity, [e] overall
Littlewood, 2001[63]	✓	✓	✓	☑			✓					
Carabantes, 1999[94]					↔							Three domains statistically significant, three NR
Thatcher, 1999[113]							↔					Increased overall HRQoL with epo, decreased energy with epo
Sweeney, 1998[129]							☑					Possible confounder of iron
Del Mastro, 1997[99]										↔		
Kurz, 1997[105]											↔	Very small trial
Quirt, 1996[109]						↔						
Welch, 1995[116]							↔					
Rose, 1994[110]											✓[f]	[f] Only for energy
Abels, 1993[93] (including Henry, 1995[142] and Case, 1993[96])							✓[g] ☑					[g] Overall HRQoL

↔, No difference observed between intervention and control; ✓, statistically significant effect in favour of intervention group; ☑, effect in favour of intervention group but not statistically significant; ✕, statistically significant effect in favour of control group.
BSI, Brief Symptom Inventory; HUI, Health Utilities Index.

TABLE 27 *Results: Casadevall, 2004*[121]

FACT-An (34 items: score 0–136)	Baseline Mean [*n*]	Week 12 Mean [*n*]	Week 28 Mean [*n*]	Week 52 Mean [*n*]	Comments
Intervention	115.6 [29]	111.8 [19]	123.1 [15]	107.1 [10]	No SD given; also NR who had G-CSF after week 12
Control	112.5 [28]	114.4 [23]	118.3 [18]	105.4 [16]	

TABLE 28 *Results: Hedenus, 2003*[123]

FACT-F (13 items: total score 0–52)	Baseline category <24	Baseline category 25–36	Baseline category >36	Comments
Intervention $n = 152$	$n = 38$	$n = 64$	$n = 36$	Figures read off graph
Control $n = 151$	$n = 42$	$n = 63$	$n = 46$	
Week 16 intervention (mean change)	8	5	–3	
Week 16 control	6	–1	–6	

if patients had a haematological response epoetin alfa alone was given for an additional 40 weeks, with the potential to restart G-CSF if they had a relapse. The total duration of the trial was therefore 52 weeks. HRQoL was assessed using FACT-G and FACT-An at weeks 12, 28 and 52. There were several concerns relating to the study quality assessment that may have impacted on the HRQoL assessment: no blinding of patients and physicians to treatment, and the number of dropouts, which exceeded more than 10%.

Results. The trial data are summarised in *Table 27*.

Summary. Overall, no effect on quality of life was demonstrated.

Thomas, 2002[130]

Trial/population characteristics. This was an abstract publication, therefore there are scant details describing the population. In total, 112 patients undergoing chemotherapy were in the trial, 62 of whom had the intervention epoetin alfa. Results given are for 12 weeks. FACT-An and LASA (CLAS) were used. The authors reported that for CLAS an improvement in all CLAS scores was found at all time-points ($p = 0.05$). Study quality is difficult to assess in this type of publication owing to lack of detail of methods reported; all quality assessment parameters are therefore classified as unclear.

Results. For patients receiving epoetin alfa at 12 weeks 36% had an energy level above 20%, 25% had an increase in daily activities and 17% had an increase in HRQoL. At 12 weeks the FACT-An scores for epoetin alfa showed the highest and most significant improvement from baseline ($p < 0.05$). No data were given for the control group: the authors stated that control patients showed no improvement in energy levels and a small decrease in daily activities and overall HRQoL.

Summary. Because there are few details it is difficult to assess the quality of this trial and therefore the robustness of the results.

Hedenus, 2003[123]

Trial/population characteristics. This was a large, well-conducted trial involving 349 patients (intervention $n = 176$). It investigated darbepoetin alfa against placebo in patients with haematological malignancies (Hodgkin's disease, NHL, CLL, MM) receiving chemotherapy. Only one HRQoL measure was used, the FACT-F, which was completed every 4 weeks on day 1 of each cycle of chemotherapy before any other study procedures. Patients received darbepoetin alfa for 12 weeks and were assessed at week 16. There was only one quality assessment concern in that at 12 weeks there was more than 10% dropouts; other than this the trial was of good quality and included procedures such as blinding of patients and physicians to treatment.

Results. The results were reported in three categories, determined by baseline FACT-F scores: baseline scores less than 24, between 25 and 36, and over 36 (*Table 28*).

Overall, patients with the lowest baseline FACT-F scores showed the largest improvements by the end of treatment, and reported (no data given) that after adjusting for baseline scores increases in subscale scores were significantly greater than those observed with placebo ($p < 0.001$). The study also reported a statistically significant ($p < 0.001$) relationship between Hb change and change in FACT-F. For every 1 g dl^{-1} increase in Hb, an estimated mean increase of 1.39 in the FACT-F subscale was found (95% CI 0.83 to 1.94).

Summary. Few data were shown in the publication to enable the reader to assess the HRQoL results properly. However, the authors report that patients in the intervention group had statistically significant improvement in HRQoL as measured by the FACT-F subscale.

Huddart, 2002[125]

Trial/population characteristics. This trial was reported in an abstract publication and therefore is lacking in many details. Study quality is difficult to assess in this type of publication, so all quality assessment parameters were classified as unclear. In total, 90 patients were included, but the abstract does not report the numbers who received the intervention epoetin alfa. Patients had solid tumours and were treated with platinum-based chemotherapy. The trial authors state that it was not powered for HRQoL. HRQoL was measured using FACT-An.

Results. A trend towards an improvement was seen for the epoetin alfa group, 7.65 (95% CI 1.96 to 17.26) compared controls, 2.69 (95% CI 2.88 to 8.66).

Summary. HRQoL as measured by FACT-An improved in the intervention group.

Iconomou, 2003[126]

Trial/population characteristics. This trial, involving 122 patients (intervention $n = 61$), investigated epoetin alfa against standard care in patients undergoing chemotherapy (both platinum and non-platinum) who had a range of solid tumours (lung, breast, colorectal, ovarian, kidney, stomach and unknown primary sites). Two HRQoL measures were used, FACT-F and LASA. Measurements were from baseline to the end of the trial at 12 weeks. Neither patients nor physicians were blinded to treatment; however, the health psychologist administrating the HRQoL questionnaire was blinded. The results were not ITT, but there were less than 10% dropouts.

Results. The trial data are summarised in *Table 29*. No significant improvements in HRQoL were observed in the control group between baseline and end of treatment. In addition, the differences in mean change scores between epoetin alfa and control were statistically significant for all HRQoL measures.

Summary. All of the scales used to measure HRQoL in this trial found a statistically significant increase in favour of epoetin alfa.

TABLE 29 *Results: Iconomou, 2003[126]*

	Baseline Mean score	Week 4 Mean change score	Week 12 Mean change score
FACT-F (13 items: total score 0–52)			
Intervention (SD) [*n*]	22.1 (11.5) [61]	4.3 (SNR) [NR]	4.6 (12.5) [NR] $p < 0.01$
Control (SD) [*n*]	22.8 (11.3) [61]	NR	–1 (12.80) [NR]
CLAS energy (score 0–100)			
Intervention (SD) [*n*]	52.8 (18.4) [NR]	5.8 (NR) [NR]	7.3 mm (20.2) [NR] $p < 0.01$
Control (SD) [*n*]	51.0 (17.6) [NR]	NR	–1.4 mm (19.4) [NR]
CLAS ability (score 0–100)			
Intervention (SD) [*n*]	51.5 (20.2) [NR]	8.0 (NR) [NR]	9.7 mm (19.7) [NR] $p < 0.001$
Control (SD) [*n*]	50.6 (19.8) [NR]	NR	–1.4 mm (18.4) [NR]
CLAS overall (score 0–100)			
Intervention (SD) [*n*]	52.7 (21.3) [NR]	5.2 (NR) [NR]	8.0 mm (19.8) [NR] $p < 0.01$
Control (SD) [*n*]	51.2 (17.9)	NR	–0.9 mm (22.8) [NR]

In the paper there is a mistake in the first reference to the scale used. They used the FACT-F scale.

TABLE 30 *Results: Sweeney, 1998*[129]

Combined VAS scores: (total score 0–100)	Intervention mean score	Control mean score	*p*	Sample size epo/control
Week 1	53.6	50.0	0.74	17/15
Week 2	52.1	45.9	0.56	17/15
Week 3	57.6	53.6	0.73	17/15
Week 4	58.5	56.3	0.84	17/15
Week 5	64.6	56.9	0.47	17/15
Week 6	63.3	57.9	0.62	17/15
Week 7	72.7	56.3	0.15	14/13

Janinis, 2003[78]

Trial/population characteristics. This is an abstract publication and therefore trial details are lacking. This was a large trial of 372 patients (unknown how many patients received the intervention). No details are given as to the disease group, but patients were receiving either platinum or non-platinum chemotherapy. Epoetin alfa was the intervention and standard care the control. HRQoL was measured by FACT (FACT-G, FACT-An and FACT-F).

Results. Detailed results are not given. The abstract states that "the change in General FACT-An, Total Fatigue and Total FACT-An scores during the course of treatment adjusted for platinum and non-platinum chemotherapy was significantly different in favour of the epoetin alfa group".

Summary. Because of the lack of detail, it is difficult to appraise the robustness of the data.

Sweeney, 1998[129]

Trial/population characteristics. This trial was published in 1998, but is within the Birmingham trials. It was excluded by Cochrane because iron supplementation was only given to the intervention group. It is a small trial of 48 patients (24 in each group). The intervention was epoetin alfa against standard care. Patients had solid tumours treated with radiotherapy. HRQoL was measured using a VAS. Three aspects of HRQoL were investigated: energy level, ability to perform activities of daily living and overall quality of life. As the results were correlated for all three aspects the results were presented as a single HRQoL parameter. Scores are given per week for the 7-week duration of the trial. This trial scores poorly in the quality assessment, as there was no blinding of patients or physicians, there was an imbalance at baseline of iron supplementation, which only the epo group received, and there were more than 10% dropouts at assessment.

Results. The trial data are summarised in the *Table 30*. None of the scores reached statistical significance.

Summary. There was a general trend towards the epoetin alfa group having a better HRQoL, but none of the scores reached statistical significance. The trial authors felt that this was because there was a large variation in individual quality of life scores in the control group. There is potential confounding of iron supplementation in this trial.

Vansteenkiste, 2002[64]

Trial/population characteristics. This was a well-conducted, large trial involving 314 patients (intervention $n = 156$) who had solid tumours and were treated with platinum-based chemotherapy. Quality assessment indicated that it was a well-conducted trial; however, only 81% of patients were analysed for HRQoL. The intervention was darbepoetin alfa against placebo. HRQoL was measured using FACT-F.

Results. Unfortunately, the results are reported as percentage improved, and actual numbers of patients are not given. The results therefore are "56% (95% CI = 47% to 65% of patients in darbepoetin alfa group and 44% (95% CI = 35% to 52%) of patients in the placebo group had an improvement in the FACT-F scale score ($p = 0.52$). Although any improvement in the FACT-F scale score may be clinically meaningful, analyses to investigate the proportion of patients with at least a 25% improvement from baseline were done. 32% (95% CI = 23% to 40%) of patients in treatment group and 19% (95% CI = 12% to 26%) placebo showed at least a 25% improvement (mean diff. = 14% 95% CI = 2% to 23% $p = 0.019$)".

Summary. There was an improvement in FACT-F scale score in patients receiving darbepoetin alfa, but it was not significantly significant.

Notes. There is another publication connected to this trial describing HRQoL data of a sort.[143] The objective of Tchekmedyian[143] was to examine the relationship between changes in depression and anxiety levels and changes in fatigue levels among anaemic patients with lung cancer who participated in the trial as described above. Although it uses the same trial data the aims and therefore the results are not relevant to this review.

Cochrane trials with new data from more recent publications

Boogaerts, 2003[131] (reported in Cochrane as Coiffier, 2001[65])

Trial/population characteristics. This trial was conducted on 262 patients (intervention $n = 133$). There were several concerns relating to study quality assessment that may have impacted on the HRQoL assessment; these were: no blinding of patients and physicians to treatment, and the number of dropouts reported for this outcome (SF-36 = 26% dropout, FACT-F=13% dropout, FACT-An = 14% dropout and VAS =20% dropout). Three HRQoL scales were used, FACT (FACT-F and FACT-An), SF-36 and a VAS. The intervention was epoetin beta and the patient population was a mix of solid and haematological tumours. The trial duration was 12 weeks. Chemotherapy was given, but it is unclear how many patients were receiving platinum-based chemotherapy. Results are presented as last observation carried forward (LOCF) for patients with missing values at the final visit.

Results. The trial data are summarised in *Table 31*. All changes in the epoetin beta group were statistically significant, except for FACT-An ($p = 0.068$). No differences in benefit were found in patients with solid and haematological malignancies. Patients who had a haematological response experienced a greater improvement in HRQoL from baseline to final visit than patients who did not.

Summary. Most HRQoL measures found a statistically significant difference between intervention and control, FACT-F being the exception. There was more than 10% dropout, which has the potential to bias the results.

Littlewood, 2001[63] (see also Fairclough[141] and Fallowfield[140])

Trial/population characteristics. The trial described by Littlewood[63] was a large, well-conducted trial involving 375 patients (intervention $n = 251$). It investigated epoetin alfa against placebo in a mixed population of patients with solid and haematological malignancies receiving non-platinum-based chemotherapy. Three HRQoL measures were used: FACT (FACT-G, FACT-F and FACT-An reported), LASA and SF-36. Additional multivariate analyses are reported by Fallowfield,[140] and Fairclough[141] subjected this data to 'missing not at random' (MNAR) and 'missing at random' (MAR) analyses.

Results. The trial data are summarised in *Table 32*. In addition, Fallowfield[140] analysed the HRQoL in patients who had had disease progression and those who had not and found that patients undergoing disease progression (approximately 28% of this trial) did not have a HRQoL benefit (conclusions based on multiple linear regression results).

TABLE 31 *Results: Boogaerts, 2003[131]*

	Baseline Mean score	Week 3–4 Mean change score	Week 6–8 Mean change score	Week 12 Mean change score
FACT-An (7 items: score 0–28)				
Intervention (SD)	20 (3.8)	0.8 (0.3)	1.0 (0.4)	0.9 (0.5)
Control (SD) (not LOCF)	21 (4.4)	0.4 (0.5)	0 (0.3)	–0.1 (0.4)
FACT-F (13 items: score 0–52)				
Intervention (SD) (not LOCF)	27 (12)	3.5 (1.25)	4.5 (1.5)	5.5 (1.5)
Control (SD) (not LOCF)	31 (11)	1.25 (1.0)	0.75 (1.5)	0.5 (1.5)
SF-36 (score 0–100%)				
Intervention (SD) (not LOCF)	35 (8.4)	2 (1.0)	3.25 (1.0)	3.5 (1.5)
Control (SD) (not LOCF)	38 (9.5)	1.0 (0.5)	0.5 (0.5)	–0.7 (0.8)
VAS				
Intervention (SD) (not LOCF)	56 (17)	5.0 (2)	7.0 (2)	11 (2)
Control (SD) (not LOCF)	62 (17)	0.5 (0.75)	0.5 (1.0)	–0.5 (–2.0)

TABLE 32 *Results: Littlewood, 2001*[63]

	Baseline Fairclough, 2003[141]	Week 16 Univariate analysis, Littlewood, 2001[63]	Week 16 Multivariate analysis, Fallowfield, 2002[140]	Week 16 MAR, Fairclough, 2003[141]	Week 16 MNAR, Fairclough, 2003[141]
	Mean [*n*]	Mean change from baseline [*n*]			
FACT-G (27 items: total score 0–108)					
Intervention	74.0 [?]	2.5 [194]*	2.01 [175]*	2.03 [?]	–0.41 [?]
Control	69.6 [?]	–3.6 [88]*	–2.48 [78]*	–2.44 [?]	–3.92 [?]
FACT-An (fatigue)[a] (13 items: total score 0–52)					
Intervention	29.8 [?]	3.0 [200]*	2.70 [185]*	2.85 [?]	0.81[?]
Control	28.1 [?]	–2.2 [90]	–1.70 [81]	–1.25 [?]	–2.56 [?]
CLAS energy (total score 0–100)					
Intervention	45.1 [?]	8.06 [228]*	7.17 [215]*	9.56 [?]	5.56 [?]
Control	461 [?]	–5.81 [108]	–3.04 [97]	–4.06 [?]	–7.18 [?]
CLAS activity (total score 0–100)					
Intervention	46.5 [?]	7.51 [228]*	7.78 [196]*	8.33 [?]	3.26 [?]
Control	46.2 [?]	–5.99 [108]	–1.96 [88]	–5.47 [?]	–9.01 [?]
CLAS overall (total score 0–100)					
Intervention	50.6 [?]	4.79 [228]*	4.46[215]*	6.64[?]*	2.08[?]
Control	49.4 [?]	–5.97 [107]	–4.10[96]	–5.41 [?]	–8.80 [?]
SF-36 PCS (physical component summary)					
Intervention	36.4 [?]	1.77 [179]	1.27 [160]	1.81 [?]	Not est.
Control	34.3 [?]	–0.53 [86]	0.05 [77]	0.09 [?]	Not est.
SF-36 MCS (mental component summary)					
Intervention	45.8 [?]	2.14 [179]	1.88 [153]	1.39 [?]	0.14 [?]
Control	41.8 [?]	–0.25 [86]	0.35 [72]	–0.03 [?]	–0.85 [?]

[a] The study used the FACT-F subscale but refers to it as the FACT-An fatigue subscale.
[?] numbers unknown.
* p = statistically significant.

Summary. This trial measured HRQoL using cancer-specific and non-cancer-specific scales. The data also underwent sensitivity analysis and similar findings were found. Overall, HRQoL as measured by the FACT and LASA inventories was statistically significantly higher in patients receiving epoetin alfa than in patients receiving placebo. MNAR analysis gave a more conservative estimate, but it was nevertheless also in favour of the intervention group. HRQoL as measured by the generic scale SF-36 also found an improvement, but it did not reach statistical significance.

Österborg, 2002[108]

Trial/population characteristics. This trial was reported in the Cochrane review from information provided by the trial authors. The updated publication of 2002 contains more HRQoL information that has not been described in the Cochrane review and is described below. The trial had a large sample size of 243 (intervention n = 170). The intervention was epoetin beta with a placebo control. Patients had haematological malignancies. There were some dropouts in the HRQoL study, but no more than 10% were lost. Only the FACT scale was used, but results from FACT-G, FACT-F and FACT-An were reported, as well as subgroup analysis of patients who had a haematological response to epoetin beta and those who did not.

Results. The trial data are summarised in *Table 33*. Improvements were found to reach significance after 12 and 16 weeks of treatment.

TABLE 33 *Results: Österborg, 2002*[108]

Study	Baseline	Week 4	Week 8	Week 12	Week 16
FACT-G (29 items: total score 0–116) mean score ± SD					
All patients: intervention	*n* = 129 69.1 ± 14.4	*n* = 128 1.7 ± 11.8	*n* = 118 3.7 ± 13.0	*n* = 114 5.9 ± 14.5*	*n* = 106 6.5 ± 13.8
All patients: control	*n* = 129 68.5 ± 15.0	*n* = 120 2.2 ± 10.1	*n* = 112 2.9 ± 11.5	*n* = 104 2.6 ± 12.9	*n* = 103 3.1 ± 12.1
Intervention: responders	*n* = 92 70.6 ± 12.9	*n* = 91 1.5 ± 12.2	*n* = 87 4.9 ± 12.4†	*n* = 88 6.9 ± 14.3†	*n* = 83 7.8 ± 13.4†
Intervention: non-responders	*n* = 37 65.6 ± 17.2	*n* = 37 2.0 ± 10.8	*n* = 31 0.5 ± 14.2	*n* = 26 2.6 ± 14.7	*n* = 23 1.9 ± 14.5
FACT-F (13 items: total score 0–52) mean score ± SD					
All patients: intervention	*n* = 160 28.8 ± 10.7	*n* = 157 2.2 ± 8.7	*n* = 148 2.8 ± 10.8	*n* = 145 4.2 ± 11.7	*n* = 133 5.2 ± 12.2
All patients: control	*n* = 157 29.2 ± 11.0	*n* = 157 1.8 ± 8.4	*n* = 145 1.9 ± 9.8	*n* = 135 2.5 ± 10.9	*n* = 130 3.0 ± 12.1
Intervention: responders	*n* = 114 30.4 ± 10.1	*n* = 112 2.5 ± 8.3†	*n* = 108 3.8 ± 10.5	*n* = 110 5.3 ± 10.5†	*n* = 102 6.3 ± 10.5†
Intervention: non-responders	*n* = 46 24.8 ± 11.2	*n* = 45 1.3 ± 9.5	*n* = 40 0.2 ± 11.4	*n* = 35 0.5 ± 14.3	*n* = 31 1.7 ± 15.0
FACT-An (7 items: total score 0-28) mean score ± SD					
All patients: intervention	*n* = 128 115.2 ± 28.0	*n* = 127 4.9 ± 21.4	*n* = 118 7.9 ± 25.7	*n* = 114 13.1 ± 27.6*	*n* = 105 14.8 ± 28.0*
All patients: control	*n* = 121 114.0 ± 28.3	*n* = 119 5.3 ± 19.5	*n* = 110 7.4 ± 22.7	*n* = 102 7.1 ± 26.3	*n* = 101 8.7 ± 28.9
Intervention: responders	*n* = 92 118.9 ± 25.1	*n* = 91 5.1 ± 21.6	*n* = 87 9.7 ± 25.2†	*n* = 88 15.2 ± 26.3†	*n* = 82 17.4 ± 25.9
Intervention: non-responders	*n* = 36 105.7 ± 32.9	*n* = 36 4.3 ± 21.0	*n* = 31 3.0 ± 27	*n* = 26 5.8 ± 31.0	*n* = 23 5.8 ± 33.7

* Statistically significant difference from placebo ($p < 0.05$).
† Statistically significant difference from non-responder group ($p < 0.05$).

Summary. Statistically significant improvements in FACT-G and FACT-An scores were found at weeks 12 and 16. Patients who had a haematological response were also found to have improved FACT-G, FACT-An and FACT-F scores.

Cochrane trials

Abels, 1993[93] (also includes Henry, 1994[102] Case, 1993[96])

Trial/population characteristics. This was a large trial of 413 patients, split into three patient populations: patients receiving chemotherapy, patients receiving cyclic non-cisplatin-containing chemotherapy, and patients receiving cyclic cisplatin-containing chemotherapy (hence the multiple publications). A mix of malignancies was included. For the purposes of HRQoL the trial was taken as a whole. HRQoL was assessed using VAS and investigated energy level, ability to perform daily activities and overall quality of life. Assessment was made at baseline and study end.

Results. The trial data are summarised in *Table 34*.

Summary. A statistically significant improvement was found for overall HRQoL and in patients who responded to treatment.

Carabantes, 1999[94]

Trial/population characteristics. This small trial of 35 patients (intervention $n = 20$) investigated epoetin alfa versus standard care. patients had solid tumours, mainly lung and ovarian and were being treated with platinum-based chemotherapy. The NHP was used to measure changes in HRQoL.

Results. This was an abstract publication and therefore details are lacking regarding the results of HRQoL. The authors report that there "were statistically significant increases in the intervention group for energy ($p < 0.03$), mobility ($p < 0.04$) and days of restricted activity ($p < 0.04$)".

TABLE 34 *Results: Abels, 1993*[93]

Change from baseline	Intervention (n = 159)	Control (n = 143)	Epo responders only (n = 83)
Energy level	7.2	4.3	13*
Daily activity	5.8	1	11.5*
Overall HRQoL	5*	–2.1	9.5*

* Statistically significant ($p < 0.05$).

Summary. Statistically significant increases were found in three out of the six components measured by the NHP. As this is an abstract publication with scant data it is difficult to examine the robustness of the data.

Dammacco, 2001[98]

Trial/population characteristics. This trial involved 145 patients, of whom 66 (intervention) and 72 (control) undertook HRQoL assessment. HRQoL was measured by the NHP and CLAS and undertaken by patients on day 1 and at the end of weeks 4, 8 and 12 of the double-blind phase of this trial. (ECOG performance scores also undertaken by the physician.) Patients had MM and were being treated with platinum-based chemotherapy. This was a good-quality study; however, there were more than 10% dropouts observed in the control group.

Results. No raw data were given. "In the epoetin alfa group a significant improvement was noted in the NHP scales for emotional reactions ($p < 0.001$) and social isolation ($p = 0.05$) and for CLAS items energy level ($p = 0.01$) and ability to do daily activities ($p < 0.001$) with a trend towards significance for CLAS overall HRQoL ($p = 0.07$). In the placebo group only the NHP scale sleep showed significant ($p = 0.03$) improvement between baseline and week 12 with the CLAS overall HRQoL virtually unchanged from baseline ($p = 0.86$)."

Summary. These results are difficult to assess properly as actual data were not given. The summary is in favour of improved HRQoL for intervention groups, particularly those domains that require the patient to be active. The HRQoL domain sleep was improved in the control group.

Del Mastro, 1997[99]

Trial/population characteristics. This was a small trial of 62 patients (intervention $n = 31$), with only 53 patients (intervention $n = 27$) undertaking HRQoL assessment. HRQoL was measured by the PDI at baseline, during treatment and at follow-up. All patients were given G-CSF supplementation, and were suffering from breast cancer and treated with chemotherapy. A couple of study quality parameters impacted on HRQoL; these were: no blinding of patients and physicians to treatment.

Results. No differences were found between intervention and control groups ($p = 0.4$).

Summary. This small trial found no differences between the groups when HRQoL was measured using the PDI. A confounder may have been G-CSF, which was given to all patients.

Kurz, 1997[105]

Trial/population characteristics. This was a small placebo trial with 35 patients (intervention $n = 23$) suffering from gynaecological malignancies. The intervention was epoetin alfa. HRQoL was measured by a non-validated VAS questionnaire (comprising ten items) completed by the patient at the beginning of treatment and then every fourth week before receiving chemotherapy. HRQoL scores were derived from the average value of the scores on the ten items at weeks 4, 8 and 12 minus the pretreatment score. The study period was 12 weeks and was assessed as being good quality.

Results. The trial data are summarised in *Table 35*. No results were statistically significant. An analysis

TABLE 35 *Results: Kurz, 1997*[105]

	Intervention (mean)	Control (mean)
Feeling of well-being	0.004	–0.16
Mood	–0.21	–0.18
Level of activity	0.26	0.58
Pain	0.37	–0.26
Nausea	–0.11	–0.43
Appetite	–0.32	–0.07
Physical ability	–0.33	–0.32
Social activities	–0.04	–0.51
Anxiety	1.92	2.45
Treatment is helping	1.76	2.34

of only patients having a haematological response to epoetin found that physical ability showed a significant improvement ($p = 0.02$), but only 13 patients were involved in this analysis.

Summary. No differences were found.

Quirt, 1996[109]
Trial/population characteristics. This small trial of 54 patients (intervention $n = 27$) investigated epoetin alfa against placebo. It is an abstract publication and therefore lacks detail; however, as it was placebo controlled it was assumed that patients and physicians were blinded to treatment. The patients had a mix of solid and haematological tumours and the study duration was 16 weeks. HRQoL was measured by questionnaire.

Results. No difference in HRQoL was identified.

Summary. This small study did not find an HRQoL difference.

Rose, 1994[110]
Trial/population characteristics. This large trial of 221 patients (intervention $n = 142$) investigated epoetin alfa against placebo. Patients had a haematological malignancy (CLL) and were not receiving chemotherapy. HRQoL was measured at baseline and at 6 and 12 weeks. The questionnaire used combined validated psychometric scales including energy, physical/social/cognitive role function and mental health. This was assessed as good quality in all but allocation concealment, where it was unclear.

Results. This was an abstract publication and therefore limited data are given for the results. The authors report that energy scores were statistically significantly in favour of epoetin alfa ($p < 0.05$); they also report that patients whose Hct reached 38% had significant improvements in energy, self-rated health, physical function, role function/physical, role function/emotional, social function and mental health ($p < 0.01$ to $p < 0.004$).

Summary. Energy levels improved in the epoetin alfa group. It is difficult to assess the robustness of this paper as it is only an abstract and therefore data are not presented in full.

Thatcher, 1999[113]
Trial/population characteristics. This trial had a total of 86 patients (intervention $n = 42$) and investigated epoetin alfa against standard treatment. Patients had solid malignancies (NSCLC) and were treated primarily with platinum-based chemotherapy. HRQoL was assessed by an HRQoL questionnaire and the WHO performance score. The HRQoL questionnaire assessed energy, daily activity and overall HRQoL. A couple of study quality parameters impacted on HRQoL; these were: no blinding of patients and physicians to treatment.

Results. There were no significant changes from baseline at the end of the study in any group, with the exception of a significant improvement in HRQoL in the epoetin alfa group for 450 IU kg^{-1} per week, where a change of 11.7 ± 30.6 was found ($p < 0.05$ versus baseline). A positive change (but not statistically significant) was found in all groups (including the controls) except for epoetin alfa 450 IU kg^{-1} per week, where a change of -2.3 ± 31.9 was noted for energy levels.

Summary. All of the groups improved. The study authors concluded that this was expected because all of the patients at study end had similar Hb values (approximately 10–11 g dl^{-1}).

Welch, 1995[116]
Trial/population characteristics. This small trial of 30 patients (intervention $n = 15$) assessed epoetin alfa against standard care. Patients had ovarian malignancies and were treated with platinum-based chemotherapy. HRQoL was assessed by a VAS, which included questions related to energy, ability to carry out daily activities and overall quality of life. Assessment was made at baseline and at exit of the study. There were several concerns relating to study quality assessment that may have impacted on the HRQoL assessment; these were: no blinding of patients and physicians to treatment; in addition, it was unclear as to the method of randomisation and whether allocation concealment had occurred.

Results. No differences were found between the intervention and control groups.

Summary. This small trial found no differences in the HRQoL as measured by the VAS between the intervention and control groups.

Discussion

Overall, the vote-counting analysis showed a positive direction of effect in favour of epo on HRQoL. However, as noted in previous reviews,[144] there is a potential for a variety of within-study methodological problems that may bias the results. For example, "data may be skewed by missing values" or "shifts in patients' responses over time",[144] particularly when patients are asked to repeat questionnaires. Techniques such as MNAR

and MAR analysis, as demonstrated in the Littlewood trial data set,[140] can greatly assist in analysis of these data sets. Fewer than half of the trials included in this review were placebo controlled; therefore, patients would probably have known their treatment allocation, which may also have affected how they rated their quality of life.

The use of different assessment scales can limit the comparison between trials,[144] and make general assessments of study quality difficult. The trials included in this review used a variety of scales, including FACT, SF-36, NHP, PDI, VAS (both three and ten items) and HUI. While many of these tools have been tested for reliability, validity and sensitivity, this has not always been undertaken in this clinical population. The rationale for the choice of quality of life measures was often not reported by the trials and some of the scales may have been inappropriate or too basic to examine the factors affecting the quality of life in this population. This review found an improvement in favour of epo for FACT-G and FACT-An; however, both these have demonstrated a sensitivity towards Hb level (see the section 'Fatigue', p. 8). A non-significant improvement to FACT-F may indicate that fatigue in cancer patients is multifactorial and that while decreasing anaemia helps, it does not completely eliminate fatigue.[126] SF-36, where measured in conjunction with other cancer-specific scales (e.g. Littlewood[63] and Boogaerts[131]), suggested that there is an improvement in overall quality of life, but it is not statistically significant in Littlewood, suggesting that the cancer-specific scales and generic scales have different sensitivities.

The Birmingham update identified nine large trials that have used validated HRQoL measures. They were all reasonably well-conducted trials and therefore the data are reasonably robust. Boogaerts[131] may be problematic in that the dropout rate was over 10%. In comparison, most of the trials identified by Cochrane were small, and used mainly non-validated scales. The small trials tended to give neutral results, which could be because they are not sufficiently powered to answer the HRQoL question.[27] The comparison of the Cochrane review with this update indicates the importance of the data set when considering a review's conclusions. All of the previous systematic reviews used data from before 2002, and all included different populations (e.g. Ross[138] included renal patients as well as cancer patients). Different trial designs were also included across the reviews, which may have led to the differing conclusions, as well as how the data were analysed.

The review by Jones,[137] which included a substantial amount of unpublished data, offers a tantalising glance at what can be done if a more detailed data set is available. One of the major problems with the published trial reports included in this review was the lack of detailed reporting of the HRQoL outcomes, which made it unfeasible to undertake more detailed analysis. As stated earlier, vote counting was the most appropriate method given the data set.

Conclusions: HRQoL

Overall, the vote-counting analysis showed a positive direction of effect in favour of epo on HRQoL. However, for reasons discussed above, the importance to the patient of changes in HRQoL remains uncertain, although continuing work in this area of research may provide information about population norms, which should greatly assist in interpretation of these data in the future. The RCTs included in this review currently provide little information to assist in the translation of improvements in HRQoL into changes in utility, a key step in the estimation of cost utility.

Overall summary of effectiveness results

In total, 46 RCTs were included within this systematic review, 27 of which were included in the previous Cochrane review.[48] All 46 trials compared epo plus supportive care for anaemia (including transfusions) with supportive care for anaemia alone (including transfusions).

The new trials did not make a major difference to effectiveness estimates, with the exception of survival (*Table 36*).

The best estimate of haematological response (improvement by 2 g dl^{-1}) was RR 3.4 (95% CI 3.0 to 3.8), based on 22 RCTs; a typical response rate for epo was 50%. 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 any subgroups examined. Data on HRQoL collected by 20 trials showed a broadly positive effect, although it is not clear how these results translate into utility gains. Further detailed analysis is required regarding the size of the effect and the clinical importance of this. Published information on side-effects was of poor quality. There is growing evidence of excess side-effects with epo, particularly thrombotic events such as DVT.

TABLE 36 *Summary of effectiveness results*

	Cochrane (2004; 3): *n* = 27 RCTs (3287 participants)							Birmingham update to Cochrane review: *n* =46 RCTs (total 7304)						
	***n* (trials)**	**Measure**	**Point estimate**	**95% CI**	**Hetero-geneity**	**Funnel plot**	**Any subgroup effects**	***n* (trials)**	**Measure**	**Point estimate**	**95% CI**	**Hetero-geneity**	**Funnel plot**	**Any subgroup effects**
HaemR	14	RR (fixed)	3.6	3.17 to 4.23	Borderline	Asymmetry	None	22	RR (fixed)	3.4	3.01 to 3.83	None	No clear asymmetry	None
Hb change (post–pre)	6	MD[a]	Study range	+0.34 to +3.3 g dl^{-1}	Marked	NR	Yes	20	WMD	1.63 g dl^{-1}	1.46 to 1.80 g dl^{-1}	Borderline	Possible asymmetry	Possible: malignancy treatment and epo agent
Hb end of trial	Not analysed							Not analysed						
Risk of RBCT	25	RR (fixed)	0.67	0.62 to 0.73	Marked	NR	Yes[b]	35	RR (fixed)	0.63	0.58 to 0.67	Marked	Asymmetric	Some
Mean units transfused per patient	13	WMD (fixed)	–1.0	–1.31 to –0.70	None	No asymmetry	None	14	WMD (fixed)	–1.05	–1.32 to –0.78	None	NR	–
Tumour response (CR)	7	RR (fixed)	1.36	1.07 to 1.72	Borderline	No asymmetry	Not done	8	RR (fixed)	1.31	1.08 to 1.60	Borderline	No asymmetry	–
Survival	19	HR	0.84	0.69 to 1.02	None	No asymmetry	None	28	HR	1.03	0.92 to 1.16	Marked (p = 0.08)	Some asymmetry	Yes

continued

TABLE 36 *Summary of effectiveness results (cont'd)*

	Cochrane (2004; 3): *n* = 27 RCTs (3287 participants)							NICE update to Cochrane review: *n* = 49 RCTs (total 7304)						
	n **(trials)**	**Measure**	**Point estimate**	**95% CI**	**Hetero-geneity**	**Funnel plot**	**Any subgroup effects**	***n*** **(trials)**	**Measure**	**Point estimate**	**95% CI**	**Hetero-geneity**	**Funnel plot**	**Any subgroup effects**
Serious adverse events	Not analysed overall							+13	Epo: 1118 events in 1076 patients (1/person) Control: 752 events in 825 patients (0.9/person)					
AE: thrombotic	12	RR (fixed)	1.58[c]	0.94 to 2.66	None	Asymmetry	None	+13	Events epo vs control	31 vs 14	Includes 20 vs 9 categorised as 'vascular' Unable to quantify five-fold excess on epo arm in study by Leyland-Jones[118] (1% vs 0.2%)			
AE: hypertension	12	RR (fixed)	1.19	0.96 to 1.49	Borderline	Asymmetry	NR	+13	Events epo vs control	3 vs 0	May be some hypertension cases included in 'vascular' events counted with thrombotic events			
AE: haemorrhage/ low platelet	8	RR (fixed)	1.26	0.85 to 1.86	None	No asymmetry	Not done	+13	Events epo vs control	No events	May be some haemorrhage/low platelet cases included in 'vascular ' events counted with thrombotic events			
AE; rash/irritation/ pruritus	8	RR (fixed)	1.17	0.63 to 2.18	Borderline	No asymmetry	Not done	+13	Events epo vs control	1 vs 0				
AE: seizures	3	RR (fixed)	1.19	0.33 to 4.35	None	NR	Not done	+13	Events epo vs control	No events				
AE: aplasia	6	No cases of epo antibodies in six studies specifically addressing issue						+13	No further cases identified					

[a] Mean Hb change in Epo – mean Hb change in control for each study. Hb change in control groups –3.05; –0.65; –0.2; –0.04; +0.49; +0.60.
[b] Baseline Hb (esp. 10–12 vs <10); malignancy type (esp. solid vs other); treatment type (platinum vs other); publication (esp. abstract vs full text or unpublished). Regression model contains "type of concealment", "different malignancies" and "type of publication".
[c] Thrombotic events: 43/1019 epo vs 14/719 control. Hypertension: 138/1009 epo vs 64/647 control.
CR, complete response.

The Cochrane review suggested a survival advantage for epo, with HR 0.84 (95% CI 0.69 to 1.02), based on 19 RCTs. The update, based on 28 RCTs, suggests no difference, with HR 1.03 (95% CI 0.88 to 1.21) (variance estimate inflated for substantive heterogeneity, $\chi^2 = 37.75$, 27 df, $p = 0.08$). 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. Our conclusions are, however, broadly in line with those of an FDA safety briefing,[92] which broadly recommended that: patients with an Hb above 12 g dl^{-1} 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.

Chapter 5

Cost-effectiveness

Review of previous economic evaluations

Methods

Aims

The purpose of this review was to identify and appraise past economic evaluations of erythropoietin in the treatment of anaemia associated with cancer treatment. A particular goal was to understand how and why estimates of cost-effectiveness differed from one economic evaluation to the next in relation to:

- nature of the evaluation
- quality of reporting/conduct
- key parameters used.

Search

The following sources were searched up to 30 July 2004 to identify economic evaluations as part of a wider search to identify all aspects of information on costs, cost-effectiveness and quality of life outcomes:

- MEDLINE (Ovid) 1966 to July week 4 2004
- EMBASE (Ovid) 1980 to 2004 week 30
- Database of Reviews of Effects (DARE) 2004 Issue 3
- NHS Economic Evaluations Database (NHS EED) 2004 Issue 3
- Office of Health Economics Health Economic Evaluation Database (OHE HEED) July 2004 issue.

The search strategy, detailed in full in Appendix 3, combined groups of terms capturing the intervention of interest (erythropoietin), with terms capturing the target condition (cancer), with terms capturing the study design of interest (cost-effectiveness, cost and quality of life). There were no language restrictions. The industry submissions to NICE, November 2004, from the three industry sponsors, were searched for additional references.

Inclusion criteria

The original intention had been to restrict the review to cost–utility studies undertaken since 2000. However, because several widely cited studies were published in the period 1995–2000, the search period and range of included study designs were extended. The review reported here was thus of all economic evaluations (cost–benefit, cost-utility, cost–effectiveness and cost–consequence analyses) of erythropoietin for anaemia associated with cancer treatment from 1995 to July 2004. Inclusion decisions were made by one reviewer (CH).

Data abstraction and appraisal strategy

Key details of the included studies were abstracted using the framework developed and applied in past technology appraisals undertaken by the West Midlands group [e.g. *Health Technol Assess* 2001;**5**(2)]. Judgements about quality were made on the basis of the checklist suggested by Drummond and co-workers.[145] One point was allocated for each question in the checklist (with the exception of question 10, which is open) to give a summary mark out of 10. The primary data abstraction was undertaken by one reviewer (CH), with checking of data by a second reviewer (GLY).

Analysis

This was qualitative, based on the patterns in the tabulated extracted data. Draft conclusions from the initial reviewer (CH), in particular addressing the objective to identify the reasons for variation in results, were independently scrutinised and amended by two other reviewers (JR and GLY).

Results

The electronic search yielded 491 citations or citations plus abstracts. No additional references were added by searching through the industry submissions to NICE (November 2004). Full text of 44 citations was obtained, the remainder being excluded as irrelevant on the basis of title and/or abstract alone. Five studies[146–150] were finally included, the remaining 39 generally being excluded because they did not address both costs and benefits together. These are recorded in *Table 37*.

The nature of the evaluations would predict possible differences in results, with important differences in evaluation type, the extent to which modelling was used and perspective. Two studies[147,149] had a societal perspective, in contrast to the other three, which took a health service perspective. The nature of the comparison was

TABLE 37 *Characteristics of included evaluations*

	Barosi, 1998[146]	**Cremieux, 1999**[147]	**Martin, 2003**[148]	**Ortega, 1998**[149]	**Sheffield, 1997**[150]
Evaluation type	Cost–utility analysis	Cost–effectiveness and cost–utility analyses	Cost–utility analysis	Cost–utility analysis	Cost–consequences analysis
Modelling used	Yes	Minimal	Yes	Minimal	Yes
Nature of modelling	Decision tree integrating data on response rate, need for blood transfusion and transfusion-related adverse events	Some integration of effects from trials data, and costs	Bootstrapping of benefits with costs. Four phases of care identified; duration in each phase estimated; costs and utilities assigned to each phase	Small amount of integration of costs from trial data	Decision tree integrating data on response rate, need for blood transfusion and adverse events (transfusion and erythropoietin related)
Perspective	Health service (Italy)	Societal (USA)	Health service (UK)	Societal (Canada)	Health service (USA)
Intervention/comparator	Erythropoietin vs transfusion alone	Erythropoietin vs transfusion alone	Erythropoietin (epoetin-alfa) vs placebo	Erythropoietin (epoetin alfa) vs transfusion alone	Erythropoietin vs transfusion alone
Population	Typical cancer patient receiving chemotherapy	Typical cancer patient receiving chemotherapy	Stage IV breast cancer receiving chemotherapy	Typical cancer patient receiving chemotherapy	Typical cancer patient receiving chemotherapy
Outcomes considered	Transfusions; transfusion-related adverse events; response rates; quality of life	Transfusions; response rates; quality of life	Transfusions; quality of life; survival	Transfusions	Transfusions; transfusion-related adverse events; response rates; erythropoietin-related adverse events
Time-frame	4 months (baseline assumption of 5 years survival)	4 months	1–3 years; extrapolation beyond 3 years as part of sensitivity analyses	3 months	6 months
Discounting	Costs 3% p.a. Benefits 3% p.a.	Stated to be none	Costs 6% p.a. Benefits 1.5% p.a.	For willingness-to-pay figures for general population only: 5% p.a.	Not mentioned
Funding	None mentioned	Ortho Biotec	Johnson & Johnson	Jansen-Ortho	None mentioned

TABLE 38 *Quality of previous evaluations*

Generally score 1 for yes; 0 for no	Barosi, 1998[146]	Cremieux, 1999[147]	Martin, 2003[148]	Ortega, 1998[149]	Sheffield, 1997[150]
1. Is there a well-defined question?	1	1	1	1	1
2. Is there comprehensive description of alternatives?	1	1	1	1	1
3. Are all important and relevant costs and outcomes for each alternative identified?	1	1	1	1	1
4. Has clinical effectiveness been established?	½	1	1	1	1
5. Are costs and outcomes measured accurately?	1	1	1	1	½
6. Are costs and outcomes valued credibly?	1	1	1	1	½
7. Are costs and outcomes adjusted for differential timing? (Also score 1 if no, but short time-frame makes this adjustment unnecessary)	1	1	1	1	1
8. Is there an incremental analysis of costs and consequences?	1	½	1	1	½
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of costs and consequences?	1	1	1	1	1
10. How far do study results include all issues of concern to users?	Not counted towards total quality score				
11. Are the results generalisable to the setting of interest in the review?	1	1	½	1	1
Total score	9½	9½	9½	10	8½

similar in all evaluations, as was the population, with the possible exception of the study by Martin[148] which specifically considered breast cancer patients, whereas all other evaluations considered a hypothetical typical cancer patient requiring chemotherapy.

The most striking difference was the range of outcomes considered in the evaluations. Again the evaluation by Martin[148] stands out, being the only one to incorporate possible differences in survival, with an accompanying need to consider a much longer time-frame (1–3 years compared with 3–6 months). All studies considered the impact of reduced need for transfusion, in most cases accompanied by differences in response rate (response defined as reversal of anaemia). Two studies[146,150] attempted to incorporate the effect of adverse events particularly of transfusions. However, the cost and disutility were observed to be minimal, suggesting that not considering adverse events in the other included studies is probably not as big a difference as it might at first appear. Three studies[147–149] were explicitly industry sponsored.

Quality of previous evaluations

A summary of the assessments of quality of conduct and reporting of the five included studies is recorded in *Table 38*. The main purpose of this analysis was to identify any studies where there were major lapses in method or reporting standards that might of themselves be potential explanatory factors for any differences between the results of the evaluations.

The quality assessment in *Table 38* demonstrates that in general terms all studies were well conducted, as judged by the criteria suggested in the Drummond checklist.[145] Although there may be differences between the evaluations in what outcomes were considered important, for instance, all studies were explicit about what these were and explained the choices made. On this basis, quality

of conduct and reporting of the economic evaluations, as opposed to justified difference in approach, does not appear to be a major distinguishing feature between the included studies.

Key parameters

The key parameters used to populate the base-case cost-effectiveness estimates quoted in the next section are as indicated in *Table 39*.

There was great variation in the way the effectiveness results were expressed and incorporated into each of the five included economic evaluations. That by Martin[148] again stands out because it focuses on the effect of possible improvements in survival, ignoring changes arising from improvement in anaemia and quality of life associated with erythropoietin. The survival data used have a hazard ratio of approximately 0.72, which is optimistic relative to the summary hazard ratio obtained in the past Cochrane review[48] and the updated analysis provided in this report. The study by Ortega[149] is also difficult to cross-compare because it translates benefits into willingness to pay as assessed by a number of respondents both with and without cancer. The benefits explained to these respondents seem to have been restricted to those associated with reduction in exposure to transfusions; a different result may have been obtained if benefits associated with improved control of anaemia had been included. The absolute risk reduction, 29%, used in the Ortega evaluation[149] seems optimistic relative to the results of the Cochrane review[48] concerning this parameter.

In the remaining three studies, anaemia response rates and amount of blood transfused were the key effectiveness parameters. There is reasonable agreement concerning the response rates for erythropoietin – 40–55% (assuming that a mean increase of 2.1 g dl^{-1} is roughly equivalent to 50% achieving a 2 g dl^{-1} Hb increase) – which are in turn consistent with the values obtained in the past Cochrane review.[48] In contrast, there is great variation for the response rates claimed for patients not receiving erythropoietin. The measured rates of below 10% in the evaluations by Barosi[146] and Cremieux[147] are plausible; the 100% assumed response rate in the evaluation by Sheffield[150] is not. Concerning the amounts of blood transfused, although there is disagreement about the amounts transfused in erythropoietin and control arms there is consensus in the evaluations by Barosi[146] and Cremieux[147] that the difference amounts to about 0.25 units per patient per month. The size of the difference is not clear for the evaluation by Sheffield,[150] but again the assumption about transfusion levels on the control arms, of 2 units per patient per month, undermines the credibility of the evaluation.

Only three out of the five included economic evaluations incorporated the impact on quality of life. As for other effects, the variation in approach limits the amount of cross-comparison that can be made. However, as above, the study by Martin[148] must be distinguished. In the studies by Barosi[146] and Cremieux[147] the main focus was on adjusting the quantity of life (assumed to be the same for both erythropoietin and transfusion-only groups) for improved quality of life resulting from improved control of anaemia in the erythropoietin group (utility benefit +0.14 in Barosi[146] and +0.09 or +0.18 in Cremieux[147]). In contrast no such utility benefit was incorporated in the evaluation by Martin.[148] Instead, the longer survival period claimed to be associated with erythropoietin was assumed to impart improved quality of life because greater periods would necessarily be spent in the 'follow-up' phase (utility 0.76), in contrast to 'active', 'supportive' and 'terminal' phases (utilities 0.64, 0.33 and 0.13, respectively).

Finally, in relation to key parameters, costs and cost difference seem to be consistent across all included evaluations despite the differences in cost year, setting and source of unit costs. The minimum cost difference was US$3530; the maximum US$6174 (corrected value used for the Sheffield evaluation[150]) or GB£4253 (depending on the exchange rate used). Where the data were clear, the major driver of cost difference was predictably erythropoietin cost.

Results

The results of the included studies are summarised in *Table 40*.

Marked variation is the most notable feature in the results. The results by Sheffield[150] are the least optimistic, but should probably be discounted because, retrospectively at least, their assumption about response likely to arise from a transfusion only strategy is implausible. After this, the study by Barosi[146] provides the next most unfavourable assessment, suggesting that the cost per QALY at about US$190,000 is well in excess of standard thresholds. Although it considers impact on quality of life up to the end of the treatment period, it does not consider possible influence of

TABLE 39 *Key parameters*

	Barosi, 1998[146]	**Cremieux, 1999[147]**	**Martin, 2003[148]**	**Ortega, 1998[149]**	**Sheffield, 1997[150]**
Effectiveness (source): transfusion, response rate, survival	Glaspy, 1997 (cohort)	Abels 1993 (RCT) and two community cohort studies (Glaspy, 1997[50] and Demetri, 1998[51])	Littlewood, 2001 (RCT): breast cancer subgroup (36 receiving erythropoietin and 19 placebo)	Abels, 1991 (RCT)	Basket of eight RCTs, particularly Abels, 1993[93] Case, 1993[96]
Effectiveness (data): transfusion, response rate	Erythropoietin: 0.29 units per month approximately 55% have >2 g dl^{-1} Hb increase Transfusion only: 0.55 units per month approximately 7% have >2 g dl^{-1} Hb increase	Erythropoietin: 2.5 units over 4 months Hb increased by mean of 2.1 g dl^{-1} over 4 months Transfusion only: 3.5 units over 4 months Hb increased by mean of 0.4 g dl^{-1} over 4 months	Both groups: effects on transfusion just impact on cost difference effect on reversal of anaemia not included in model	Both groups: 29% risk reduction of transfusion in erythropoietin group response rate apparently not included in benefits Benefits above expressed as willingness to pay by 100 cancer patients and 50 members of general population	Erythropoietin: transfusion requirements modelled RR (>2 g dl^{-1} Hb increase) 40% Transfusion only: assumed to be 2 units per month response rate assumed to be 100%
Effective (data): survival	None	None	Approximate HR 0.72	None	None
QoL/utility (source)	Glaspy, 1997	Abels, 1993	Brown, 2001	Not considered	Not considered
QoL/utility (data)	Results for QoL measured on VAS (0–100) used directly as utility: basal 0.47 after anaemia correction with erythropoietin 0.61	Direct use of LASA of QoL: erythropoietin: +8.3 mm transfusion only: –1.0 mm Indirect use of LASA: 9.3% or 18.4% benefit in utility, erythropoietin relative to placebo, depending on calculation method used	Utilities (standard gamble technique in 30 UK oncology nurses) for each of four phases during period of survival for each patient: active 0.64 follow-up 0.73 supportive 0.33 terminal 0.13	Not considered	Not considered
Costs (source)	Drug tariff (Italy) and various sources of literature	Retail price (USA) and various sources of literature, including Sheffield[150]	BNF and various sources of literature	Source of drug costs not stated; blood transfusion costs from literature (Canada)	As applying at Cedars-Sinai Medical Center (USA)
Cost year	Not stated	1997	2000	Not stated	1995

QoL, quality of life.

TABLE 40 *Results of previous evaluations*

	Barosi, 1998[146]	**Cremieux, 1999[147]**	**Martin, 2003[148]**	**Ortega, 1998[149]**	**Sheffield, 1997[150]**
Measure	Cost per QALY	Cost-effectiveness ratio and cost per QALY	Cost per QALY	Net incremental cost	Cost relative to response
Cost year	Not stated; US$	1997; US$	2000; GB£	Not stated; US$	1995; US$
Base case	$189,652 per QALY	Outcome achieved with $0.81 of erythropoietin assisted care, requires $1 of standard care $110,769 or $214,391 per QALY (9% or 18% utility benefit, respectively); validity of use of cost per QALY questioned by authors	£8851 per QALY	$2943 (cisplatin chemotherapy)	Erythropoietin is dominated by transfusion alone (worse response at greater cost)
Chance variation in base case	Not stated	Not stated	94% probability ICER <£30,000 per QALY	95% CI $2655 to 3230 (cisplatin chemotherapy)	Not stated
Sensitivity analyses	Results said to be insensitive to changes in probabilities of blood-borne infections, QoL of responding patients and cancer-related mortality	Primary cost-effectiveness result said to be robust to a broad range of plausible assumptions	"Sensitivity analyses show that the base case results are robust under various alternative assumptions concerning the major components of our analysis" However, cost per QALY appears to fall to £39,322 when all participants in Littlewood trial are analysed	"Comprehensive sensitivity analysis". Although not detailed, results said to be insensitive to changes in parameters	Sensitivity analysis carried out. "Lower erythropoietin dosages and higher numbers of transfused units in the transfusion only group yielded approximately equivalent costs"

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

survival, which is understandable as this potential impact had not been raised at the time this analysis was conducted. In contrast, the study by Martin,[148] which does consider impact on survival, has a markedly optimistic assessment, estimating a cost–utility of £9,000 per QALY, with a 94% probability that the true cost–utility lies below a £30,000 per QALY threshold. The evaluation would have presumably been even more favourable had it incorporated improved quality of life resulting from reversal of anaemia in the erythropoietin group; however, the sensitivity of the result to the trial data used in the evaluation needs to be noted.

Of the two other evaluations, the cost–benefit analysis by Ortega[149] is again unfavourable, suggesting that individuals appear to be only willing to pay a small fraction of the additional cost associated with erythropoietin treatment. However, the main benefits presented appear to be restricted to avoidance of transfusion and it seems likely that a different assessment would have been obtained if other possible benefits, such as improved quality of life arising from reversal of anaemia and improved survival, had been considered. Finally, the analysis by Cremieux[147] presents a mixed assessment. Its cost-effectiveness analysis attempts to suggest that the cost of using erythropoietin to achieve the same outcome in terms of Hb level is 81% of that required to achieve the same outcome (if it could be achieved) with transfusion alone. This, however, ignores the key question of whether the incremental benefit is worth the cost irrespective of how the improved outcome is achieved. Cremieux[147] also presents a cost–utility analysis, although arguing strongly against its validity. This is congruent with the cost per QALY provided by Barosi:[146] US$214,000 or US$111,000, depending on how the impact on quality of life measured in trials is numerically translated into changes in utility.

Conclusions

Past economic evaluations present a highly inconsistent view of the cost-effectiveness and cost–utility of erythropoietin treatment relative to transfusion-only support in people having cancer chemotherapy. In the context of this report, this variability and the fact that views about the main relevant effects of erythropoietin have developed considerably over the past 10 years, suggest that most attention should be paid to new economic evaluations. However, the qualitative analysis presented here suggests that the range of outcomes considered in the evaluations is an important explanatory variable for the different results in past assessments, and that how this is dealt with in current economic evaluations should receive careful scrutiny. Past evaluations suggest that whether and how possible survival benefits are incorporated in economic models have a critical influence on the view that emerges concerning cost-effectiveness.

Factors that appear to be less important in determining the observed differences in results are:

- inclusion of side-effects related to either blood transfusion or erythropoietin
- costs, there being a high degree of consistency about the incremental cost, which is mainly attributable to the cost of erythropoietin.

The first point suggests that it would seem reasonable for current models to ignore the impact of side-effects in economic evaluations, unless the estimates of frequency of important adverse events is felt to have changed markedly. The second suggests that careful consideration needs to be given to any current economic evaluation departing markedly from past assessments that incremental cost is largely that associated with provision of the erythropoietin.

Summary

A systematic review of past economic evaluations from 1995 to 2004 was conducted. Five economic evaluations were initially included, but the estimates provided by one of these[150] were undermined by the unrealistic nature of some of its assumptions. There was marked variation on the results of the remaining four. At one extreme, a cost per QALY of US$190,000 suggested poor efficiency; at the other a value of £9000 per QALY suggested that benefits associated with erythropoietin are achieved at reasonable cost. Qualitative analysis of evaluation characteristics, study quality and key parameters of past economic evaluations suggested that the main factor driving the difference was the range of benefits that the evaluations attempted to capture. The study incorporating survival benefit was the most optimistic.[148]

Review of company models

Introduction

This section reviews the three company submissions, each of which included a model. Some general points are then made about these models in relation to the major uncertainties that need to be explored in any further modelling. The assessments were carried out by JR and GLY.

Amgen model

The Amgen cost-effectiveness model described in their industry submission to NICE (Amgen Ltd. Clinical and cost effectiveness of darbepoetin alfa in cancer treatment-induced anaemia. Industry submission to NICE; November 2004) used patient-specific data on 1262 patients enrolled in Phase II and III darbepoetin trials. Two models were provided, each with a different time-frame: a decision tree for 25 weeks comprised the reference case, supplemented by a Markov model over 2.75 years. The results of the first model were used to populate the second, which includes a survival benefit. Life expectancy was modelled from the pooled trial data. The utility scores were based on Hb levels, both of which are based on an active-controlled darbepoetin trial.

Unit costs were based on official drug prices, NBS blood costs and the OHE database for hospital costs [serious adverse events (SAEs), specifically hospital treatment of DVT and of persistently anaemic patients].

Sensitivity analyses were reported for survival benefits, Hb baseline levels (<10 versus 10–11), the extra cost to the NHS for management of persistently anaemic patients, the cost of blood production versus opportunity cost, different dosing strategies, modelling blood usage required to achieve darbepoetin outcomes, and varying survival outcomes.

The results were as follows:

- £159,000 per QALY over the 27-week reference case
- £23,600 per QALY over 2.75 years, based on assuming a survival gain.

When blood was used to achieve an equivalent Hb outcome darbepoetin was cost equivalent, and the opportunity cost of blood was put at £1523, compared with a production cost of £120.

The utility values by Hb are shown in *Table 41*, based on an unpublished EuroQol 5 Dimensions (EQ-5D) study from a Phase III active controlled darbepoetin trial, which collected weekly data from around 100 patients over 16 weeks.

TABLE 41 *Utility weights by Hb level*

Hb	Mean	*n*
<8	0.564	265
8–9	0.639	625
9–10	0.623	1345
10–11	0.699	1791
11–12	0.728	1414
≥ 12	0.750	1417

Source: unpublished Amgen study included in industry submission to NICE, November 2004.

Reference case analysis

The model was based on the protocols of three clinical trials and on current recommendations for use. In the trials a patient's response was evaluated at week 6 and if the response criterion (Hb up 1 unit) had not been met, the dose was doubled. If after 8 weeks the response was still inadequate, treatment was stopped. In non-responders the Hb value at week 8 was carried forward.

Patients in the decision-tree model were allocated to the six Hb (and utility) levels (*Table 42*) with weekly changes computed (cycle 1 week). The area under the curve was used to estimate the total difference in utility for each branch over the trial period (Hb levels interpolated were between points in time).

These results were amended to include post-trial period differences in Hb and utility, as "it is unrealistic to assume that patients in both arms of the trial immediately return to identical states at the end of the treatment period. Once patients have completed chemotherapy, Hb gradually returns to normal as the bone marrow recovers from myelosuppressive effects of the treatment" (Amgen Ltd, Industry submission to NICE, p. 47). The post-trial changes in Hb were modelled as 0.1 g dl^{-1} per week from week 14 to 26, based on changes observed in the trials for the first 2 weeks post-treatment. This amendment, termed 'normalisation', is new in the relevant literature and was a shared feature of the three company submissions. As shown in *Figure 15*, its effect is roughly to double the trial estimate of the utility gain attributed to epo treatment.

The reference case estimated cost per QALY of £159,000 was based on the inclusion of the post trial gains.

The Markov model extended the reference case results to include survival gains due to darbepoetin, using a hazard ratio based on the pooled analysis of 0.88 (95% CI 0.75 to 1.01). The utility score in the follow-up period was assumed to be as baseline (0.66). The model included stochastic (survival probability per day)

TABLE 42 *Cost, QALY and cost per QALY: Amgen model*

	Analysis period	Cost (SE)	QALY (SE)	Incremental cost per QALY (95% CI)
Darbepoetin	27-week reference case	£3,570 (50)	0.0309 (0.0067)	
No darbepoetin		£1,156 (50)	0.0146 (0.0060)	
Difference		£2,594	0.0163	£159,339 (£140,000 to £187,000)
	Survival estimate over 2.75 years			
Erythropoietic agent		£3,750	408 days	
No erythropoietic agent		£1,156	368 days	
Difference		£2,594	40 days	£23,546 (£12,000 to £320,000)

Source: Amgen submission, Table 23.

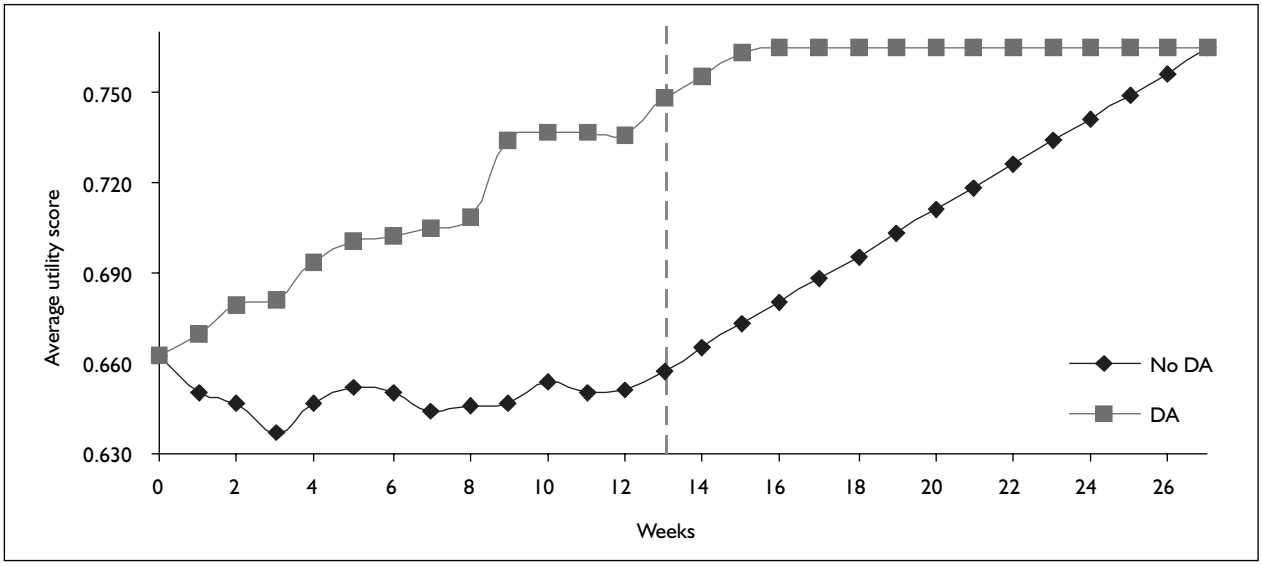

FIGURE 15 *Modelled QALY estimates for reference case analysis. DA, darbepoetin alfa. (Reproduced from the Amgen Industry submission to NICE, November 2004.)*

and deterministic (costs and effect estimates from the decision-tree model) elements. Monte Carlo simulations (10,000 interactions) were used to generate a cost-effectiveness acceptability curve (CEAC). The cost per QALY in this analysis was £23,600.

Sensitivity analyses

Given that the inclusion of a survival gain improves the cost per QALY from £159,000 to £23,600, the sensitivity analysis around the survival gain is of particular interest. The mean survival gain due to darbepoetin was 52 days (95% CI –5 to 102 days). With the lower estimate, the alternative of no treatment would dominate (poorer outcome with darbepoetin at greater cost) and with the higher estimate the cost per QALY would be just over £9,000.

Other univariate sensitivity analyses showed the results to be robust to reasonable changes in parameter values.

The Amgen probabilistic sensitivity analysis (which according to the NICE guidelines should involve fitting distributions to all parameters) was based on fitting distributions to only two parameters in the Markov model: baseline utility score and the extra cost for management of persistently anaemic patients. Unsurprisingly, this showed a "100% chance that the incremental cost-effectiveness result is under the [£30,000] threshold value"

(p. 55, figure in brackets added). The omission of survival gain from the sensitivity analysis is striking.

Criticisms

The key factor leading to a relatively low ICER of £23,600 is inclusion of survival gain despite the estimate not being statistically significant. The omission of survival gain from the probabilistic sensitivity analysis cannot be justified. The other criticism has to do with the inclusion of post-trial Hb gains termed normalisation above.

Ortho Biotec model

The Ortho Biotec (OB) model described in the industry submission to NICE (Ortho Biotec UK. Technology appraised of erythropoietins for the management of cancer-related anaemia. Sponsor submission to NICE; November 2004) compared the cost-effectiveness of epoetin alfa with standard treatment using blood transfusion for chemotherapy-induced anaemia. The time-frame was 36 months and the model included a survival gain. The stochastic model in Excel comprised three components:

- cost-effectiveness evaluation based on clinical trials and subgroups
- extrapolation of benefit beyond the clinical trial
- subgroup analysis to estimate service and budget impact.

Pooled patient-specific data from three relevant RCTs were stratified and bootstrapped to provide distributions for the following parameters: cost of prior treatment, QALYs at entry, Hb days at entry, the proportion dying during initial treatment, time on initial treatment and hazard ratio to estimate standard care median survival.

The assumptions in the Markov model were as follows:

- Normalisation of Hb levels post-trial at 0.2 g dl^{-1} per week, up to an end-point of 13. ('Normalisation' as defined above in the Amgen model refers to extrapolation of the Hb difference between treatment and control groups post-treatment)
- a survival gain, based on a single trial (Littlewood[63])
- Continued disbenefit post-trial due to patients having been fatigued during the trial (used in sensitivity analysis only).

The utility values are shown in *Table 43*, based on an unpublished OB-sponsored study of community values of different levels of fatigue.

TABLE 43 *Hb and utility levels*

Level	Utility from TTO	SD
No	0.86	0.14
Mild	0.78	0.17
Moderate	0.67	0.21
Severe	0.48	0.21

Source: unpublished Ortho Biotec study, industry submission to NICE, November 2004.
TTO, time trade-off.

Both TTO and standard gamble (SG) utility values were provided in an appendix, showing the TTO method giving more favourable results than SG. A novel case was made by OB for using TTO rather than SG scores (claimed to be better for trading small gains and losses).

The gain in survival was based on one of the three trials (Littlewood[63]), rather than on the less favourable result from three trials combined. The Littlewood study had a median survival of 17 months for the epoetin alfa group compared with 11 months for the placebo, giving a hazard ratio of 0.647. "These data were also used to estimate a constant transition probability post trial" (Ortho Biotech UK, Industry submission to NICE, p. 30).

Costs included the cost of epoetin alfa, blood transfusions, blood units and SAEs. Eighty per cent of patients were assumed to self-administer the subcutaneous injections. (The costs of epoetin alfa were adjusted in line with the Eprex guarantee scheme in sensitivity analysis.)

Results

The incremental cost per QALY results are shown in *Table 44*.

Sensitivity analysis

One-way sensitivity analyses were carried out on the utilities (including disbenefits of fatigue), survival estimates and the impact of the Eprex guarantee scheme. As the survival estimates had the greatest impact, only these are summarised here. Two different scenarios were explored: limiting the time-frame for survival to 24 months, which gave an ICER of £23,800, and using the Cochrane-adjusted HR of 0.81, which gave an ICER of £29,900. This was similar to that for Amgen, which had a slightly higher HR of 0.88 and an ICER of £23,000. (Note that the unadjusted Cochrane HR was 0.84, 95% CI 0.69 to 1.02.)

TABLE 44 *OB model results: incremental cost per QALY, by Hb and tumour*

Tumour type	Hb subgroup	Incremental cost	Incremental cost per QALY
All	All	£4,021	£12,952
	<10	£4,310	£14,807
	10–12	£3,886	£12,174
Solid tumours	All	£3,516	£11,404
Haematological	All	£5,123	£1,578

Although a CEAC was provided, showing "there is a probability of 1.0 of achieving a cost per QALY of £15,000 or less", no information was provided on the parameters to which distributions were fitted. Given that the results are close to the mean ICER of £13,000, the probabilistic sensitivity analysis does not appear to have included the major uncertainty around survival gains. Consequently, the CEAC is of no value.

Criticisms

The four main criticisms of the OB model are first that it combines Hb and mortality gains, even though the latter are only statistically significant in one trial and not in the meta-analysis. Secondly, it uses central estimates for survival gains and not the 95% confidence intervals from either Littlewood[63] (statistically significant but wide) or Cochrane[48] (not statistically significant). This reduces the value of the sensitivity analysis around these estimates. Thirdly, it relies on normalisation, but this has a lesser impact on the results than the mortality assumptions. Fourthly, the sensitivity analyses do not explore the major uncertainties, particularly those associated with survival gains.

Roche model

The Roche industry submission to NICE, on NeoRecormon® (epoetin beta) (Achieving chemical excellence in the treatment of cancer related anaemia. Industry submission to NICE; 4 November 2004) built on previously published work in relation to:

- comparative clinical effectiveness
- utility scores
- survival benefit
- subgroup analysis.

A simple decision-tree model was used to estimate the ICER. The model used

- event probability from pooled RCTs
- normalisation from a small audit
- utility values from an unpublished study by Sosa (2004). Included in an industry submission to NICE.

TABLE 45 *Roche Hb and utility values*

	n	Mean utility	SD
No anaemia (13)	106	0.86	0.14
Mild (10.2)	106	0.78	0.17
Moderate (8.7)	106	0.61	0.21
Severe (7.2)	106	0.48	0.21

Source: Roche, unpublished study.

- unit costs from standard sources
- expert opinion where necessary.

Utility values were based on those shown in *Table 45*, based on a company-sponsored study of the general public.

Baseline utility was an average of those in published studies. Hb levels were taken from RCTs.

Normalisation (as defined above in the Amgen model) was assumed with two levels: 13 for solid and 11.9 for haematological tumours. A gain of 0.2 g dl^{-1} per week was assumed, based on "expert opinion as well as real life audit data".

The hazard ratios (for survival) were based on the Cochrane review[48] for all cancers supplemented by use of a hazard ratio of 0.49 for solid tumours, again from the same source. The time-frame is unclear, but based on Office for National Statistics (ONS) life expectancy.

Results

The results in *Table 46* show an ICER of £28,000 for solid tumours and £84,000 for haematological tumours. The difference is due entirely to the assumed lack of a mortality gain in the haematological tumours. By implication, the ICER for solid tumours can be derived from this table as £81,000. (The ICER for haematological malignancies has no survival gain and is 3510/0.042 = 83,571. Taking 3727/0.046 gives 81,022, the ICER for solid tumour without any mortality gain.)

TABLE 46 *Roche model: incremental costs, effects and cost per QALY*

	Incremental cost	Incremental HRQoL	Incremental life-year	Incremental QALY	Cost per QALY
Solid	£3,727	0.046	0.086	0.132	£28,221
Haematological	£3,510	0.042	0.00	0.042	£83,705

TABLE 47 *Utility by Hb level: three companies*

OB/Roche	OB	Roche		Amgen
Anaemia category Hb (g dl^{-1})	**Utility**	**Utility**	**Anaemia category Hb (g dl^{-1})**	**Utility**
No anaemia (mean 13)	0.86	0.86	≥ 12	0.750
Mild (mean 10.2)	0.78	0.78	11 to <12 10 to <11	0.728 0.699
Moderate (mean 8.7)	0.61	0.61	9 to <10 8 to <9	0.623 0.639
Severe (mean 7.2)	0.48	0.48	<8	0.564

Sensitivity analyses

Although a range of analyses was presented, this section concentrates on those to do with survival. With the Cochrane HR of 0.49 (95% CI 0.25 to 0.94), use of the upper and lower confidence intervals gave ICERs of £20,600 to £67,600 for solid tumours. A hazard ratio of 0.53 would be required to generate an ICER of £30,000.

A probabilistic sensitivity analysis was carried out based on fitting distributions to all parameters in the model for one type of solid tumour only: male testicular cancer. The results are presented graphically without comment. They show a probability of around 0.6 that the intervention is effective at a threshold value of £30,000.

An additional willingness-to-pay analysis was included.

Criticisms

The main criticism is that the model incorporates mortality gains from epo treatment that lack robust evidence. Secondly, although a full probabilistic sensitivity analysis was carried out, the results are reported only for one type of cancer. Thirdly, the model relies on assumptions of 'normalisation'.

Comparing the three submissions

This section compares the three submissions in relation to utilities, mortality and ICERs.

Utilities

Two companies used a four-level classification, the other company a six-level classification (*Table 47*). Those with four levels had similar values, but these were considerably different from the six-level values used by Amgen. However, these differences are of less impact on the results than the shared assumption by all three companies of 'normalisation'. All three used the same assumption that Hb differences due to treatment persisted beyond the end of the trial period, and that progress in Hb levels back to normal was at a fixed rate (0.2 g dl^{-1} per week in OB and Roche; 0.1 g dl^{-1} per week in Amgen). As noted in the text above, this assumption roughly doubles the gain in utility attributable to treatment (Doubling if 0.1 g dl^{-1} per week is assumed, based on *Figure 15* from Amgen. The gain would be less than double if the faster normalisation rate of 0.2 g dl^{-1} per week were used, as in the other company models.) No report of any study on normalisation has been located. The shared estimate used by the companies is attributed to clinical expertise.

Mortality

All three companies assumed mortality gains due to reduced Hb levels from treatment. The Amgen model showed results with and without the mortality assumption, indicating that this assumption reduced the ICER from £159,000 to £23,600. As noted above, the meta-analytic results

TABLE 48 *Incremental cost per QALY: three companies*

	Amgen Darbepoetin	OB Epoetin alfa	Roche Epoetin beta Solid tumours	Roche Epoetin beta Haematological
No survival gain	£159,000		£81,000 (estimated)	£84,000 (HR 1.0)
With survival gain	£24,000	£13,000	£28,000	

do not show a statistically significant mortality difference. All of the company submissions reported a range of one-way sensitivity analyses on the effects of using different estimates of the mortality gains, but none reported the full range of possible values and none reported a probabilistic sensitivity analysis that included the uncertainty around mortality effects for all cancers.

ICERs

The results in terms of ICERs from the three companies are shown in *Table 48*, indicating that when survival gains were included the range was from £13,000 to £28,000. The one company that provided an estimate without a survival gain had an ICER of £159,000. For Roche the ICER without any mortality gain has been estimated at £81,000 for solid tumours (and £81,000–83,000 for all tumours). These results highlight the importance of assumptions regarding survival gains.

The Birmingham epo model

Model structure

An individual sampling model (the Birmingham epo model) was developed to assess the cost-effectiveness of epo treatment compared with standard care with blood transfusion alone. All authors and clinical advisors contributed comments on the model structure, which was also informed by a detailed patient pathway (see Appendix 1). The model was structured to enable the scenarios of three company models to be rerun and assessed.

Fourteen health states were defined by Hb levels (including death) in the epo treatment arm and eight in the standard care arm (*Table 49*).

The model has a 3-year time frame in which the base case is six 4-week cycles for chemotherapy treatment followed by an off-chemotherapy period (33 4-week cycles). A fixed 4-week cycle length is defined.

TABLE 49 *Health states in the Birmingham epo model*

1. On epo, Hb level <8
2. On epo, Hb level 8–9
3. On epo, Hb level 9–10
4. On epo, Hb level 10–11
5. On epo, Hb level 11–12
6. On epo, Hb level 12–13
7. Off epo, Hb level <8
8. Off epo, Hb level 8–9
9. Off epo, Hb level 9–10
10. Off epo, Hb level 10–11
11. Off epo, Hb level 11–12
12. Off epo, Hb level 12–13
13. Hb level >13
14. Death

A large number of patients were simulated and characterised by their baseline Hb levels at the start of chemotherapy. Cost and QALYs are accumulated as patients go through the model. The initial distribution of patients at different Hb levels was averaged from individual patient clinical trial data submitted by two companies (OB and Amgen) (*Table 50*).

Model assumptions

Patients in the model were characterised only by their baseline Hb level at the start of chemotherapy. No other characteristic, such as cancer type or chemotherapy treatment, was included, but if necessary these could be run as separate groups with different baseline Hb levels.

The two arms, epo and standard care, started at the beginning of chemotherapy. In the treatment arm, epo was given when the patient's Hb level fell below 13 g dl^{-1}. A full dose was assumed when Hb was less than 12 g dl^{-1} and half doses when Hb levels were between 12 and 13 g $dl^{-1}1$. Patients were taken off epo treatment if and when their Hb reached 13 g dl^{-1}.

Response to epo was defined as a 2 g dl^{-1} increase in a given Hb level. As indicated in *Table 50*, patients were categorised into Hb-level categories that were 1 unit apart, so a response to epo meant

TABLE 50 *Baseline Hb distributions from company submissions*

	Amgen		OB		Average	
Hb g dl^{-1}	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
<8	122	5.7	17	3.1	139	5.2
8–9	351	16.4	65	12.0	416	15.5
9–10	613	28.7	156	28.8	769	28.7
10–11	783	36.6	170	31.4	953	35.6
11–12	233	10.9	113	20.9	346	12.9
12–13	33	1.5	17	3.1	50	1.9
⩾13	2	0.1	3	0.6	5	0.2

that patients would move up two states. No response in the first cycle was allowed, which implied no response within the first 4 weeks. It was also assumed that once a patient had responded to epo, he or she continued to respond to epo until taken off treatment. The percentage response to epo treatment was assumed to be independent of their Hb levels.

Dose escalation was not considered in the Birmingham epo model. Stopping rules were applied for those who did not respond to epo treatment up to a maximum of three cycles (12 weeks). Once patients were off epo treatment they followed the same pathways as those in the standard care arm.

Blood transfusion was applied to both arms (comprising the only treatment in the standard care arm). Transfusion was only considered when Hb levels were less than 10 g dl^{-1}. The probability of patients needing transfusion, 0.31, was applied to Hb levels that were less than 8 g dl^{-1}, between 8 and 9 g dl^{-1} and between 9 and 10 g dl^{-1}. Once patients' Hb levels reached 10 g dl^{-1}, no transfusion was considered.

Patients had different probabilities both for being transfused and for the number of units of RBCs in the epo treatment arm compared with the standard care arm. The relative risk of receiving RBCT, taken from the systematic review, was 0.63 (95% CI 0.58 to 0.67) for epo versus standard care. The relative number of RBC units per transfusion for the epo arm versus standard care was –1.05 (95% CI –1.32 to –0.78). The average number of units of RBCs for standard care was 2 units.

A standard response to blood transfusion was assumed equal to a 1 g dl^{-1} increase in Hb level. This meant that patients moved up one state from any given Hb level. The response to blood transfusion was assumed immediately at the end of the cycle, but lasting for only one cycle. If the patient was not given a blood transfusion in the following cycle, the patient's Hb level dropped back to the previous level. However, if another transfusion was given, the patient stayed in that state.

Extrapolation beyond chemotherapy treatment periods

At the end of chemotherapy (six cycles), patients were assumed to undergo 'normalisation' as their Hb levels recovered to normal. As noted above, normalisation is not supported by any evidence. Normalisation in the Birmingham epo model approximated the recovery rate of 0.2 g dl^{-1} per week shared by two company models. However, individual patients' Hb levels were used instead of average Hb values at the end of chemotherapy. Patients' Hb levels were assumed to increase by one state for every cycle (4 weeks) after the chemotherapy treatment. Patients were tracked for their Hb level after the chemotherapy treatment period, and once patient Hb levels reached 13 g dl^{-1}, they were assumed to remain in that health state. Utility values were applied to each Hb level.

Model inputs

Parameters were derived from background literature, in-house systematic reviews of parameter assessments and data provided in the company models.

Survival

As the evidence remains uncertain about survival benefits due to epo treatment, the model allows the survival benefit to be to be 'triggered' on and off. The in-house systematic review, updating the existing Cochrane review estimate, had a hazard ratio for epo treatment arm versus standard care of 1.03 (95% CI 0.88 to 1.21). In the base case, no survival gain was assumed. Sensitivity analysis used the lower confidence interval of 0.88. *Table 51*

TABLE 51 *Survival hazard ratios for epo versus standard care*

	Roche	Amgen	OB	In-house
HR (95% CI)	Solid tumour: 0.49 (0.25 to 0.94) Haematological malignancies: 1.0 (0.67 to 1.49)	All types 0.88 (0.76 to 1.10)	All types 0.647 $p = 0.052$	Systematic review: all types: 1.03 (0.88 to 1.21) Birmingham epo model: baseline HR 1.0. HR 0.88 for sensitivity analysis

TABLE 52 *Costs for epo treatment and blood transfusion*

	Amgen	OB	Roche	Average
	Darbepoetin alfa	*Epoetin alfa*	*Epoetin beta*	
Epo costs				
Unit cost for epo (£)	1.676 mg^{-1} Dose 2.25 $\mu g\ kg^{-1}$ week	83.3 per dose 3 doses per week	83.8 per dose 3 doses per week	83.8 per dose
Administration	8.01 per dose 3 doses per week 24.04 per week	8.05 per dose 3 doses per week 24.15 per week	34 per week	8.01 per dose
SAE	185	101	101	101
Probability of SAE	0.05	0.05		0.05
Total cost of epo per week (£)	264.0 Dose at 2.25 $\mu g\ kg^{-1}$ per week	275.6 3 times per week	289.7 3 times per week	276.7
Total cost, 4 weeks (£)	1102.2	1087.9	1091.8	1106.7
Blood transfusion costs				
Blood unit cost (£)	120	120.22	120.22	120.22
Blood transfusion administration	153 per unit	412.34 per transfusion in hospital	413 per transfusion in hospital	413 per transfusion in hospital
Cost of adverse event (£)			101	
Total cost per blood transfusion (£)	278.85	278.79	272.94	276.86

shows the hazard ratios from company submissions and the in-house systematic review.

The baseline mortality can be specific to any cancer site. The model has been set to cover hazard rates from 0.01 to 0.10 per 4-week cycle. If an exponential survival function is applied, this would indicate a mean survival between 0.8 and 7.8 years, which would cover most cancer types. The baseline mortality in the Birmingham epo model is 0.05, implying a mean survival time of 1.54 years.

Resource use and costs

Resource use was considered from the NHS perspective. Only costs relevant to the NHS were included. The cost for epo treatment included the drug cost, administration costs and treatment of SAEs. The cost for blood transfusion included costs of transfusion, of administration and of treatment for SAEs. The unit costs were consistent both between company models and with the information obtained in background searches (*Table 52*).

Utility scores

Utility scores by the Hb levels used in the Birmingham epo model, derived from the company submissions, are shown in *Table 53*. Data were derived using two different methods, TTO and EQ-5D. The values for different companies based on TTO were similar to one another, as were those based on EQ-5D. The Birmingham epo model base case used TTO values, with EQ-5D

TABLE 53 *Utility score by Hb level*

	EQ-5D		TTO	
Hb health state (g dl^{-1})	**Amgen**	**OB2**	**OB4**	**Roche**
<8	0.564	0.564	0.466	0.481
8–9	0.639	0.608	0.563	0.615
9–10	0.623	0.629	0.631	0.615
10–11	0.699	0.665	0.692	0.781
11–12	0.728	0.715	0.749	0.781
12–13	0.75	0.750	0.789	0.781
>13	0.75	0.750	0.810	0.856

TABLE 54 *ICERs with and without survival gain*

	Mean QALY gain	Mean cost increase	ICER
1. Base case 1 with normalisation but no survival gain	0.030	£4,450	£150,342 (£112,559 to 225,520)
2. As 1 but no normalisation, no survival gain	0.032	£4,452	£140,829 (£137,094 to 144,753)
3. As 1 but with survival gain HR 0.88 (lower 95% CI)	0.115	£4,537	£39,568 (£37,188 to 42,260)

TABLE 55 *Relationship between hazard ratio and ICER*

HR	QALY difference	Cost	ICER
1.00 (base case)	0.030	£4,450	**£150,342** (£112,559 to 225,520)
0.88 (Amgen value and lower CI from this review)	0.115	£4,537	**£39,568** (£37,188 to 42,260)
0.84 (Cochrane estimate)	0.144	£4,567	**£31,639** (£30,093 to 33,344)
0.647 (OB value)	0.331	£4,703	**£14,223** (£13,890 to 14,572)

used in sensitivity analysis. For both base case and sensitivity analysis, the OB values were used, on the basis that these were based on a community sample in which the same people were exposed to the different methods. Further, one of the Amgen EQ-5D scores was anomalous (for Hb health state 9–10, the utility was 0.623, less than that for the (better) Hb health state of 8–9, which was 0.639). (The utility score in the Birmingham epo model was held constant at the value for Hb = 7 g dl^{-1}, for those whose Hb value was lower than 7 g dl^{-1}. It was also held constant at the value of Hb = 13 g dl^{-1} for those whose Hb level was above 13 g dl^{-1}.)

Results

The model was run for 50,000–100,000 patients to obtain a good approximation of the assumed population mean. The results of the Birmingham epo model were similar to those of the companies, in that a relatively high ICER resulted when no survival gain was attributed to epo, mean £150,000. This fell sharply to a mean of £40,000, when a survival hazard ratio of 0.88, the lower, most favourable confidence interval, was assumed. When neither normalisation nor survival gain was assumed, the cost per QALY rose to £141,000 (*Table 54*).

One-way sensitivity analysis, appropriate given the importance of survival assumptions on the ICER, explored the relation between hazard ratio and ICER, indicating that each 0.01 rise in the former in favour of epo reduced the ICER by around £1,000 in the range 0.84–0.88 (*Table 55*).

Sensitivity analysis: alternative utility values
When EQ-5D-based utility values were used instead of those based on TTO, the base-case ICER rose from £150,000 to £218,000.

Although the Birmingham epo model was set up to enable probabilistic sensitivity analysis incorporating the uncertainty to do with each parameter, it is clear from the above that the major uncertainty related less to parameter estimates than to whether or not a mortality reduction can be assumed. In the absence of an assumed mortality gain, the ICER for epo against standard care is well above £100,000. Given the centrality of the assumption on survival gain to the cost per QALY, it was deemed unnecessary to proceed to a full probabilistic sensitivity analysis.

Overall conclusions and summary: economic analysis

A systematic review of past economic evaluations from 1995 to 2004 was conducted. Five economic evaluations were initially included, but the estimates provided by one of these[150] was undermined by the unrealistic nature of some of its assumptions. There was marked variation in the results of the remaining four. At one extreme a cost per QALY of £190,000 suggested poor efficiency; at the other a value of £9,000 per QALY suggested that benefits associated with erythropoietin are achieved at reasonable cost. Qualitative analysis of evaluation characteristics, study quality and key parameters of past economic evaluations suggested that the main factor driving the difference was the range of benefits that the evaluations attempted to capture. The study incorporating survival benefit was the most optimistic.[148]

Three economic models were submitted by the manufacturers; one each for darbepoetin, epoetin alfa and epoetin beta. All of the models considered possible benefits accruing from improved haematological response, improved quality of life and survival gain with epo. A novel feature not encountered in economic evaluations before 2004 was the concept of a 'normalisation' period after chemotherapy/epo treatment has been completed. This assumes that because there is a difference in Hb levels at the end of treatment, which will not disappear immediately, it is reasonable to extrapolate the difference post-treatment. Normalisation rates have not been directly measured, so assumptions have had to be made concerning these rates. Two models assumed 0.2 g dl^{-1} per week, largely based on clinical opinion. On this basis a 2 g dl^{-1} difference in Hb would take 10 weeks to reverse; simple geometry suggests that this approximately doubles the quality of life benefit accruing.

The base case in the Amgen submission for darbepoetin was £159,000 per QALY; this result did not consider survival. When survival was considered the cost–utility was £24,000 (95% CI £12,000–320,000); the survival benefit was taken as a hazard ratio of 0.88. The reference case for epoetin alfa submitted by Ortho Biotec claimed a cost–utility of £13,000. This includes a large survival benefit derived from the RCT by Littlewood[63] (HR 0.65). When the adjusted hazard ratio of 0.81 from the Cochrane review was used in the sensitivity analysis, the cost–utility for epoetin alfa was similar to that obtained for darbepoetin, £30,000.

No cost–utility data were presented by OB for epoetin alfa, assuming no survival advantage (i.e. HR 1.0).

The approach to assessing cost–utility from Roche for epoetin beta was different in that it considered solid and haematological tumours separately. The models for epoetin beta do incorporate survival benefit. The Roche cost–utility for solid tumours was £28,000. The hazard ratio underpinning this estimate was taken from the Cochrane review subgroup (HR 0.49). The cost–utility for haematological malignancies was £84,000. The hazard ratio underpinning this estimate was taken from the Cochrane review subgroup (HR 1.0). A new individual sampling model, the Birmingham epo model, was developed in-house to assess the cost-effectiveness of epo treatment compared with standard care with blood transfusion alone.

The Birmingham epo model base-case estimate of cost–utility in the absence of survival benefit, but with normalisation, was £150,000. Running the model with the most favourable estimate (lower 95% CI) for survival (0.88) gave a cost per QALY of £39,568.

Further analyses, particularly probabilistic sensitivity analyses, were not considered appropriate given the central importance of the assumption on survival gains attributable to epo.

The key conclusions are:

- Where survival benefit is assumed with a hazard ratio of less than 0.84, the cost-effectiveness of

epo relative to standard care falls below £30,000.
- In the absence of survival benefit, cost-effectiveness estimates are unfavourable.

As discussed in the section 'Overall summary of effectiveness results' (p. 81), there is still great uncertainty about whether a survival benefit exists, what the size of it might be and what the cause of observed heterogeneity in survival results is due to. Better estimates of cost–utility must await further research on survival becoming available. Further exploration of whether a favourable cost-effectiveness ratio could be obtained in the absence of a survival benefit may also be useful. However, it seems unlikely that cost–utility will become favourable unless:

- better targeting of epo greatly improves response rates, and/or
- costs associated with epo are dramatically reduced, and/or
- costs associated with transfusion are dramatically increased, and/or
- estimates of quality of life gain associated with reversal of anaemia are altered.

Chapter 8 considers how plausible these alternatives might be. It also considers whether there are other factors that need to be taken into account in the overall assessment of the potential value of epo. Most importantly, it considers the prospects for better quality survival data, from completed but currently unpublished studies, ongoing studies or new RCTs.

Chapter 6

Implications for other parties

In addition to the benefits, harms and costs associated with epo treatment outlined in the previous sections, there are several implications for other parties.

For patients themselves, although improved measures of quality of life have gone a long way towards improving assessment of the impact relevant to the patient, quality of life tools may still not fully capture all the impacts of anaemia associated with quality of life. The fluctuation of effects from day to day and the fact that the impact may be on the frequency with which anaemia symptoms are felt over a period is a major challenge, particularly given that there may be an important difference in the profile of Hb levels in epo compared with transfusion alone.

A further challenge is to weigh the potential impact of rare but potentially very serious adverse events, which although they apply mainly to blood transfusions, also affect epo with respect to red cell aplasia. Not only are the adverse events extremely difficult to quantify (true confidence intervals may cover a very wide range of risk), but it is also extremely difficult to gauge impact should the event occur. Thus, the possibility of hepatitis B infection at a frequency of 1 per 50,000 units of RBCs transfused may sound highly threatening, if not put into the context that this risk is likely to have decreased over time, that the impact of hepatitis B virus is variable and is amenable to treatment, that sequelae may occur many years in the future and that there is the possibility that the events in question may be overtaken by events associated with the cancer itself.

'Costs' to patients and carers are not considered in the analyses, because the health service is suggested to be the most appropriate perspective for economic evaluations for NICE. Nonetheless, it is important to note that costs to the patient of attending for transfusions as a day case may be considerable, and may be reduced by the use of erythropoietin. It is further worth noting that the costs may extend to carers, who may have to support the patient directly or take over childcare duties. These costs extend far beyond the financial, time associated with transfusion being perceived as particularly precious in situations where there could be growing realisation that remaining lifespan is limited and where contact with healthcare services may already be intense. The full extent of these factors is considered in greater detail in patient organisations' submissions to NICE.

Chapter 7

Factors relevant to the NHS

National Service Framework and other national guidance

Improvement in cancer services is a declared priority for the NHS. This includes improvement in services that target quality of life and palliation, and erythropoietin certainly fits this category. As already indicated, the possibility for its use has been mentioned in a number of guidelines. However, the recommendations either are framed as options for treatment in current circumstances, or are guidelines that are not directly operative in the UK. There is certainly no current UK guidance suggesting that epo should be an audit criterion. Further, none of the guidelines mentioned attempts to assess both effectiveness and cost-effectiveness, which is the critical additional issue being addressed in this report. Comments suggesting that uptake of epo in the UK is low and a sign of inferior care need to be carefully considered in this context.

Impact on the NBS

A considerable amount of comment has been made about the potential impact of wider use of epo on the continued excellence of the NBS. While it is undoubted that use of epo would reduce red cell transfusions, it is unclear whether this reduction is important from the NBS perspective. This question would be best answered by the NBS, and the reviewers recommend that this specific question be posed to the NBS.

The more important suggestion is the possibility that blood transfusions alone may be increasingly used to improve anaemia to the degree achieved for epo, and this would require a level of blood use that is unsustainable. Whether the higher level of use could be achieved is again a question that would be better answered by the NBS directly. However, as important a consideration is the need for confirmation that the cost of achieving an improvement in Hb with epo is deemed acceptable relative to the size of the benefit, and this is the purpose of this appraisal. If it is not, there may be an issue about whether blood could be used to achieve the same effect at a more acceptable cost, but it is clear to the reviewers that this is a second order question.

Equity

A potentially difficult issue is that epo is already available for patients with renal failure. This raises the economic and ethical question of whether the cost to benefit relationship should be considered across all patient groups who might benefit or in specific groups in isolation. The question is whether highly favourable cost-effectiveness in one group might justifiably offset marginal cost-effectiveness in another.

Budget impact

The possible budget impact has been suggested to be substantial, estimates of £25 million per annum being typical, and possibly conservative. In the context of palliation and support it is worth noting that the average annual budget is £2.1 million for each of the 132 hospices included in a survey of the 142 in England over the period 2000–2002. Most of this money is currently raised by donation.[153]

Chapter 8
Overall discussion

Clinical effectiveness

The estimates of effectiveness were informed by the results from a total of 46 RCTs, combining those identified in a previous Cochrane review with more recent RCTs identified by the Birmingham review team. These trials compared epo plus supportive care for anaemia, including transfusions, with supportive care for anaemia alone. The best estimates of effect on the key outcomes are given in *Table 56*.

Most outcomes were contributed to by only a minority of the available RCTs. Although in most cases this was due to trials not reporting particular outcomes, it was occasionally due to results for a particular outcome being reported in a manner different from the majority; that is, using a different definition of haematological response.

The new trials did not make a major difference to effectiveness estimates, with the exception of survival.

The best estimate of haematological response (improvement by 2 g dl^{-1}) was RR 3.4 (95% CI 3.0 to 3.8), based on 22 RCTs, with the response rate for epo being 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 any subgroups examined. Data on HRQoL collected in 20 trials showed a broadly positive effect; however, it is not clear how these results translate into utility gains. Further detailed analysis is required regarding the size of the effect and the clinical importance of this. Published information on side-effects was of poor quality. There is growing evidence of excess side-effects with epo, particularly thrombotic events such as DVT, but is still unclear whether these could be accounted for by chance alone. No reports of red cell aplasia were identified in the trials reviewed.

The Cochrane review[48] suggested a survival advantage for epo (HR 0.84, 95% CI 0.69 to 1.02), based on 19 RCTs. The update, based on 28 RCTs, suggests no survival difference (HR 1.03, 95% CI 0.88 to 1.21) (variance estimate inflated for substantive heterogeneity, $\chi^2 = 37.75$, 27 df, $p = 0.08$; see the section 'Results', p. 52, for details regarding this variance). 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 reviewers' conclusions are, however, broadly in line with those of an FDA safety briefing,[92] which broadly recommended that: patients with an Hb level above 12 g dl^{-1} 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

A systematic review identified five past economic evaluations with mixed results; the most

TABLE 56 *Trial comparison between epo and supportive care for anaemia*

	n (trials)	Measure	Point estimate	95% CI	Comments
HaemR	22	RR (fixed)	3.4	3.01 to 3.83	
Risk of RBCT	35	RR (fixed)	0.63	0.58 to 0.67	
Mean units transfused per participant	14	WMD (fixed)	–1.05	(–1.32 to –0.78 units)	
Survival	25	HR	1.03	(0.88 to 1.21)	Marked change from Cochrane review
Adverse events	13	Increased thrombotic events noted in some trials			

TABLE 57 *Main results: cost-effectiveness*

	Agent	Incremental cost	Incremental life-year	Incremental QALY	Cost per QALY
Model includes no survival benefit					
Amgen: all tumours	Darbepoetin	£2,594	0.00	0.0163	£159,339
Roche: haematological malignancies	Epo beta	£3,510	0.00 *Assumed HR of 1.00*	0.042	£83,705
Birmingham: all tumours	Any	£4,450	0.00 *Assumed HR of 1.00*	0.030	£ 150,342
Survival benefit included					
Amgen: all tumours	Darbepoetin	£2,594	*Assumed HR of 0.88*	0.110	£23,546
Ortho Biotec: all tumours	Epo alfa	£4,021	*Assumed HR of 0.647*	0.310	£12,952
Roche: solid tumours	Epo-beta	£3,727	0.086 *Assumed HR of 0.49*	0.132	£28,221
Birmingham: all tumours	Any	£ 4,537	*Assumed HR of 0.88*	0.115	£ 39,568

favourable assessment considered the possibility of a survival advantage. The majority were pessimistic concerning the cost-effectiveness of epo. However, continuing development in the evidence of effectiveness during the period when the past economic evaluations were being conducted suggested that up-to-date analyses were important for obtaining a fair assessment of the relationship between benefits, disbenefits and costs. A summary of the main results from the manufacturers of epo and the in-house model is given in *Table 57*.

The critical influence of the effect on survival was reinforced in the three economic models submitted. Cost per QALY (base-case estimates) ranged from £13,000 to £28,000 where survival benefits were included, but from £84,000 to £159,000 with no survival advantages. For the Birmingham epo economic model the base-case estimate with no impact on survival was £150,000 per QALY. When a survival gain was included, based on assuming a hazard ratio of 0.88 (the lower, most favourable 95% CI), the cost–utility improved to £39,568. Higher ICERs resulted from the use of EQ-5D values instead of TTO utility values.

Assumptions, limitations and uncertainties

Concerning the main issue identified, the critical relationship between the survival estimate and cost-effectiveness, the authors are confident. This technology assessment builds on existing secondary research and economic evaluations, and the results are a logical extension of earlier conclusions.

There are some important sources of uncertainty affecting the conclusions at a higher level of detail. These are presented below.

Heterogeneity

There is variability in effectiveness results, some of which is greater than could be accounted for by chance alone. Investigation into the source of this has not resolved the cause. Unfortunately, failure to elucidate the source of heterogeneity is not unusual in meta-analyses, particularly when the results are being analysed at trial level. IPD meta-analysis may be of use in investigating these effects further.

Possible publication bias

There was some evidence in both the original Cochrane review and the present update that the results from small, negative trials may not be available for inclusion in the systematic reviews. Further, there was also some evidence that partially published results (i.e. early reports in conference abstracts) were giving more optimistic estimates of effect. If present, important publication bias would suggest that some of the summary estimates obtained may overestimate the true effect size. Exercising caution concerning the size of effect estimates may also be required

because of the possibility of selective reporting of outcomes. This is a related phenomenon to publication bias, in that in an RCT which has been reported, outcomes whose results are negative or do not reach statistical significance may not appear in published reports of those trials.

Limited detail from published studies

This was often the major factor limiting the assessment of the trials regarding study quality, population characteristics and analysis of the results. Limited details of results in part led to the small proportion of included studies contributing to some of the summary estimates in the meta-analyses. The Cochrane review had previously demonstrated that, although time-consuming, further information can be successfully collected from investigators and manufacturers. However, the reviewers did not have time to apply the same process to the RCTs identified for the Birmingham update. A striking illustration of this is the quality assessment, where quality parameters of studies identified for this update were often classified as unclear, in contrast to the studies included in the Cochrane review where many of these details were elucidated from the trial authors.

Although manufacturers collaborated to a considerable degree, level of detail was also a limiting factor for the economic modelling. Anonymised data at individual level would undoubtedly have greatly extended the sensitivity analyses. Such data would also be essential for fully exploring the observed heterogeneity in the meta-analyses.

Limited numbers of RCTs

Although there is a considerable body of RCT evidence in this area, there is also considerable heterogeneity in trial designs and patient populations, therefore definitive answers are not available from the information obtainable from the published literature. The impact on survival and adverse event rates is discussed in more detail below. Beyond these, there was an almost complete absence of information on the rate at which Hb returns to normal, particularly in the control arm, at the end of the trial treatment period. Such a normalisation period has not previously been incorporated into economic evaluations and appears to influence cost–utility to an important degree. It should thus be more reliably quantified.

Other factors

There are clearly some other factors that fall outside the suggested perspective for economic evaluation (NHS perspective), which should be considered qualitatively at least. The most significant of these are direct costs (financial and other) to patients and carers. The additional value of conserving blood, an increasingly scarce resource, has also been highlighted by many parties, and the blood services are probably in the best positions to judge just how much weight should be placed on the speculations offered in this respect.

The impact of these general sources of uncertainty on the key outcomes are as follows:

- Survival is the key outcome, both in its own right and in its impact on cost-effectiveness. It is potentially affected by all of the first four sources of uncertainty. There is marked heterogeneity, with as yet no clear, or complete, explanation for this. This does not necessarily mean there are no important subgroup effects; a more likely explanation is that there are insufficient data reliably to prove or refute important effects. Uncertainty could be reduced considerably with the existing data through an IPD meta-analysis; the authors understand that the Cochrane review group has started an update of its IPD meta-analysis of this topic. Continued vigilance for possible publication bias is also important for an estimate where there is not as yet a clear view on whether the true value implies benefit, no effect or disbenefit. Current data suggest that care should be taken in treating patients with relatively high Hb levels, that Hb should not be increased too rapidly with the use of epo, and that benefits observed in one setting may not be observed in others, particularly with respect to cancer type and concomitant cytotoxic treatment type.
- Haematological response seems a robust estimate, without evidence of marked heterogeneity or subgroup effects.
- Hb change and numbers transfused do, however, have important heterogeneity, which may possibly indicate subgroup effects that have not been completely excluded.
- There is some evidence of an impact on HRQoL. However, there is continuing uncertainty about the size of this effect and how this translates into clinically meaningful benefits.
- Adverse events are again affected by all sources of uncertainty. Quality of information is probably the most important issue that needs to be overcome. Identifying important but rare adverse events is a continuing challenge. From trial data it is not possible to exclude red cell aplasia, with

an incidence of 18 cases per 100,000 patient-years or less. Infections at a frequency of 1:10,000 were suggested to be important in considering the effectiveness of RBCTs.

In the specific context of economic evaluation, costs seem remarkably consistent across all evaluations, with the main determinant of cost difference being the purchase cost of the drugs. This does not mean that further change may not occur. Indeed, there have been some recent changes in dosing regimen that have had small cost implications. Net cost takes into account the reduction in use of RBCTs, and so any continuing increase in the cost of transfusions may have an impact.

Cost-effectiveness and cost–utility are the measures ultimately affected by all the uncertainty identified above. Although all factors are important to some degree, survival has emerged as the most influential parameter. It is highly unlikely that plausible changes in other variables, even if combined, would overturn the effect of survival. If a moderate survival benefit (similar in size to the estimate suggested by the Cochrane review) is thought to be the true measure of impact on survival, the net benefit associated with epo seems to justify the costs. If there is no survival benefit, cost-effectiveness is difficult to demonstrate. If there is survival disadvantage (similar in size to that suggested in this update to the Cochrane review), then epo may be rejected on clinical or cost-effectiveness grounds, or both.

In the scenario of the true effect on survival being no difference, unfavourable estimates of cost-effectiveness might be mitigated to some extent with:

- better targeting of epo; unfortunately, several sources are pessimistic about the degree to which response can be further improved
- decreased drug cost: this is possible and patent expiry may have an influence on this
- increased cost of RBCT: the size of this would need to be very large, and suggestions about blood becoming so scarce as to make such costs plausible seem highly speculative, requiring further appraisal. They assume, for instance, that there are no alternative means to spare blood other than epo, and this is not the case.

Need for further research

In the authors' view the main priority should be for further research.

The main target should be improving estimates of impact on survival. In the first instance this should be through more detailed secondary research, such as the IPD meta-analysis that has been commenced 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 not present in previous models, which improve its flexibility in exploring different scenarios in the future. Funding to support further refinement and validation would thus be of assistance.

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. Further research into the rate of normalisation would therefore be beneficial.

Chapter 9

Overall conclusions

Epo is effective in improving haematological response and reducing RBCT requirements. It also appears to improve HRQoL. Its impact on side-effects and survival remains highly uncertain. If there is no impact on survival, it seems highly unlikely to be considered that epo is a cost-effective use of healthcare resources.

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Contribution of authors

Jayne Wilson (Lead Systematic Reviewer) co-authored the protocol and was responsible for the effectiveness part of the review (excluding survival analysis) and development of the patient pathway. Her responsibilities included inclusion/exclusion of studies, co-data extraction, data analysis and coordination of the review's day-to-day progress and activities. She was the main author of the methods and effectiveness sections, and read and commented on the completed review. Guiqing 'Lily' Yao (Health Economist) commented on the protocol, critiqued the three submitted industry models, developed and ran the Birmingham model and was the main author on the economic modelling section, commented on the literature survey on previous economic evaluations, and read and commented on the completed review. James Raftery (Professor of Health Economics) commented on the protocol, critiqued the economic data in the industry submissions, helped to develop the Birmingham economic model, co-authored the economic modelling section, commented on the literature survey on previous economic evaluations, and read and commented on the completed review. Julia Bohlius (Systematic Reviewer) commented on the protocol and was the second reviewer on all of the effectiveness sections of the review (excluding quality of life outcomes). Her responsibilities included inclusion/exclusion of studies, co-data extraction and data analysis. She was the lead reviewer of the Cochrane review on which this review was built, and therefore shared data previously incorporated into the Cochrane review. She read and commented on the completed review. Susan Brunskill (Senior Information Scientist) commented on the protocol, had co-responsibility for the review of effectiveness regarding quality of life outcomes, and read and commented on the completed review. Josie Sandercock (Medical Statistician) commented on the protocol, was responsible for the review of effectiveness regarding survival outcomes, gave statistical advice throughout the review, and read and commented on the completed review. Sue Bayliss (Information Specialist) commented on the protocol, was responsible for the literature searches, included/excluded ongoing trials, and read and commented on the completed review. Paul Moss (Professor of Haematology) commented on the protocol, was a subject specific advisor through the review process, commented on patient pathways, and read and commented on the completed review. Simon Stanworth (Consultant Haematologist) commented on the protocol, was a subject specific advisor through the review process, commented on patient pathways, and read and commented on the completed review. Chris Hyde (Senior Lecturer in Public Health) co-authored the protocol, was the main author of the background section, advised on the systematic review of effectiveness, was the main reviewer for systematic review of previous economic analyses, contributed to the development of the economic model, drafted and coordinated different components of the final report, and had overall responsibility for the delivery of the project.

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Appendix 1

Patient pathway

An outline view of the patient pathway is shown in *Figure 16*.

- Crudely, there are three types of care for patients with malignancy: patients who are not on any chemotherapy or radiotherapy (sheet 1, *Figure 17*), patients on chemotherapy/radiotherapy following an ongoing regimen, where the disease/treatment process is more akin to chronic disease management (sheet 1, *Figure 17*), and patients on chemotherapy/radiotherapy following a predicted number of treatment cycles, akin to acute disease management (sheet 1, *Figure 17*).
- Patients are diagnosed with anaemia (possibly by periodic testing of Hb or clinical assessment); once diagnosed with anaemia, they go into the pathway described in sheet 2 (*Figure 18*). If the anaemia is thought to be due to epo deficiency, they continue through the pathway.
- Different levels of Hb direct the type of treatment that the patient will receive.
- Throughout the whole of the pathway, the route the patient takes is determined by:
  - the type of cancer, which determines the type of cancer treatment (sheet 1, *Figure 17*)
  - where the patient is in their cancer treatment (sheet 1, *Figure 17*)
  - Hb level (sheet 2, *Figure 18*)
  - their clinical status (all sheets).

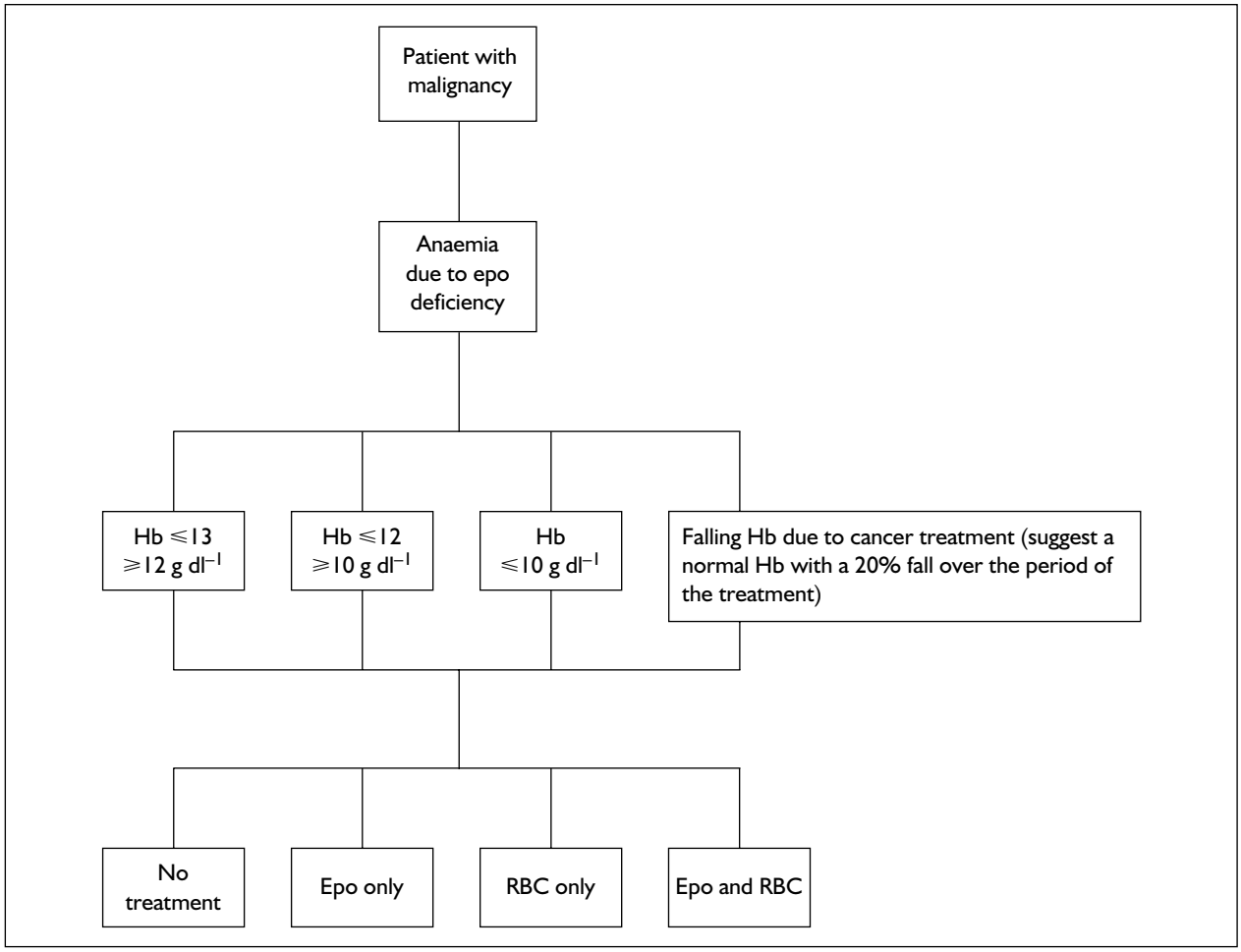

FIGURE 16 *Patient pathway outline view*

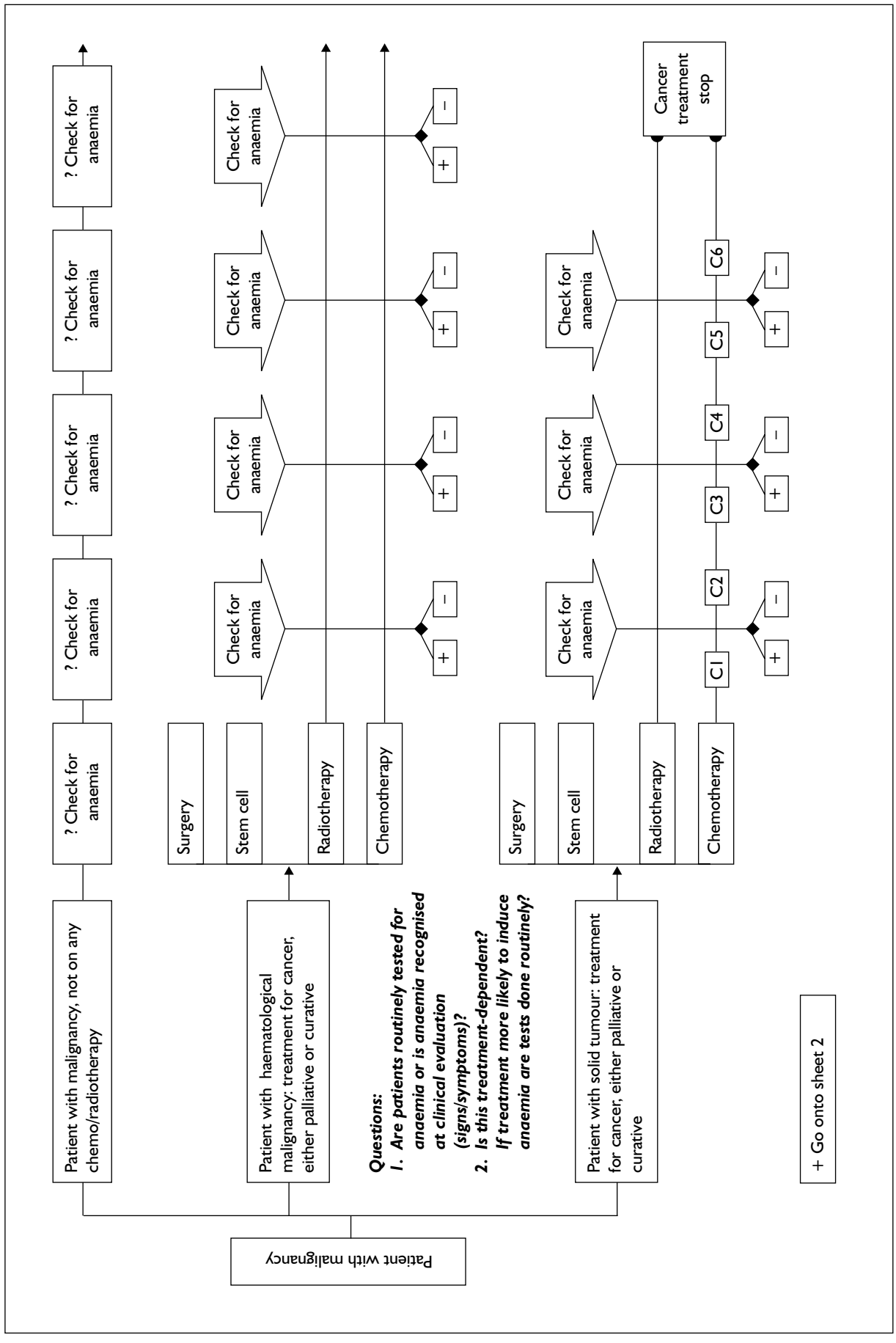

FIGURE 17 *Patient pathway: sheet 1. C, cycle of chemotherapy.*

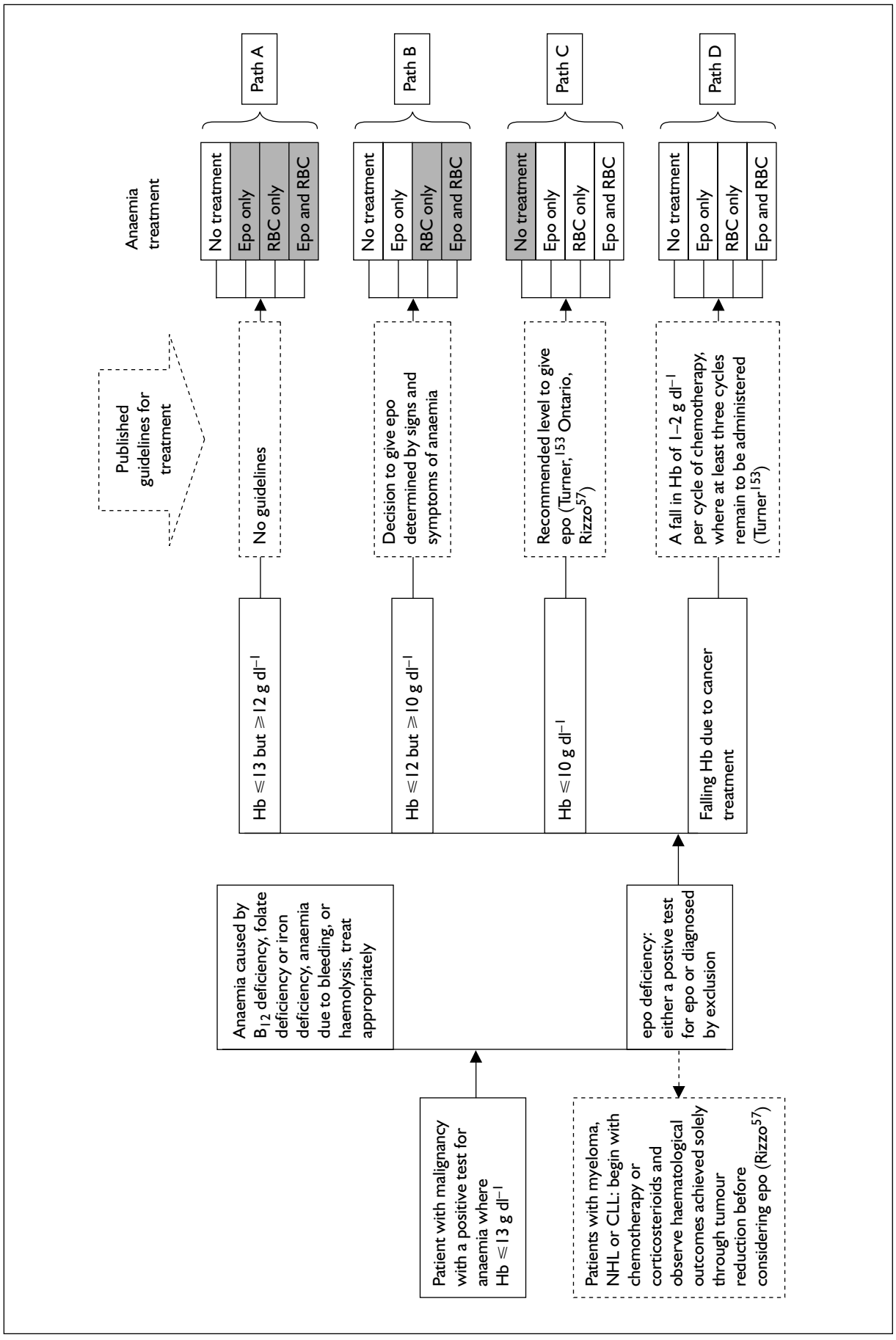

FIGURE 18 *Patient pathway: sheet 2. Shaded options are unlikely.*

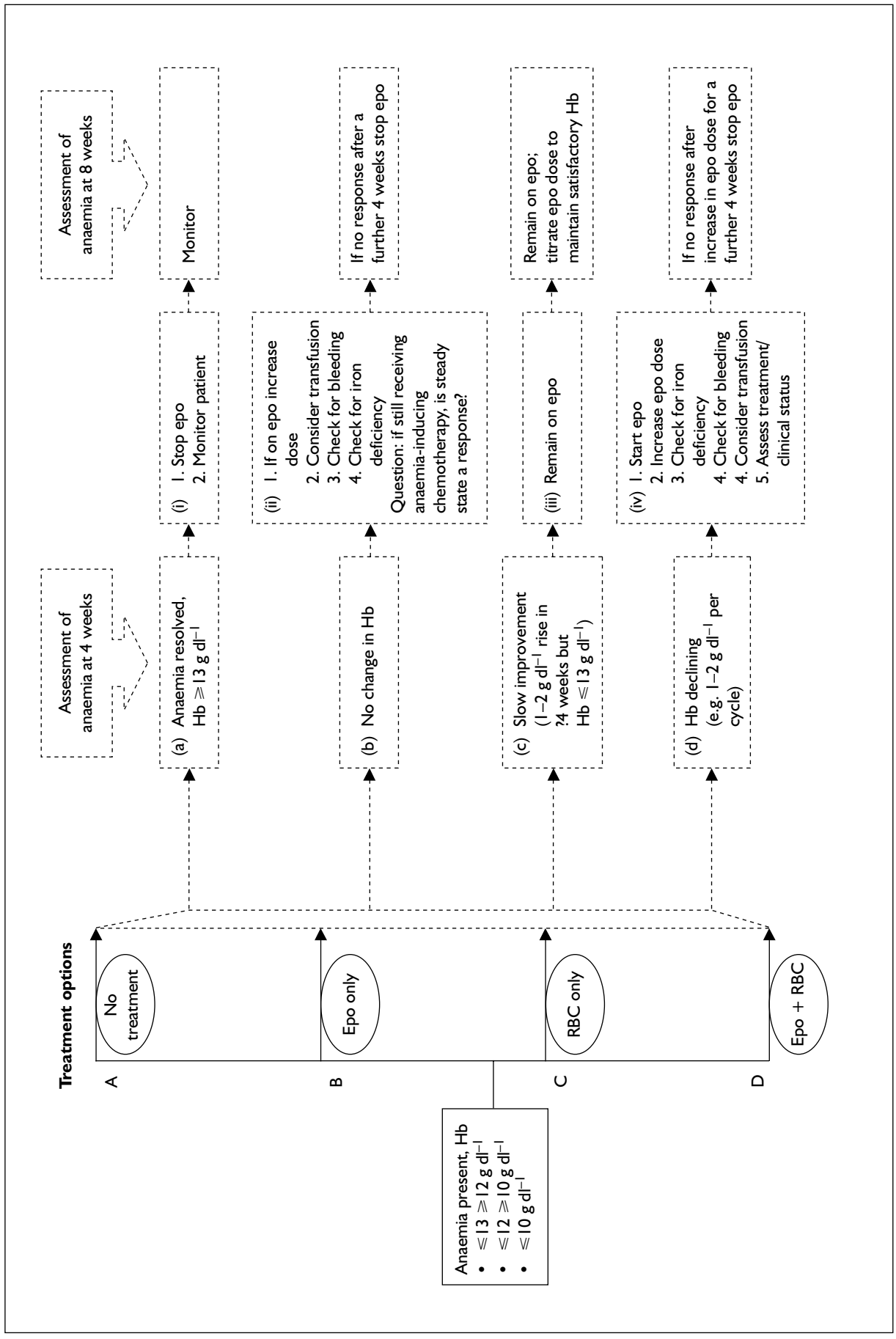

FIGURE 19 *Patient pathway: sheet 3. Dotted line: generic pathway for all anaemia treatment (A–D).*

Appendix 2

Licence indications

TABLE 58 *Licence indications for epoetin alfa, epoetin beta and darbepoetin alfa*

	Epoetin alfa
	Data taken from SPC included in the Industry submission to NICE, November 2004
Patient	Adults receiving chemotherapy, patients should have anaemia (e.g. ≤ 10.5 g dl^{-1}). Hb concentration aimed for is approximately 12 g dl^{-1}
Dose	Starting dose 150 IU kg^{-1} given s.c. three times per week. If after 4 weeks the Hb has increased by less than 1 g dl^{-1} the dose can be increased to 300 IU kg^{-1} three times per week. If a rise of >2 g dl^{-1} per month occurs the dose should be reduced by 25–50% and if the Hb exceeds 14 g dl^{-1} the treatment should be discontinued until it falls below 12 g dl^{-1} and then reinstated at 75% of the previous dose
	October 2004: epoetin alfa gained regulatory approval for a once-weekly licence in the UK
Duration	Should continue until 1 month after the end of chemotherapy
Disease	Solid tumours, malignant lymphoma, multiple myeloma
	Epoetin beta
	Data taken from SPC included in the Industry submission to NICE, November 2004
Patient	Prevention and treatment of anaemia in adult patients with solid tumours who are treated with platinum-based chemotherapy, prone to induce anaemia (cisplatin: 75 mg m^{-2} per cycle; carboplatin: 350 mg m^{-2} per cycle) and Hb is ≤ 13 g dl^{-1} at the start of chemotherapy
	Treatment of anaemia in adult patients with multiple myeloma, low-grade NHL or CLL, who have a relative erythropoietin deficiency and are receiving antitumour therapy. Erythropoietin deficiency is defined as an inappropriately low serum erythropoietin level in relation to the degree of anaemia (e.g. serum erythropoietin level of ≤ 100 mU ml^{-1} at an Hb level of 9–10 g dl^{-1}, serum erythropoietin level of ≤ 180 mU ml^{-1} at an Hb of 8–9 g dl^{-1}, serum erythropoietin level of ≤ 300 mU ml^{-1} at an Hb of ≤ 8 g dl^{-1})
Dose	Solid tumours: initial dose 450 IU kg^{-1} per week (in three to seven divided doses). After 4 weeks if patient has not had a satisfactory response then the dose can be doubled. If Hb falls by more than 1 g dl^{-1} in the first cycle further therapy may not be effective. An increase of ≥ 2 g dl^{-1} per month should have a dose reduction of 50%. If Hb goes beyond 14 g dl^{-1}, therapy should stop until Hb falls back to ≤ 12 g dl^{-1} and then restarted at 50% of the previous weekly dose
	Haematological tumours: weekly dose of 450 IU kg^{-1} per week (in a single dose or in three to seven divided doses). If after 4 weeks' therapy Hb has not increased by at least 1 g dl^{-1} a dose increase to 900 IU kg^{-1} per week (given in two to seven divided doses) may be considered. If after 8 weeks there has been no response to treatment it should be discontinued. If Hb increased by >2 g dl^{-1} within 4 weeks the dose should be halved. If Hb exceeds 14 g dl^{-1}, therapy should be stopped until Hb is ≤ 13 g dl^{-1} then reinstated at 50% of the previous weekly dose
	The maximum dose should not exceed 900 IU kg^{-1} body weight per week
	A delay in response has been found in patients with CLL compared to patients with MM, NHL and solid tumours
Duration	Solid tumours: therapy should be continued for up to 3 weeks after the end of chemotherapy
Disease	Solid tumours (receiving platinum-based chemotherapy), MM, NHL, CLL (with erythropoietin deficiency)

continued

TABLE 58 *Licence indications (cont'd)*

	Darbepoetin alfa ***Data taken from Industry submission to NICE, November 2004 (these data are not from the SPC; unable to locate them)***
Patient	Anaemic patients with both solid and lymphoproliferative disorders regardless of chemotherapy type or endogenous erythropoietin level (excludes radiotherapy treatment) s.c. administration per week or every 3 weeks
Dose	2.25 $\mu g\ kg^{-1}$ per week or 6.75 $\mu g\ kg^{-1}$ every 3 weeks. After 4 weeks if the increase in Hb is inadequate ($<1\ g\ dl^{-1}$) the dose can be doubled (4.5 $\mu g\ kg^{-1}$ per week). If response remains inadequate after another 4 weeks therapy may not be effective. If clinical response (fatigue Hb) is inadequate after 9 weeks further therapy may not be effective
Duration	NR
Disease	Adult cancer patients with non-myeloid malignancies receiving chemotherapy. Anaemia is defined as Hb $\leq 11\ g\ dl^{-1}$

SPC, summary of product characteristics.

Appendix 3

Study search and identification

Search strategy: clinical effectiveness

Database: Cochrane Library 2004 Issue 3

Search strategy:

#1 erythropoietin
#2 exp ERYTHROPOIETIN/
#3 epoetin
#4 epo
#5 (epoetin next alfa)
#6 (epoetin next beta)
#7 (darbepoetin next alfa)
#8 eprex
#9 neorecormon
#10 aranesp
#11 procrit
#12 (recombinant near erythropoietin)
#13 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14 anemia
#15 (anemi* near cancer)
#16 (anaemi* near cancer)
#17 ANEMIA dt:th
#18 anaemia
#19 (#14 or #15 or #16 or #17 or #18)
#20 (#13 and #19)

Database: Ovid MEDLINE(R) 1966 to September week 1 2004

Search strategy (epo):

1 exp ERYTHROPOIETIN, RECOMBINANT/ or erythropoietin.mp. or exp ERYTHROPOIETIN/
2 exp EPOETIN ALFA/ or epoetin.mp.
3 epo.mp.
4 epoetin alfa.mp.
5 epoetin beta.mp.
6 eprex.mp.
7 neorecormon.mp.
8 aranesp.mp.
9 procrit.mp.
10 recombinant erythropoietin.mp.
11 or/1-10
12 exp ANEMIA/dt, th [Drug Therapy, Therapy]
13 anemia.mp.
14 anaemia.mp.
15 (anemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
16 (anaemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 or/12-16
18 malignan$.mp.
19 cancer$.mp. or exp Neoplasms/
20 oncolog$.tw.
21 myelodysplas$.tw.
22 chemotherapy.mp.
23 tumo?r$.mp.
24 carcinom$.mp.
25 or/18-24
26 randomized controlled trial.pt.
27 controlled clinical trial.pt.
28 randomized controlled trials.sh.
29 random allocation.sh.
30 double blind method.sh.
31 single-blind method.sh.
32 or/26-31
33 (animals not human).sh.
34 32 not 33
35 clinical trial.pt.
36 exp clinical trials/
37 (clin$ adj25 trial$).ti,ab.
38 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
39 placebos.sh.
40 placebo$.ti,ab.
41 random$.ti,ab.
42 research design.sh.
43 or/35-42
44 43 not 33
45 44 not 34
46 comparative study.sh.
47 exp evaluation studies/
48 follow up studies.sh.
49 prospective studies.sh.
50 (control$ or prospectiv$ or volunteer$).ti,ab.
51 or/46-50
52 51 not 33
53 52 not (34 or 45)
54 34 or 45 or 53
55 11 and 17
56 55 and 25
57 56 and 54
58 limit 57 to yr=2000-2004

Database: Ovid MEDLINE(R) 1966 to September week 1 2004

Search strategy (darbepoetin):

1 darbepoetin alfa.mp.
2 aranesp.mp.
3 or/1-2
4 exp ANEMIA/dt, th [Drug Therapy, Therapy]
5 anemia.mp.
6 anaemia.mp.
7 (anemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 (anaemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9 or/4-8
10 malignan$.mp.
11 cancer$.mp. or exp Neoplasms/
12 oncolog$.tw.
13 myelodysplas$.tw.
14 chemotherapy.mp.
15 tumo?r$.mp.
16 carcinom$.mp.
17 or/10-16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 randomized controlled trials.sh.
21 random allocation.sh.
22 double blind method.sh.
23 single-blind method.sh.
24 or/18-23
25 (animals not human).sh.
26 24 not 25
27 clinical trial.pt.
28 exp clinical trials/
29 (clin$ adj25 trial$).ti,ab.
30 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
31 placebos.sh.
32 placebo$.ti,ab.
33 random$.ti,ab.
34 research design.sh.
35 or/27-34
36 35 not 25
37 36 not 26
38 comparative study.sh.
39 exp evaluation studies/
40 follow up studies.sh.
41 prospective studies.sh.
42 (control$ or prospectiv$ or volunteer$).ti,ab.
43 or/38-42
44 43 not 25
45 44 not (26 or 37)
46 26 or 37 or 45
47 3 and 9
48 17 and 47
49 46 and 48
50 limit 49 to yr=1996-2004

Database: EMBASE 1980 to 2004 week 36

Search strategy (epo):

1 erythropoietin.mp. or exp ERYTHROPOIETIN/ or exp RECOMBINANT ERYTHROPOIETIN/
2 epoetin.mp.
3 epo.mp.
4 eprex.mp.
5 neorecormon.mp.
6 procrit.mp.
7 recombinant erythropoietin.mp.
8 exp ANEMIA/ or anemia.mp.
9 anaemi$.tw.
10 anemi$.mp.
11 (anemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
12 (anaemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
13 or/8-12
14 malignan$.mp.
15 cancer$.mp. or exp CANCER/
16 exp NEOPLASM/ or neoplasm$.mp.
17 oncology.mp. or exp ONCOLOGY/
18 exp MYELODYSPLASIA/
19 myelodysplas$.tw.
20 chemotherapy.mp. or exp CHEMOTHERAPY/
21 exp TUMOR/ or tumo?r$.mp.
22 carcinom$.mp.
23 or/14-22
24 randomized controlled trial/
25 exp clinical trial/
26 exp controlled study/
27 double blind procedure/
28 randomization/
29 placebo/
30 single blind procedure/
31 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
32 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
33 (placebo$ or matched communities or matched schools or matched populations).mp.
34 (comparison group$ or control group$).mp.
35 (clinical trial$ or random$).mp.
36 (quasiexperimental or quasi experimental or pseudo experimental).mp.
37 matched pairs.mp.
38 or/24-37

39 or/1-7
40 13 and 39
41 23 and 40
42 38 and 41
43 limit 42 to yr=2000-2004

Database: EMBASE 1980 to 2004 week 36

Search strategy (darbepoetin):

1 darbepoetin alfa.mp. or exp Novel Erythropoiesis Stimulating Protein/
2 aranesp.mp.
3 nesp.mp.
4 exp darbepoetin/ or exp darbepoetin alfa/ or exp darbepoietin alfa/
5 or/1-4
6 exp ANEMIA/ or anemia.mp.
7 anaemi$.tw.
8 anemi$.mp.
9 (anemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
10 (anaemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
11 or/6-10
12 malignan$.mp.
13 cancer$.mp. or exp CANCER/
14 exp NEOPLASM/ or neoplasm$.mp.
15 oncology.mp. or exp ONCOLOGY/
16 exp MYELODYSPLASIA/
17 myelodysplas$.tw.
18 chemotherapy.mp. or exp CHEMOTHERAPY/
19 exp TUMOR/ or tumo?r$.mp.
20 carcinom$.mp.
21 or/12-20
22 randomized controlled trial/
23 exp clinical trial/
24 exp controlled study/
25 double blind procedure/
26 randomization/
27 placebo/
28 single blind procedure/
29 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
30 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
31 (placebo$ or matched communities or matched schools or matched populations).mp.
32 (comparison group$ or control group$).mp.
33 (clinical trial$ or random$).mp.
34 (quasiexperimental or quasi experimental or pseudo experimental).mp.
35 matched pairs.mp.
36 or/22-35
37 5 and 11
38 37 and 21
39 36 and 38
40 limit 39 to yr=1996-2004

Database: CINAHL 1982 to September week 1 2004

Search strategy:

1 erythropoietin.mp. or exp ERYTHROPOIETIN/
2 epo.mp.
3 epoetin.mp.
4 darbepoetin.mp.
5 eprex.mp.
6 neorecormon.tw.
7 aranesp.mp
8 procrit.mp.
9 (recombinant adj3 erythropoietin).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
10 or/1-9
11 exp ANEMIA/
12 anemi$.tw.
13 anaemi$.tw.
14 or/11-13
15 10 and 14
16 cancer$.mp. or exp Neoplasms/
17 neoplasm$.tw.
18 malignan$.mp.
19 oncolog$.tw.
20 exp ONCOLOGY/
21 myelodysplas$.tw.
22 chemotherapy.mp. or exp CHEMOTHERAPY, CANCER/
23 tumo?r$.mp.
24 carcinoma$.mp. or exp CARCINOMA/
25 or/16-24
26 15 and 25
27 exp Clinical Trials/
28 26 and 27

Search strategy: cost-effectiveness

Database: Ovid MEDLINE(R) 1966 to July week 4 2004

Search strategy (cost):

1 exp ERYTHROPOIETIN, RECOMBINANT/ or erythropoietin.mp. or exp ERYTHROPOIETIN/
2 exp EPOETIN ALFA/ or epoetin.mp.
3 epo.mp.
4 epoetin alfa.mp.
5 epoetin beta.mp.

6 darbepoetin alfa.mp.
7 eprex.mp.
8 neorecormon.mp.
9 aranesp.mp.
10 procrit.mp.
11 recombinant erythropoietin.mp.
12 or/1-11
13 exp ANEMIA/dt, th [Drug Therapy, Therapy]
14 anemia.mp.
15 anaemia.mp.
16 (anemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 (anaemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18 or/13-17
19 12 and 18
20 economics/
21 exp "costs and cost analysis"/
22 cost of illness/
23 exp health care costs/
24 economic value of life/
25 exp economics medical/
26 exp economics hospital/
27 economics pharmaceutical/
28 exp "fees and charges"/
29 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
30 (expenditure$ not energy).tw.
31 (value adj1 money).tw.
32 budget$.tw.
33 or/20-32
34 19 and 33
35 malignan$.mp.
36 cancer$.mp. or exp Neoplasms/
37 oncolog$.tw.
38 myelodysplas$.tw.
39 chemotherapy.mp.
40 tumo?r$.mp.
41 carcinom$.mp.
42 or/35-41
43 34 and 42

Database: Ovid MEDLINE(R) 1966 to July week 4 2004

Search strategy (model):

1 exp ERYTHROPOIETIN, RECOMBINANT/ or erythropoietin.mp. or exp ERYTHROPOIETIN/
2 exp EPOETIN ALFA/ or epoetin.mp.
3 epo.mp.
4 epoetin alfa.mp.
5 epoetin beta.mp.
6 darbepoetin alfa.mp.
7 eprex.mp.
8 neorecormon.mp.
9 aranesp.mp.
10 procrit.mp.
11 recombinant erythropoietin.mp.
12 or/1-11
13 exp ANEMIA/dt, th [Drug Therapy, Therapy]
14 anemia.mp.
15 anaemia.mp.
16 (anemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 (anaemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18 or/13-17
19 12 and 18
20 malignan$.mp.
21 cancer$.mp. or exp Neoplasms/
22 oncolog$.tw.
23 myelodysplas$.tw.
24 chemotherapy.mp.
25 tumo?r$.mp.
26 carcinom$.mp.
27 or/20-26
28 19 and 27
29 decision support techniques/
30 markov.mp.
31 exp models economic/
32 decision analysis.mp.
33 cost benefit analysis/
34 or/29-33
35 28 and 34

Database: Ovid MEDLINE(R) 1966 to July week 4 2004

Search strategy (quality of life):

1 exp ERYTHROPOIETIN, RECOMBINANT/ or erythropoietin.mp. or exp ERYTHROPOIETIN/
2 exp EPOETIN ALFA/ or epoetin.mp.
3 epo.mp.
4 epoetin alfa.mp.
5 epoetin beta.mp.
6 darbepoetin alfa.mp.
7 eprex.mp.
8 neorecormon.mp.
9 aranesp.mp.
10 procrit.mp.
11 recombinant erythropoietin.mp.
12 or/1-11
13 exp ANEMIA/dt, th [Drug Therapy, Therapy]
14 anemia.mp.
15 anaemia.mp.
16 (anemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]

17 (anaemi$ adj3 cancer).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18 or/13-17
19 12 and 18
20 malignan$.mp.
21 cancer$.mp. or exp Neoplasms/
22 oncolog$.tw.
23 myelodysplas$.tw.
24 chemotherapy.mp.
25 tumo?r$.mp.
26 carcinom$.mp.
27 or/20-26
28 19 and 27
29 quality of life/
30 life style/
31 health status/
32 health status indicators/
33 or/29-32
34 28 and 33

Database: EMBASE 1980 to 2004 week 30

Search strategy (cost):

1 erythropoietin.mp. or exp ERYTHROPOIETIN/ or exp RECOMBINANT ERYTHROPOIETIN/
2 epoetin.mp.
3 epo.mp.
4 exp darbepoetin/ or darbepoetin.mp. or exp darbepoietin alfa/
5 eprex.mp.
6 neorecormon.mp.
7 aranesp.mp. or exp Novel Erythropoiesis Stimulating Protein/
8 procrit.mp.
9 recombinant erythropoietin.mp.
10 or/1-9
11 exp ANEMIA/ or anemia.mp.
12 anaemi$.tw.
13 anemi$.mp.
14 (anemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
15 (anaemi$ adj3 cancer$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
16 or/11-15
17 malignan$.mp.
18 cancer$.mp. or exp CANCER/
19 exp NEOPLASM/ or neoplasm$.mp.
20 oncology.mp. or exp ONCOLOGY/
21 exp MYELODYSPLASIA/
22 myelodysplas$.tw.
23 chemotherapy.mp. or exp CHEMOTHERAPY/
24 exp TUMOR/ or tumo?r$.mp.
25 carcinom$.mp.
26 or/17-25
27 10 and 16
28 26 and 27
29 cost benefit analysis/
30 cost effectiveness analysis/
31 cost minimization analysis/
32 cost utility analysis/
33 economic evaluation/
34 (cost or costs or costed or costly or costing).tw.
35 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
36 (technology adj assessment$).tw.
37 or/29-36
38 28 and 37

Database: Ovid MEDLINE(R) 1966 to November week 2 2004

Search strategy (additional quality of life search):

1 malignan$.mp.
2 cancer$.mp. or exp Neoplasms/
3 oncolog$.tw.
4 myelodysplas$.tw.
5 chemotherapy.mp.
6 tumo?r$.mp.
7 carcinom$.mp.
8 or/1-7
9 quality of life/
10 life style/
11 health status/
12 health status indicators/
13 or/9-12
14 hb.mp.
15 exp Hemoglobins/ or haemoglobin$.mp.
16 hemoglobin$.mp.
17 (he?moglobin$ adj3 level$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18 or/14-17
19 8 and 13
20 19 and 18
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 randomized controlled trials.sh.
24 random allocation.sh.
25 double blind method.sh.
26 single-blind method.sh.
27 or/21-26
28 (animals not human).sh.
29 27 not 28
30 clinical trial.pt.
31 exp clinical trials/
32 (clin$ adj25 trial$).ti,ab.

33 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
34 placebos.sh.
35 placebo$.ti,ab.
36 random$.ti,ab.
37 research design.sh.
38 or/30-37
39 38 not 28
40 39 not 29
41 comparative study.sh.
42 exp evaluation studies/
43 follow up studies.sh.
44 prospective studies.sh.
45 (control$ or prospectiv$ or volunteer$).ti,ab.
46 or/41-45
47 46 not 28
48 47 not (29 or 40)
49 29 or 40 or 48
50 20 and 49

Identified studies

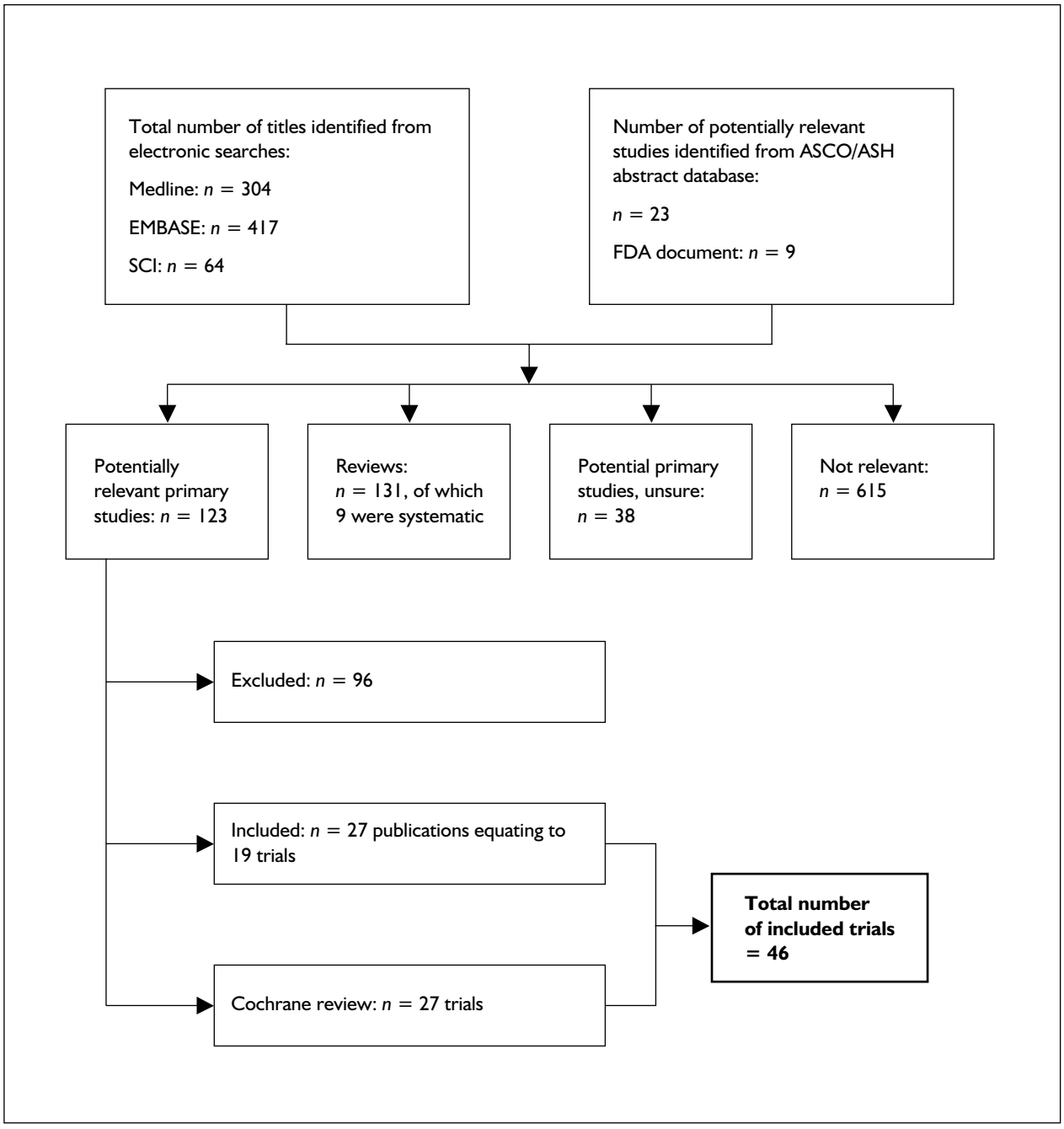

FIGURE 20 *Study flow diagram*

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Appendix 4

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Appendix 5

Study characteristics

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Aravantinos, 2003[119] **Hb, Hct, patients' RBCT**	*n* = 24 Age (years): 59 (18–76) % Male: 8% Hb baseline (g dl^{-1}): 9.8 (±0.5) Iron baseline: NR Erythropoietin baseline: NR	*n* = 23 Age (years): 64 (23–75) % Male: 7% Hb baseline (g dl^{-1}): 9.3 (±0.8) Iron baseline: NR Erythropoietin baseline: NR	Brand: rHuEPO (assume epoetin alfa) Dose: 450 IU kg^{-1} per week Dose adjustment: yes; decreasing Duration of epo tx: NR Duration of trial: NR	Standard care	Iron: fixed G-CSF: no Transfusion trigger: Hb <9 g dl^{-1} (Hb inclusion criteria level: <10.5 g dl^{-1})	Disease: solid Treatment: chemo: plat and non-plat	Yes
Bamias, 2003[120] **Hb, patients' RBCT** **(HRQoL in a subset)**	*n* = 72 Age (years): 60 (18–77) % Male: 49% Hb baseline (g dl^{-1}): 11.5 (11.1–11.9) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 24.8 (16.6–37)	*n* = 72 Age (years): 62 (19–80) % Male: 54% Hb baseline (g dl^{-1}): 11.5 (11.2–11.8) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 12.5 (8.7–18)	Brand: epoetin alfa Dose: 30,000 IU per week Dose adjustment: yes; decreasing Duration of epo tx: 21–24 weeks (duration of chemo) Duration of trial: duration of chemo plus 3 weeks	Standard care	Iron: NR G-CSF: NR Transfusion trigger: prn (Hb inclusion criteria level: <13 g dl^{-1})	Disease: solid Treatment: chemo: plat	No: dose
Blohmer, 2003[71]	*n* = 128 Age (years): <35 % Male: 0% Hb baseline (g dl^{-1}): 12 Iron baseline: NR Erythropoietin baseline: NR	*n* = 128 Age (years): <35 % Male: 0% Hb baseline (g dl^{-1}): 12 Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: NR Dose adjustment: NR Duration of epo tx: over 20 weeks Duration of trial: survival over 2 years	NR	Iron: epo arm only G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria: NR)	Disease: solid cervical cancer Treatment: chemo + radiotherapy	No: unsure of dose; also patients had adjuvant radiotherapy

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Casadevall, 2004[121] **HaemR, HRQoL, also a cost study**	*n* = 30 Age (years): 73 (43–80) % Male: 47% Hb baseline (g dl^{-1}): 8.6 (±1.2) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 178.8 (±124.4)	*n* = 30 Age (years): 71 (48–89) % Male: 53% Hb baseline (g dl^{-1}): 8.6 (±1.1) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 138 (±132.2)	Brand: epoetin alfa Dose: 60,000 IU per week Dose adjustment: NR Duration of epo tx: 12 weeks Duration of trial: 52 weeks		Iron: NR G-CSF: NR Transfusion trigger: (Hb inclusion criteria level: <10 g dl^{-1})	Disease: MDS Treatment: NR	No: dose and disease
Hedenus, 2002[122]a **HaemR, Hb, RBCT**	*n* = 11 Age (years): 64 (26–80) % Male: 64% Hb baseline (g dl^{-1}): 9.7 (0.8) Iron baseline (U/l median range): 515 (76–1931) Erythropoietin baseline (mU ml^{-1}): 46 (12–208)	*n* = 11 Age (years): 63 (25–80) % Male: 18% Hb baseline (g dl^{-1}): 9.5 (1.0) Iron baseline: 524 (14–2178) Erythropoietin baseline (mU ml^{-1}): 45 (12–132)	Brand: darbepoetin alfa Dose: 1.0 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks on epo plus 4 weeks (16 weeks)	Placebo	Iron: NR G-CSF: NR Transfusion trigger: Hb <8 g dl^{-1} (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: haem Treatment: chemo: myelosuppressive	No: lower than recommended dose
Hedenus, 2002[122]b **HaemR, Hb, RBCT**	*n* = 22 Age (years): 69 (20–84) % Male: 64% Hb baseline (g dl^{-1}): 9.4 (1.3) Iron baseline (U/l median range): 430 (15–1288) Erythropoietin baseline (mU ml^{-1}): 69 (12–227)	*n* = 11 Age (years): 63 (25–80) % Male: 18% Hb baseline (g dl^{-1}): 9.5 (1.0) Iron baseline: 524 (14–2178) Erythropoietin baseline (mU ml^{-1}): 45 (12–132)	Brand: darbepoetin alfa Dose: 2.25 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks on epo plus 4 weeks (16 weeks)	Placebo	Iron: NR G-CSF: NR Transfusion trigger: Hb <8 g dl^{-1} (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: haem Treatment: chemo: myelosuppressive	Yes

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Hedenus, 2002[122]c **HaemR, Hb, RBCT**	*n* = 22 Age (years): 70 (52–84) % Male: 64% Hb baseline (g dl^{-1}): 9.7 (0.9) Iron baseline (U/l median range): 358 (14–1939) Erythropoietin baseline (mU ml^{-1}): 57 (12–227)	*n* = 11 Age (years): 63 (25–80) % Male: 18% Hb baseline (g dl^{-1}): 9.5 (1.0) Iron baseline: 524 (14–2178) Erythropoietin baseline (mU ml^{-1}): 45 (12–132)	Brand: darbepoetin alfa Dose: 4.5 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks on epo plus 4 weeks (16 weeks)	Placebo	Iron: NR G-CSF: NR Transfusion trigger: Hb <8 g dl^{-1} (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: haem Treatment: chemo: myelosuppressive	Yes
Hedenus, 2003[123] **HaemR, RBCT (week 5 to end), AE, HRQoL (FACT-F)**	*n* = 176 Age (years): 64.8 (SD 13.8) % Male: 50% Hb baseline (g dl^{-1}): 9.59 (SD 1.22) Iron baseline (U/l median range): st% 26.5 (5–95) Erythropoietin baseline (mU ml^{-1}): 68.99 (2.3–1522.7)	*n* = 173 Age (years): 64.6 (SD 12.2) % Male: 46% Hb baseline (g dl^{-1}): 9.5 (SD 1.21) Iron baseline: st% 25 (4–95) Erythropoietin baseline (mU ml^{-1}): 235.5 (10.9–3169.1)	Brand: darbepoetin alfa Dose: 2.25 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: time on epo plus 4 weeks (16 weeks)	Placebo	Iron: prn G-CSF: NR Transfusion trigger: Hb <8 g dl^{-1} or prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: haem Treatment: NR	No: not correct malignancy treatment or population

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Henke, 2003[124] **HaemR, Hb, AE, tumour progression**	*n* = 180 Age (years): 58 (25–81) % Male: 88% Hb baseline (g dl^{-1}): 11.7 (8.5–14.4) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 11 (11–446.2) [11 is how it is reported in the paper (supposed to be a median)]	*n* = 171 Age (years): 57 % Male: 85% Hb baseline (g dl^{-1}): 11.8 (6.9–14.6) Iron baseline: NR Erythropoietin baseline (mU ml^{-1}): 11 (3.3–1681)	Brand: epoetin beta Dose: 900 IU kg^{-1} per week Dose adjustment: yes Duration of epo tx: median 43 days Duration of trial: unsure	Placebo	Iron: prn G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: <12 g dl^{-1})	Disease: solid (head/neck) Treatment: radiotherapy	No: radiotherapy
Henze, 2002[77] **Abstract**	*n* = assume 116 Age: children, age NR % Male: NR Hb baseline: NR Erythropoietin baseline: NR	*n* = assume 116 Age: children, age NR % Male: NR Hb baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 600 or 900 IU kg^{-1} per week Dose adjustment: NR Duration of epo tx: over 20 weeks Duration of trial: over 20 weeks	NR	Iron: NR G-CSF: NR Transfusion trigger: NR	Disease: mixed (ALL 37% of population) Treatment: chemo	No: children
Huddart, 2002[125] **HaemR, HRQoL (FACT-An)** **Abstract**	*n* = NR (total for trial = 90) Age: NR % Male: NR Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	*n* = NR (total for trial = 90) Age: NR % Male: NR Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 30,000 per week Dose adjustment: yes Duration of epo tx: given for 4–6 cycles of chemo plus 4 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: <10 g dl^{-1})	Disease: solid Treatment: chemo: plat	No: dose not by weight

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Iconomou, 2003[126] **HaemR, HRQoL (FACT-An, CLAS)**	*n* = 57 Age (years): 60.6 (33–85) % Male: 39% Hb baseline (g dl^{-1}): 10.1 (±0.6) Iron baseline: NR Erythropoietin baseline: NR	*n* = 55 Age (years): 62.6 (34–80) % Male: 44% Hb baseline (g dl^{-1}): 10.1 (±0.6) Iron baseline: NR Erythropoietin baseline: NR	Brand: rHuEPO (assume epoetin alfa) Dose: 30,000 IU per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Standard care	Iron: Yes G-CSF: NR Transfusion trigger: Hb 7.5 g dl^{-1} or prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: plat and non-plat	No: dose not by weight
Janinis, 2003[78] **Abstract**	*n* = assume 186 Age: NR % Male: NR Hb baseline (g dl^{-1}): 10.5 Erythropoietin baseline: NR	*n* = assume 186 Age: NR % Male: NR Hb baseline (g dl^{-1}): 10.5 Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 30,000 IU per week Dose adjustment: NR Duration of epo tx: NR	Standard care	Iron: Fixed G-CSF: NR Transfusion trigger: NR	Disease: solid Treatment: mixed, plat and non-plat	No: dose not licensed
Kotasek, 2003[90]a **HaemR, Hb, RBCT, HRQoL** **(two publications, abstract[79])**	*n* = 32 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 μg l^{-1} Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31 % Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 μg l^{-1} Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 1.5 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	No: dose lower than licence

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Kotasek, 2003[90]b **HaemR, Hb, RBCT, HRQoL** **(two publications, abstract[79])**	*n* = 17 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31% Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 2.25 $\mu g\ kg^{-1}$ per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	Yes
Kotasek, 2003[90]c **HaemR, Hb, RBCT, HRQoL** **(two publications[79])**	*n* = 46 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31% Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 3.0 $\mu g\ kg^{-1}$ per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	Yes

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Kotasek, 2003[90]d **HaemR, Hb, RBCT, HRQoL** **(two publications[79])**	*n* = 28 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31% Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 4.0 $\mu g\ kg^{-1}$ per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	Yes
Kotasek, 2003[90]e **HaemR, Hb, RBCT, HRQoL** **(two publications[79])**	*n* = 35 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31% Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 4.5 $\mu g\ kg^{-1}$ per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	Yes: maximum licensed dose

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Kotasek, 2003[90]f **HaemR, Hb, RBCT, HRQoL** **(two publications[79])**	*n* = 40 Age (years): 58.3 (SD 11.9) % Male: 28% Hb baseline (g dl^{-1}): 9.93 (1.0) Iron baseline: 11% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 17% of patients >100 mU ml^{-1}	*n* = 51 Age (years): 56.2 (SD 12.4) % Male: 31% Hb baseline (g dl^{-1}): 9.87 (1.12) Iron baseline: 6% of patients ferritin <50 $\mu g\ l^{-1}$ Erythropoietin baseline: 15% of patients >100 mU ml^{-1}	Brand: darbepoetin alfa Dose: 5.0 $\mu g\ kg^{-1}$ per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chemo: detail not given	No: dose higher than licence
Leyland-Jones, 2003[118] **Survival**	*n* = NR (total for trial 939) Age: NR % Male: 0% Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	*n* = NR (total for trial 939) Age: NR % Male: 0% Hb baseline (g dl^{-1}): 13? Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: NR Dose adjustment: NR Duration of epo tx: NR Duration of trial: 12–19 months	Placebo	Iron: NR G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: 13 g dl^{-1}, aim of study to keep Hb >12 <14 g dl^{-1})	Disease: solid (metastatic breast) Treatment: NR	No: do not know chemo treatment or epoetin alfa dose
Rosen, 2003[127] **Hb, patients RBCT**	*n* = 47 Age (years): 56 (35–80) % Male: 71% Hb baseline (g dl^{-1}): <10 Iron baseline: NR Erythropoietin baseline: NR	*n* = 43 Age (years): 56 (35–80) % Male: 71% Hb baseline (g dl^{-1}): <10 Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 40,000 IU per week Dose adjustment: NR Duration of epo tx: 14 weeks starting with first week of radio chemotherapy; continued for a further 4 weeks Duration of trial: 48 months	Standard care; iron not given	Iron: fixed for intervention arm, control did not receive iron G-CSF: NR Transfusion trigger: <10 g dl^{-1} if on day 0–5 of chemo cycle (Hb inclusion criteria level: ≤16 g dl^{-1})	Disease: solid (head/neck) Treatment: chemo + radiotherapy	No: dose not per patient's weight

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Rosenzweig, 2004[128] **Hb, HRQoL, AE, survival**	*n* = 14 Age (years): 55.9 (±11.7) % Male: 0% Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	*n* = 13 Age (years): 53.9 (±14.2) % Male: 0% Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 40,000 IU per week Dose adjustment: yes increasing Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Standard care	Iron: NR G-CSF: NR Transfusion trigger: prn (Hb inclusion criteria level: <12 g dl^{-1})	Disease: solid (metastatic breast) Treatment: chemo	No: dose not per patient's weight
Smith, 2003[91]a **HaemR, Hb, RBCT, AE (HRQoL, but not reported as RCT data)**	*n* = 21 Age (years): 64 (SD 16.6) % Male: 14% Hb baseline (g dl^{-1}): 9.24 (SD 1.38) Iron baseline: sf 92.0 Erythropoietin baseline (mU ml^{-1}): 46.22	*n* = 22 Age (years): 68.6 (SD 17.1) % Male: 41% Hb baseline (g dl^{-1}): 9.8 (SD 0.89) Iron baseline: sf 133.5 Erythropoietin baseline (mU ml^{-1}): 25.42	Brand: darbepoetin alfa Dose: 2.25 μg kg^{-1} per week (given over 3 weeks) Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: prn G-CSF: NR Transfusion trigger: Hb 8 g dl^{-1} or prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: mixed Treatment: none	No: patients not on chemo
Smith, 2003[91]b **HaemR, Hb, RBCT, AE (HRQoL, but not reported as RCT data)**	*n* = 21 Age (years): 70.5 (SD 11.2) % Male: 38% Hb baseline (g dl^{-1}): 10.2 (SD 0.88) Iron baseline: sf 113.5 Erythropoietin baseline (mU ml^{-1}): 29.32	*n* = 22 Age (years): 68.6 (SD 17.1) % Male: 41% Hb baseline (g dl^{-1}): 9.8 (SD 0.89) Iron baseline: sf 133.5 Erythropoietin baseline (mU ml^{-1}): 25.42	Brand: darbepoetin alfa Dose: 1.69 μg kg^{-1} per week (given over 4 weeks) Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: prn G-CSF: NR Transfusion trigger: Hb 8 g dl^{-1} or prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: mixed Treatment: none	No: patients not on chemo, dose given over 4 weeks

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Smith, 2003[91]c **HaemR, Hb, RBCT, AE (HRQoL, but not reported as RCT data)**	*n* = 22 Age (years): 68.8 (SD 9.1) % Male: 50% Hb baseline (g dl^{-1}): 10.1 (SD 0.9) Iron baseline: sf 169.5 Erythropoietin baseline (mU ml^{-1}): 28.99	*n* = 22 Age (years): 68.6 (SD 17.1) % Male: 41% Hb baseline (g dl^{-1}): 9.8 (SD 0.89) Iron baseline: sf 133.5 Erythropoietin baseline (mU ml^{-1}): 25.42	Brand: darbepoetin alfa Dose: 2.5 μg kg^{-1} per week (given over 4 weeks) Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 12 weeks	Placebo	Iron: prn G-CSF: NR Transfusion trigger: Hb 8 g dl^{-1} or prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: mixed Treatment: none	No: patients not on chemo, dose given over 4 weeks
Sweeney, 1998[129] **HaemR, AE, HRQoL**	*n* = 24 Age (years): 62.3 (NR) % Male: 63% Hb baseline (g dl^{-1}): 12.07 (NR) Iron baseline: 223.85 Erythropoietin baseline: NR	*n* = 24 Age (years): 62.7 (NR) % Male: 54% Hb baseline (g dl^{-1}): 10.72 (NR) Iron baseline: 347.76 Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 1000 IU kg^{-1} per week Dose adjustment: yes Duration of epo tx: 7 weeks maximum Duration of trial: 85 weeks	Standard care; iron not given	Iron: yes for intervention arm, no for control G-CSF: NR Transfusion trigger: NR (Hb inclusion criteria level: <12 g dl^{-1})	Disease: solid Treatment: radiotherapy	No: dose higher than licence, patients received radiotherapy
Thomas, 2002[130] **HaemR, RBCT, HRQol (FACT-An, CLAS)** **Abstract**	*n* = 62 Age: NR % Male: NR Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	*n* = 65 Age: NR % Male: NR Hb baseline: NR Iron baseline: NR Erythropoietin baseline: NR	Brand: epoetin alfa Dose: 30,000 IU per week Dose adjustment: no; fixed Duration of epo tx: 28 weeks Duration of trial: 28 weeks	Standard care	Iron: NR G-CSF: NR Transfusion trigger: prn (Hb inclusion criteria level: ≤12 g dl^{-1})	Disease: NR Treatment: chemotherapy	No: dose not per patients weight

continued

TABLE 59 *Study characteristics: intervention, update 2001 to October 2004 (Birmingham) (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Vansteenkiste, 2002[64] **HaemR, Hb, RBCT (from week 5 and week 1), HRQoL, AE, disease progression and survival**	*n* = 156 Age (years): 61.6 (SD 8.8) % Male: 71% Hb baseline (g dl^{-1}): 10.28 (SD 1.08) Iron baseline: sf 552.22 (SD 453.45) Erythropoietin baseline (mU ml^{-1}): 51.10 (SD 71.72)	*n* = 158 Age (years): 61.3 (SD 8.8) % Male: 73% Hb baseline (g dl^{-1}): 9.93 (SD 10.8) Iron baseline: sf 534.50 (SD 4895.0) Erythropoietin baseline (mU ml^{-1}): 53.17 (SD 58.87)	Brand: darbepoetin alfa Dose: 2.25 μg kg^{-1} per week Dose adjustment: yes Duration of epo tx: 12 weeks Duration of trial: 16 weeks	Placebo	Iron: NR G-CSF: NR Transfusion trigger: Hb 8 g dl^{-1} and prn (Hb inclusion criteria level: ≤11.0 g dl^{-1})	Disease: solid Treatment: chem: plat	Yes

Epo, erythropoietin (including epoetin alfa, epoetin beta and darbepoetin alfa); tx, treatment.

TABLE 60 *Study characteristics: intervention, Cochrane studies*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Abels, 1993[93] **HaemR, RBCT**	*n* = 65 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 59 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 300 U kg^{-1} per week Dose adjustment: Duration: 8 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: NR	Disease: mixed (exclude primary myeloid malignancy or acute leukaemia) Treatment:	No: dose lower than recommended, patients not receiving chemo

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Carabantes, 1999[94] **HaemR, patients' RBCT, HRQoL** **Abstract**	*n* = 20 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 15 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 18–24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (lung/ovary) Treatment: chemo: plat	Yes
Cascinu, 1994[95] **HaemR, Hb, RBCT, AE**	*n* = 50 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 50 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 300 IU kg^{-1} per week Dose adjustment: Duration: 9 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: some patients received G-CSF Transfusion trigger:	Disease: solid Treatment: chemo: plat	
Case, 1993[96] **HaemR, RBCT, HRQoL, AE**	*n* = 81 (analysed 79) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 76 (analysed 79) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: 12 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: prn	Disease: mixed Treatment: chemo: non-plat	Yes
Cazzola, 1995[97]c **HaemR, Hb, RBCT, AE**	*n* = 31 (analysed 31) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 29 (analysed 29) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 5000 U per day Dose adjustment: Duration: 8 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: haem Treatment: chemo: non-plat	No: dose not per licence, epo deficiency in 77% of sample

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Cazzola, 1995[97]d **HaemR, Hb, RBCT, AE**	*n* = 26 (analysed 26) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 26 (analysed 26) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 10,000 U per day Dose adjustment: 8 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: haem Treatment: chemo: non-plat	No: dose not per licence, epo deficiency in 77% of sample
Coiffier, 2001[65] **HaemR, Hb, RBCT, HRQoL** **Unpublished data, Boogaerts**	*n* = 133 (analysed 133) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 129 (analysed 129) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 12 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: Hb 8.5 g dl^{-1}	Disease: mixed: solid, haem Treatment: chemo: unclear how many solid tumour patients received plat	Unsure: should be receiving plat-based chemo for solid tumours
Dammacco, 2001[98] **HaemR, Hb, RBCT, HRQoL, AE**	*n* = 69 (analysed 69) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 76 (analysed 76) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 12 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: Hb 8 g dl^{-1} (avoided if possible if higher than this)	Disease: haem Treatment: chemo: plat	Yes
Del Mastro, 1997[99] **Hb, RBCT, HRQoL, AE**	*n* = 31 (analysed 31) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 31 (analysed 31) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin (?) Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 14 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: 5 μg kg^{-1} d4–d11 both arms Transfusion trigger:	Disease: solid (breast) Treatment: chemo	

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Dunphy, 1999[100] **Hb, RBCT**	*n* = 15 (analysed 13) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 14 (analysed 14) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin (?) Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 6 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (NSCLC) Treatment: chemo: plat	
Henke, 1999[101]a **HaemR, Hb**	*n* = 19 (analysed 19) Age: % Male: Hb baseline: Iron baseline: >10 ≤12 Erythropoietin baseline:	*n* = 11 (analysed 11) Age: % Male: Hb baseline: Iron baseline: >10 ≤12 Erythropoietin baseline:	Brand: epoetin alfa or beta (i.v.) Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 8 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid Treatment: radiotherapy	No: radiotherapy
Henke, 1999[101]b **HaemR, Hb**	*n* = 14 (analysed 14) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 11 (analysed 11) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa or beta (i.v.) Dose: 900 IU kg^{-1} per week Dose adjustment: Duration: 8 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid Treatment: radiotherapy	No: radiotherapy

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Henke, 1999[101]c **HaemR, Hb**	*n* = 6 (analysed 6) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 11 (analysed 11) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa or beta (s.c.) Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid Treatment: radiotherapy	No: radiotherapy
Henry, 1994[102] **HaemR, RBCT, HRQoL, AE**	*n* = 67 (analysed 64) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 65 (analysed 61) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 12 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: mixed Treatment: chemo: plat	Yes
Italian Cooperative Study Group, 1998[103] **HaemR, Hb, AE**	*n* = 44 (analysed 43) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 43 (analysed 42) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 8 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: Hb <8 g dl^{-1} or prn	Disease: MDS Treatment: none	No: not receiving chemo; also MDS
Kunikane, 2001[104]a **Hb, patients' RBCT**	*n* = 16 (analysed 16) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 19 (analysed 19) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 300 IU kg^{-1} per week Dose adjustment: Duration: 6 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger:	Disease: solid (NSCLC) Treatment: chemo: plat	No: dose too low

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Kunikane, 2001[104]b **Hb, patients' RBCT**	*n* = 18 (analysed 18) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 19 (analysed 19) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 600 IU kg^{-1} per week Dose adjustment: Duration: 6 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger:	Disease: solid (NSCLC) Treatment: chemo: plat	Epo deficient?
Kurz, 1997[105] **HaemR**	*n* = 23 (analysed 23) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 12 (analysed 12) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration of epo tx: Duration of trial:		Iron: G-CSF: Transfusion trigger: Hb <8 g dl^{-1} or prn	Disease: solid Treatment: chemo: plat	Yes
Littlewood, 2001[63a] **HaemR, Hb, RBCT, HRQoL, AE** **(see Appendix 4)**	*n* = 251 (analysed 251) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 124 (analysed 124) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 28 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: 8 g dl^{-1} (avoided if possible if higher than this) or prn	Disease: mixed Treatment: non-chemo: plat	Yes
Oberhoff, 1998[106] **HaemR, Hb, RBCT, AE**	*n* = 114 (analysed 114) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 104 (analysed 104) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 5000 U per day Dose adjustment: Duration: 12 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: solid Treatment: chemo: plat	No: dose not per licence

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Österborg, 1996[107]a **HaemR, Hb, RBCT, AE**	*n* = 47 (analysed 47) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 49 (analysed 49) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 10,000 U per day Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: haem Treatment: chemo: non-plat	No: dose not per licence
Österborg, 1996[107]b **HaemR, Hb, RBCT, AE**	*n* = 48 (analysed 48) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 49 (analysed 49) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 2000 U per day Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger: NR	Disease: haem Treatment: chemo: non-plat	No: dose not per licence
Österborg, 2002[108] **HaemR, Hb, RBCT, AE**	*n* = 170 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 173 Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 16 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: Hb 8.5 g dl^{-1} or prn	Disease: haem Treatment: chemo: non-plat	Yes: also had a relative erythropoietin deficiency
Quirt, 1996[109] **Hb, patients' RBCT, HRQoL** **Abstract**	*n* = 27 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 27 Age: % Male: Hb baseline (g dl^{-1}): 10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 16 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger:	Disease: mixed Treatment: chemo: unspecified	Yes

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Rose, 1994[110] **HR, patients' RBCT, HRQoL** **Abstract**	*n* = 142 (analysed 142) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 79 (analysed 79) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 12 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger:	Disease: haem (CLL) Treatment: none	No: patients not on chemo
Silvestris, 1995[111] **HaemR, AE**	*n* = 30 (analysed 27) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = 24 (analysed 22) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: haem (MM) Treatment: chemo	Yes
Ten Bokkel, 1998[112]a **Patients' RBCT, TR, AE**	*n* = 45 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 33 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (ovary) Treatment: chemo: plat	
Ten Bokkel, 1998[112]b **Patients' RBCT, TR, AE**	*n* = 42 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 33 Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 900 IU kg^{-1} per week Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (ovary) Treatment: chemo: plat	

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Thatcher, 1999[113]a **Hb, patients' RBCT, HRQoL, AE**	*n* = 42 (analysed 42) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 44 (analysed 44) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: 26 weeks Duration of epo tx: Duration of trial:	Standard treatment	Iron: G-CSF: Transfusion trigger:	Disease: solid (NSCLC) Treatment: chemo: plat	Yes
Thatcher, 1999[113]b **Patients' RBCT**	*n* = 44 (analysed 44) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 44 (analysed 44) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 900 IU kg^{-1} per week Dose adjustment: Duration: 26 weeks Duration of epo tx: Duration of trial:	Standard treatment	Iron: G-CSF: Transfusion trigger:	Disease: SCLC Treatment: chemo: plat	Yes
Thompson, 2000[114] **HaemR, patients' RBCT**	*n* = 45 (analysed 45) Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	*n* = Age: % Male: Hb baseline (g dl^{-1}): ≤10 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 450 IU kg^{-1} per week Dose adjustment: Duration: Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger: <25% Hct or prn if Hct between 25 and 30%	Disease: MDS Treatment: none	No: patients not receiving chemo
Throuvalas, 2000[115] **Patients' RBCT**	*n* = 28 (analysed 28) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 27 (analysed 26) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin (?) Dose: 50,000 U per week Dose adjustment: Duration: 6 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (cervix, bladder) Treatment: chemo: plat-based radiochemotherapy	No: dose not weight based

continued

TABLE 60 *Study characteristics: intervention, Cochrane studies (cont'd)*

	Intervention group characteristics	Control group characteristics	Study intervention	Control	Adjuvant anaemia treatment	Malignancy type and treatment	Within licence?
Welch, 1995[116] **Hb, patients'** **RBCT, AE**	*n* = 15 (analysed 15) Age: % Male: Hb baseline (g dl^{-1}): >12 Iron baseline: Erythropoietin baseline:	*n* = 15 (analysed 15) Age: % Male: Hb baseline (g dl^{-1}): <12 Iron baseline: Erythropoietin baseline:	Brand: epoetin alfa Dose: 900 IU kg^{-1} per week Dose adjustment: Duration: 24 weeks Duration of epo tx: Duration of trial:	Standard care	Iron: G-CSF: Transfusion trigger:	Disease: solid (ovary) Treatment: chemo: plat	Yes
Wurnig, 1996[117] **Hb, patients'** **RBCT, AE**	*n* = 16 (analysed 16) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	*n* = 14 (analysed 14) Age: % Male: Hb baseline (g dl^{-1}): >10 ≤12 Iron baseline: Erythropoietin baseline:	Brand: epoetin beta Dose: 1200 IU kg^{-1} per week (i.v.) Dose adjustment: Duration: 20 weeks Duration of epo tx: Duration of trial:	Placebo	Iron: G-CSF: Transfusion trigger:	Disease: solid: Ewing's or osteosarcoma Treatment: chemo: mixed, some with plat	No: dose not licensed for cancer patients, dose as recommended for autologous blood collection treatment; disease not appropriate for licence

Data were extracted from the Cochrane review, except for transfusion trigger.
[a] Although the trial is mixed, the results are reported separately for solid and haematological tumours.

Appendix 6

Quality of life scales

Table 61 provides details about each of the scales used in epoetin studies within which HRQoL was measured.

TABLE 61 *Quality of life scales*

Scale	Date	Disease/ generic	Design details	Objective	Scale components	Timescale	Reliability and validity	Comments
FACT Functional Assessment of Cancer	1990	Disease: cancer	Created in the USA by David Cella (Professor of Psychology)	Aims to measure multidimensional HRQoL in patients with a cancer diagnosis	**Modular system**: generic core (FACT-G) and add-on disease- or symptom-specific scales, e.g. FACT-An, Anaemia; FACT-F, Fatigue FACT-G has 27 items covering four components: • physical well-being (7) • social/family well-being (7) • emotional well-being (6) • functional well-being (7)[161] Two additional items assessing global HRQoL can be added to the core 27-item FACT-G	Self-administered Questions/ statements worded in the first person and relate to experiences in the past week	Data on reliability (reproducibility and internal consistency) and validity (compared with FLI-C, ECOG, POMS and TMAS) are available for the various stages of development and the generic and add-on symptom- or treatment-specific scales[161] FACT-G and FACT-An have demonstrated sensitivity to Hb level[140]	Since 1997, the scale has been known as FACIT (Functional Assessment of Chronic Illness Therapy): includes original FACT scales and new non-cancer scales, e.g. assessment of HIV
SF-36 Medical Outcomes Study, Short Form 36	1993	Generic	Created in the USA by the Rand Corporation for use in the Health Insurance/ Medical Outcomes Study (Ware *et al.*[169])	Designed to be applicable to a wide range of types and severity of conditions.[162] Developed to detect changes in health status that might be expected to occur as a result of health service use within a relatively short period[162]	Has 36 items over eight dimensions: • physical functioning (10) • social functioning (2) • role limitations due to physical health problems (4) • role limitations due to emotional problems (3) • mental health (5) • energy/vitality (4) • bodily pain (2) • general health perceptions (5) Plus: perceptions of health changes over past 12 months Scores available for scale overall and two component scales: physical and mental[163]	Self-administered Questions worded in the first person and relate to 'in general…', 'compared to 1 year ago' or 'over the past 4 weeks'	Data on reliability and validity are available for overall scale and two component scales SF-36 originally tested in the USA on 22,000 patients[162]	Following extensive use, this scale is recommended to be used alongside disease-specific measures of HRQoL[162] Now used widely in the UK and USA. UK population norms are available

continued

TABLE 61 *Quality of life scales (cont'd)*

Scale	Date	Disease/ generic	Design details	Objective	Scale components	Timescale	Reliability and validity	Comments
NHP Nottingham Health Profile	1984	Generic	Created in the UK by Hunt *et al*. Developed following interviews with lay people about the effects of illness on behaviour[164]	Not intended to measure HRQoL or detect health conditions.[164] Objective was to measure how people feel when they are experiencing various states of ill-health[164]	Measures 38 items over six domains: • physical mobility (8) • pain (8) • sleep (5) • energy level (3) • emotional reactions (9) • social isolation (5)[163]	Self-completion Statements are worded in the first person and relate to problems 'at the present moment'	Not highly sensitive: may not show scores for people in distress or improvements in minor ailments[164] In ill people, NHP has been shown to be reliable, but in 'healthy' people with few ailments will be affirmative in few sections, therefore making it difficult to compare scores over time[155,156]	First measure of perceived health to be extensively tested and used in the UK and Europe UK population norms and scale scores for individual patient groups are available Negative measure of health
FLI-C Functional Living Index – Cancer	1984	Disease: cancer	Created by Schipper *et al*. Developed by a panel of 11 people (clergy, health professionals and patients)[162]	To determine the response of patients to their illness/treatment. Proposed as an adjunct to clinical assessments of progress and toxicity in clinical trials[162]	22-item linear VAS (7-point Likert), along domains: • physical and occupational functioning • psychological state • sociability • somatic comfort[162]	Self-administered Each item covers 'now' or 'in the past 2–4 weeks'	Overall there is little information on its reliability and validity findings are varied[163] Validity (face) assessed by testing original 42 items on 300 people. Further testing and factor analysis reduced number of item to 22[162] Does not correspond very well for inpatients. Works better on an outpatient population[162,163]	Items included were selected by the panel from previous HRQoL instruments[163] Can be referred to as the Manitoba Cancer Treatment and Research Foundation Functional Living Index[162]

continued

TABLE 61 *Quality of life scales (cont'd)*

Scale	Date	Disease/ generic	Design details	Objective	Scale components	Timescale	Reliability and validity	Comments
LASA Linear Analogue Self-Assessment Scale	1976	Generic, but designed for use with cancer patients	Created by Priestman and Baum	Designed for responders to indicate their feelings (perceptions) at the current time	25-item linear VAS (10-cm lines) along domains: • symptoms and effects of disease and treatment (10) • psychological consequences (5) • 'other' physical indices (5) • personal relationships (5)[162]	Self-administered	Many references to validity, but fewer for reliability. LASA appears to be a valid tool, but it is less easy to judge the reliability of the scale. The scale is easily reproducible[162] Subscales energy, ability to do daily activities and overall HRQoL have demonstrated sensitivity to Hb levels[140]	Now known as CLAS (Cancer Linear Analogue Scale)
BSI Brief Symptom Inventory	1975	Generic: psychiatry/ psychology	Created in the USA by Derogatis. Shortened version of SCL-R-90 (Derogatis, 1975, 1977). Items for the BSI were selected based on a factor analysis of the SCL-R-90[165]	Designed to reflect the psychological distress and symptom patterns of psychiatric and medical patients, as well as community samples. Respondent reports how much the symptom/ problem distressed or bothered them	53 items measured on 5-point Likert scales from 0= not at all to 4 = extremely. Comprised of nine symptom scales: • somatisation (7) • obsessive–compulsive (6) • interpersonal sensitivity (4) • depression (6) • anxiety (6) • hostility (5) • phobic anxiety (5) • paranoid ideation (5) • psychoticism (5) plus four clinically important additional factors and three global indices: • global severity index • positive symptom distress index • positive symptom total	Self or interviewer administered Each item covers 'the intensity of distress during the past 7 days'[165]	Good reliability (test–retest and internal consistency) reported for nine symptom scales. No reliability reported for global indices Validity data available Criteria for defining low, moderate and high levels of distress are defined in cancer patients. Normed BSI scores in this group are: low <55.0, moderate 55.0–64.9 and high ≥65.0 Normed scores are available for four different groups of patients: adult non-patients, adolescents aged 13–17 years, adult psychiatric outpatients and adult psychiatric inpatients	BSI used extensively in oncology

continued

TABLE 61 *Quality of life scales (cont'd)*

Scale	Date	Disease/ generic	Design details	Objective	Scale components	Timescale	Reliability and validity	Comments
HUI Health Utilities Index		Generic	Created during 30 years' research at McMaster University, Canada. The criterion for selecting the attributes for HUI2 and HUI3 was the importance that samples of the general public placed on each attribute.[165] Attributes designed to cover a full range of abilities and disabilities	To measure health status and HRQoL. To provide large numbers of detailed descriptions of comprehensive health states[165]	Consists of two systems: HUI2 and HUI3, which together describe almost 1 million unique health states. HUI2 attributes: • sensation • mobility • emotion • cognition • self-care • pain • fertility Each domain is measured over three to five categories[165] HUI3 attributes: • emotion • cognition • pain • dexterity • vision and hearing • speech • ambulation Each domain is measured over five or six categories[165,166]	Self or interviewer administered (dependent on version of questionnaire used) Can be answered by a proxy in cases where the subject is unable to answer (child, incapacitated) HUI assesses current or usual health status	Much research and testing by the developers and independent investigators has suggested that HUI is reliable, valid and internationally generalisable Full details available at www.healthutilities.com	Has been used to develop a population health index comparing the health of subjects with a range of disabilities and diseases, and to monitor changes in health status over time[166] See www.healthutilities.com for further information about this tool

continued

TABLE 61 *Quality of life scales (cont'd)*

Scale	Date	Disease/ generic	Design details	Objective	Scale components	Timescale	Reliability and validity	Comments
PDI Psychological Distress Inventory		Disease: cancer	Created by Morasso and Costantini	To measure the level of psychological distress caused by cancer[167]	13 items measured on a 5-point Likert scale from 0 = not at all to 5 = very much. The 13 items are comprised from three categories: • reactive anxiety to cancer and its therapies, e.g. inner tension and worry • reactive depression, e.g. sorrow, decreased energy, loss of self-confidence and loss of interests • emotional reactions to changes in the body image and disturbances in interpersonal and sexual behaviours[168]	Self-administered Items relate to experiences during the past week so as to reflect the present mood of patients[168]	Noted to have high levels of reliability and validity Studies have suggested that the PDI can discriminate between patients at different stages of cancer[168]	

Numbers in parentheses represent the number of items within each of the domains covered by the HRQoL measure.
POMS, Profile of mood states; TMAS, Taylor Manifest Anxiety Scale.

Appendix 7

Ongoing trials addendum

Introduction

Ongoing trials have been described as "any trial that has started but where the results are not yet available or where only interim results are available."[170]

There are many reasons why a report should include a search for ongoing trials, an intrinsic one being for completeness in the systematic review process. Even a review such as this one, which had data from 46 completed trials can gain by looking at ongoing trials. Specifically, ongoing trials can give the reviewer an idea of how wide and how mature the research base is. Ongoing trials may also be designed to answer more focused research questions borne of previous research. Finally, a search for ongoing trials may also identify trials which investigate longer term outcomes such as survival or tumour progression.

Aim

The primary aim was to search and assess ongoing trials, the intention being one of completeness of the systematic review process. Secondary aims were to examine if ongoing trials differed from completed trials with regard to patient populations and outcomes sought and also to assess when an update of the review would be necessary.

Methods

Ongoing trials can be difficult to identify. Several sources were used within this review to try and identify ongoing trials as systematically and accurately as possible. However, because the ISRCTN has still not been widely adopted, there may be duplicate entry of trial information both within and between trial databases. To overcome this, cross-comparisons of the trial numbers and data contained within the registers have been undertaken, but it must be borne in mind that much of the information within the registers is vague making trial identification very difficult.

Search

The following searches were undertaken:

- *Electronic searching*: terms for the intervention (erythropoietin, epoetin, darbepoetin) and condition of interest (anaemia/anemia) were used to search the following trials registers: National Research Register 2004 Issue 2, Current Controlled Trials metaRegister, ClinicalTrials.gov, National Cancer Institute PDQ database and International Cancer Research Portfolio for ongoing trials. Trials were included if they met the inclusion criteria and were assessed as ongoing according to the Song and colleagues definition.[170] Finally duplicates, identified via their study identification numbers where possible, were removed, leaving a final list of 29 potentially relevant trials. (Electronic searches carried out July 2004, information checked April 2005.)
- *Handsearching*. A handsearch of the ASH/ASCO abstract list was undertaken by one reviewer (JB), and the results were checked for inclusion by a second reviewer (JW). Inclusion criteria can be found below.
- *Publications search*. A search for publications was carried out in order to eliminate any trials that had been completed and reported in the published literature. For all ongoing trials identified from the WMHTAC electronic search and for the trials identified in the Cochrane review, the names of the lead investigators were searched for within PUBMED and within the ASH/ASCO abstract website (from 2001 to 2003).

Analysis

Information was put into tables and a description of the trials was undertaken.

Results

Overall

A total of 38 trials were identified as possible ongoing trials, 21 had been previously identified as ongoing and are described as such in the Cochrane review. Of these 21, five were found to have been completed and are incorporated within the review submitted to NICE. This leaves 16 trials for which additional data were not found and therefore must be assumed to be still ongoing. The ongoing trial search for trials between 2001 and 2004 found 16 ongoing trials and one trial recently completed (see trial 4 in *Table 62*). Thus a total of 32 trials were identified as ongoing.

Epoetin alfa was the drug investigated in 24 ongoing trials, with epoetin beta being investigated in three trials, darbepoetin in one trial and the erythropoietin agent unknown in four trials. The majority of ongoing trials investigated solid tumours (n = 22) with most of these (63%) investigating single disease sites. There was a range of malignancy treatments, with chemotherapy regimes dominating (n = 14). A slightly higher proportion of the earlier trials described in the Cochrane review involved radiotherapy only (n = 5) compared to the more recent trials found for the period 2001–2004 (n = 1). Anaemia related and HRQoL outcomes were the most frequently sought-after outcomes. Six trials described by Cochrane sought survival data compared to two of the trials found in the update. For more details see *Tables 62* and *63*. A detailed description of each ongoing trial is also given in the next section. Where starting dates were given, the earliest was 1996 (trial 24), the latest 2003 (trials 7 and 12). Only three trials report a finish date (trials 7, 8 and 24). See *Figure 21*.

Width of the research base

The primary aim of the search for ongoing trials was one of completeness. This search found 32 trials which could be classed as ongoing. This accounts for just over 40% of the research base of RCT trials on erythropoietin products in patients with anaemia associated with cancer, especially that attributable to cancer treatment. The proportion of trials investigating epoetin alfa was higher for ongoing trials than for completed trials (75% vs 59%), with a higher proportion of the 2001–4 ongoing trials using epoetin alfa (81% vs 69%). Overall, epoetin alfa was the most common agent used in both completed and ongoing trials, but a greater proportion of trials that used either epoetin beta or darbepoetin alfa had been completed.

Maturity of research base

Unfortunately, a complete assessment of how mature the ongoing trials were was not possible as 66% of the trials did not present information describing the trial stage. Of the trials that did give data, three were still recruiting, four were no longer recruiting, one had been terminated and three were suspended.

Suspended trials: any trends

Four trials had been suspended and one terminated. There were no obvious links between the trials that had been suspended, i.e. the trials that had been suspended did not share patient populations or malignancy treatments. The only similarities were that all used epoetin alfa, but this could be because this was the most common agent being investigated within the ongoing trials.

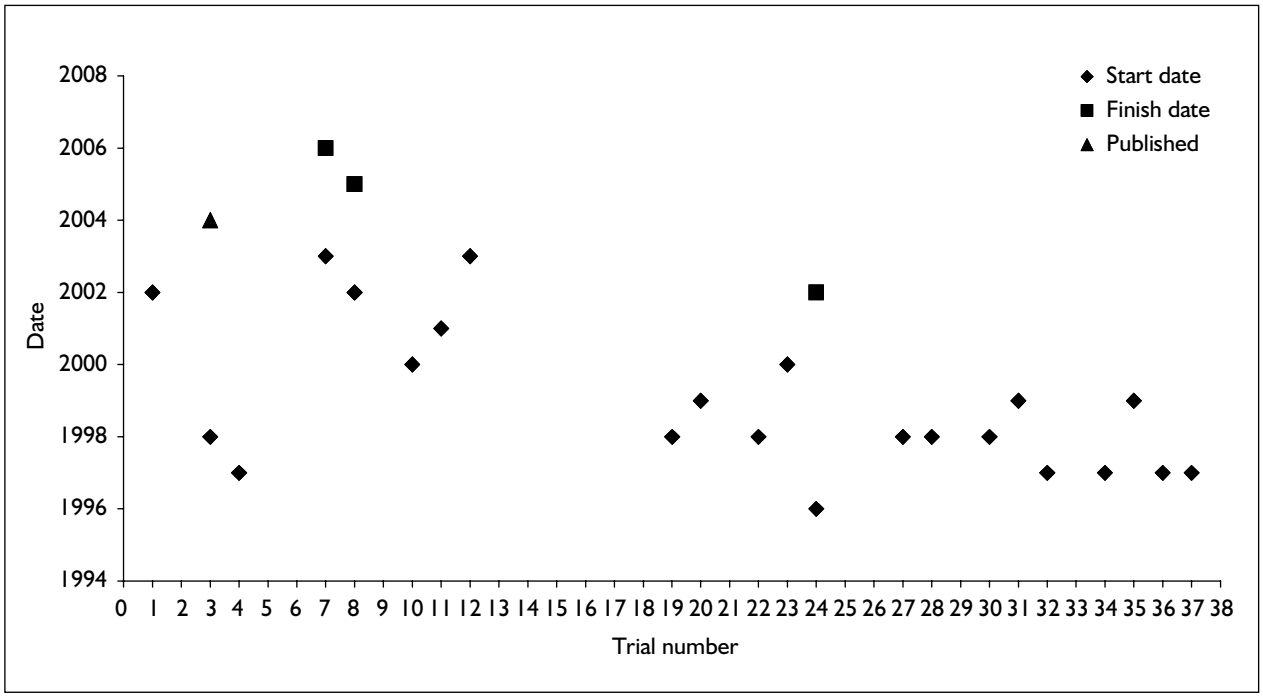

FIGURE 21 *Start and finish dates of identified ongoing trials*

Focus of the research questions within the ongoing trials

Population

In both completed and ongoing, more trials involved patients with solid tumours. However, more of the ongoing trials involved single disease sites (30% completed vs 63% ongoing). Conversely the number of trials investigating myelodysplasic syndromes (MDS) appears to be reducing over time. More trials were conducted in patients undergoing chemotherapy (44% ongoing vs 66% completed). Overall, there appears to be little difference between malignancy treatments of the completed trials and ongoing, other than for radiotherapy, where a greater proportion of the ongoing trials found by Cochrane used erythropoietin in patients undergoing radiotherapy only.

Outcome assessments

All but one of the completed trials investigated anaemia-related outcomes, with 72% of ongoing trials also stating that this was an outcome measure. More completed trials reported survival outcomes (61%) than ongoing trials (25%), however, more ongoing trials reported HRQoL, with 81% of the ongoing trials found between 2001 and 2004 measuring HRQoL. Tumour progression was more common among the ongoing trials whilst adverse events were more common among completed trials.

Update of review

Only five trials out of the 21 that Cochrane described as ongoing were found to have been completed as of October 2004. However, the WMHTAC update searches for the main review did identify 14 trials that were not described by Cochrane as ongoing, which means that 40% of trials that had been published between 2001 and 2004 had not been identified as ongoing trials by the comprehensive search of the Cochrane review. In addition, data regarding trial stage were not given for many of the ongoing trials identified. Therefore, this suggests that it would be difficult to predict how large and mature the research base is solely from a search and identification of ongoing trials, and therefore it would be difficult to predict when a review update would be needed from an ongoing trials assessment.

Conclusions

There is a very large research base evaluating the effects of erythropoietin in the treatment of anaemia associated with cancer and that attributable to cancer treatment. Forty per cent of the current research base consists of ongoing trials, with the majority investigating epoetin alfa. Patients with solid tumours predominate as does chemotherapy. The most frequent outcomes assessed by ongoing trials are anaemia related outcomes and HRQoL. Few details are available regarding the size and stage of the ongoing trials and very few report interim results.

Tables of detailed trial descriptions

TABLE 62 *Trials from 2001 to 2004 update*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
1	CDR0000069148; CCCWFU-62299; NCI-P01-0200; CCCWFU-BG01-193 AR Blackstock	NLR Start date: January 2002	Epo a	Standard	Solid – NSCLC	Chem + Rad	Unsure – epo dose unknown	Hb levels, disease progression, tumour response rate, overall survival, QoL, number of RBCT	No
2	CDR0000288821; NCCTG-N02C2; NCT00058331D DP Steensma	NLR	Epo a	Standard	Solid	?	No – unsure of malignancy treatment	RBCT, HRQoL	No
3	CDR0000066673; NCCTG-979253; NCI-P98-0133; NCT000036 TE Witzig	NLR Completed Start date: December 1998	Epo a	Placebo	Mixed Advanced malignancy	Chemo – plat	Unsure – epo dose unknown	Hb, RBCT, HRQoL	Yes – see Witzig paper
4	CDR0000066316; MSKCC-97125; NCI-G98-1436; ORTHO-PR-96-27; NCT00003341 DJ Straus	NLR Start date: December 1997	Epo a	Standard	Haem	Chemo	No – dose not per licence	HaemR, RBCT, QoL	Yes – see Straus abstract ASH 2002 828
5	CDR0000068669	NLR	Epo a	?	Solid – Head/neck	Rad	Unsure – epo dose unknown, also patients receiving radiotherapy	?	No
6	EPO-CAN-303; NCT00083434	R	Epo a	?	?	None currently	No – patients not on anti-malignancy tx	?	No

continued

TABLE 62 *Trials from 2001 to 2004 update (cont'd)*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
7	NRR 2004 Issue 2 Publication ID M0050134698 R Leonard	R Start date January 2003 Finish date: June 2006	Epo b	Standard	Solid – Met br ca	?	Unsure – epo dose unknown, also anti-malignancy tx	Anaemia related outcomes	No
8	NRR 2004 Issue 2 Study ID numbers: N0123138194, REC 01/05/53. C Chapman	R Start date: January 2002 Finish date: June 2005	Epo a	Standard	Haem – MM	Chemo	Unsure – epo dose unknown	HRQoL (FACT-An)	No
9	PR00-03-006	T	Epo a	?	Solid – GI	Chemo + Rad	Unsure – epo dose unknown	Hb, AE, TR, HRQoL	No
10	CDR0000067599; RTOG-9903, RTOG-DEV-1008, NCT00004917. M Machtay	S Start date: ? March 2000	Epo a	?	Solid – Head/neck	Rad +/– chemo	Unsure – epo dose unknown	Hb, AE, TR, HRQoL	No
11	CDR0000068641; GOG-0191, CAN-NCIC-CX4, NCT00017004 GM Thomas	S Start date: ? June 2001	Epo a	Standard	Solid – Cervix	Chemo – plat	No – prevention of anaemia	Hb – maintaining Hb levels above 12 g dl^{-1} and its effects on survival, TR, HRQoL	No
12	CDR0000069409; MDA-DM-02331; MDA-DM-0038; NCI-P02-0225; NCI00052221 MJ Fisch	S Start date: ? February 2003	Epo a	Placebo	Solid	None	No – no anti-malignancy tx	HRQoL, Fatigue	No

continued

TABLE 62 *Trials from 2001 to 2004 update (cont'd)*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
13	CDR 0000257189; AGOSG-OVAR-MO16375-MARCH; EI20217; ROCHE-MO16375; ROCH-RO2053859 H Koelbl	?	Epo b	Standard	Solid – Cervix	Chemo – plat + Rad	Unsure – epo dose unknown	Hb, AE, TR, HRQoL	No
14	V. Charu 2003 ASH #1816	Ongoing	DA (3 $\mu g\ kg^{-1}$ Q2W)	?	Mixed Lymp, Br, GU, lung	None	No – no anti-malignancy tx	Hb, RBCT, HRQoL (FACT –F)	Yes – interim
15	C Famoycin 2004 ASCO #4747	Ongoing	Epo a (40,000/wk)	Standard	Solid – RCC	Chemo – thalidomide	No – dose	TR, HRQoL	Yes – interim
16	J O'Shaughnessy ASCO 2002 #1449	Ongoing	Epo a (40,000 U/wk)	Placebo	Solid – Br ca	Chemo	No – dose	HRQoL, asthenia, cognitive function	Yes – interim
17	V Recasens ASH 2003 #1801	Ongoing	Epo a (10,000 U, 3 times a wk)	Standard	Haem – MM	Chemo	No – dose	HaemR, HRQoL, TR, Economics	Yes – interim

AE, adverse event; Br, breast; ca, cancer; chemo, chemotherapy; GI, gastrointestinal; GU, genitourinary; HaemR, haematological response; Hb, haemoglobin; HRQoL, quality of life; Met, metastatic; MM, multiple myeloma. NLR, no longer recruiting NSCLC, non-small cell lung cancer; plat, platinum-based chemotherapy; prn, as necessary; R, recruiting; rad, radiotherapy; RBCT, red blood cell transfusion; RCC, metastatic renal cell carcinoma; S, suspended; T, terminated, TR, tumour response; wk(s), week(s).

TABLE 63 *Ongoing trials described by Cochrane*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
18	Antonadou 2001	NFI	Epo ?	Standard	Solid – Pelvic	Rad	Unsure – re dose	Survival, AE	4 years disease free survival Epo group: 85.3%, control group 67.2% $p = 0.008$
19	Broadley	NFI Start date: October 1998	Epo a	Placebo	Solid Met br ca & prostate ca	None	No – no anti-malignancy tx	Hb, HRQoL	No
20	EORTC 22996-24002	NFI Start date: February 1999	Epo ?	Placebo	Solid – Head/neck	Rad	Unsure – re type of epo	Hb, AE, survival	No
21	Elsaid	NFI	Epo ?	Standard	Solid – Head/neck	Rad	Unsure – re type of epo	Hb, mucositis	No
22	Gallagher	NFI Start date: Sept 98	Epo a	Standard	Solid – Gynae	Chemo	Unsure – re dose	Hb, HRQoL	No
23	Howell	NFI Start date: August 2000	Epo a	Standard	Solid – Br ca	Chemo	Unsure – re dose	Hb. RBCT, AE, HRQoL, survival	No
24	MR4449/AR098-2	NFI Start date: June 1996 Finish date: December 2002	Epo b	Standard	Solid – Head & neck	Rad	No – should be on chemo	NR	No
25	Miller	NFI	Epo a	Standard	MDS	None	No – re anti-malignancy tx	HaemR, RBCT, TR, AE, survival	No

continued

TABLE 63 *Ongoing trials described by Cochrane (cont'd)*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
26	Moebus 2001	NFI	Epo a	Standard	Solid – Br ca	Chemo	Unsure – re dose	NR	No
27	O'Brien	NFI Start date: August 1998	Epo ?	Standard	Solid – Lung	Chemo – plat	Unsure – re type of epo	Hb, HRQoL	No
28	O'Connell	NFI Start date: December 1998	Epo a	Placebo	? advanced cancer	Chemo	Unsure – re dose	Hb, RBCT, HRQoL	No
29	Parliament	NFI	Epo a	Standard	Solid – Head/neck	Rad +/– chemo	Unsure – re dose	Hb, AE, HRQoL, TR, survival	No
30	Rudd	NFI Start date: November 1998	Epo a	Standard	Solid – Lung	Chemo	Unsure – re dose	NR	No
31	Stewart	NFI Start date: August 1999	Epo a	Standard	Solid – Head/neck	Rad	Unsure – re dose	TR, HRQoL, survival	No
32	Thomas	NFI Start date: June 1997	Epo a	Standard	Mixed	Chemo – plat	Unsure – re dose	Hb, RBCT, HRQoL	No
33	UKCCCR GN308	NFI	Epo a	Placebo	? Mixed "cancer patients"	Chemo – plat	Unsure – re dose	RBCT, HRQoL	No
34	Blohmer	Completed Start date: 1997	Epo a	Standard	Solid – Cervix	Chemo + Rad	Unsure – re dose	Hb, RBCT, survival	In main review, p. 51

continued

TABLE 63 *Ongoing trials described by Cochrane (cont'd)*

No.	Trial	Status	Agent	Control	Malignancy	Treatment	Within licence?	Outcomes sought	Results available
35	Casedevall	Completed Start date: 1999	Epo ?	Standard	MDS	None	No – MDS	HaemR, HRQoL, cost	In main review. Abstract publication
36	Thomas H	Completed Start date: July 1997	Epo a	Standard	? cancer patients	Chemo – plat	Unsure – re dose	Hb. HRQoL	In main review Abstract publication
37	Huddart	Completed Start date: November 1997	Epo a	Standard	Solid	Chemo – plat	Unsure – re dose	Hb, HRQoL	In main review. Abstract publication
38	Rosen	Completed	Epo ?	Standard	Solid – Head/neck	Rad	Unsure – re epo type	Hb, RBCT, survival	In main review. Abstract publication

AE, adverse event; chemo, chemotherapy; HaemR, haematological response; Hb, haemoglobin; HRQoL, quality of life; MDS, myelodysplasic syndrome; NFI, no further information found; NLR, No longer recruiting; plat, platinum based chemotherapy; prn, as necessary; R, recruiting; rad, radiotherapy; RBCT, red blood cell transfusion; RCC, metastatic renal cell carcinoma; S, suspended; T, terminated; TR, tumour response; wk(s), week(s).

TABLE 64 *Summary of study characteristics*

Study	2001–04 update, *n* = 16	Cochrane ongoing trials, *n* = 16	Total (%, *n* = 32)	Trials in NICE review (%, *n* = 46)	
Agent					
Epoetin alfa	13 [1, 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 16, 17]	11 [19, 22, 23, 25, 26, 28, 29, 30, 31, 32, 33]	*n* = 24 (75%)	*n* = 27 (59%) 13* + 14	
Epoetin beta	2 [7, 13]	1 [24]	*n* = 3 (9%)	*n* = 10 (22%) 1* + 9	
Darbepoetin alfa	1 [14]	0	*n* = 1 (3%)	*n* = 5* (10%)	
Either epo a or epo b				*n* = 1* (2%)	
Unknown	0	4 [18, 20, 21, 27]	*n* = 4 (13%)	*n* = 3 (7%)	
Tumour types					
Solid mixed sites	1 [12]	1 [19]	*n* = 2 (6%)	*n* = 11 (24%) 7* + 4	*NICE review
Solid single sites	9 [1 (NSCLC), 10, 5 (head/neck), 9 (GI), 11, 13 (cervix), 15 (RCC), 7, 16 (breast)]	11 [20, 21, 24, 29, 31 (head/neck), 18 (pelvic), 22 (gynae), 23, 26 (breast), 30, 27 (lung)]	*n* = 20 (63%)	*n* = 14 (30%) 4 + 10*	*Henke 2003 (head/neck), *Rosen 2003 (head/neck), *Leyland-Jones 2003 (met breast), *Rosenweig 2004 (met breast), Del Maestro 1997 (breast) Carabantes 1999 (lung/ovary), Dunphy 1999 (NSCLC), Kunikane 2001 (NSCLC), Thatcher 1999 (NSCLC), Ten Bokkel 1998 (ovary), Welch 1995 (ovary), *Blohmer 2003 (cervical), Throuvalas 2000 (cervix/bladder), Wurnig 1996 (Ewing's osteosarcoma)
Haem mixed	1 [4]	2 [17, 8 MM]	*n* = 3 (9%)	*n* = 2 (4%)	Rose 1994 (CLL), Silvestris 1995 (MM)
MDS	0	1 [25]	*n* = 1 (3%)	*n* = 7 (15%) 2* + 5	*Casedevall 2004, Italian 1998, Thompson 2000
Mixed populations	2 [2, 14]	2 [32, 33]	*n* = 4 (13%)	*n* = 7 (15%) 1* + 6	
Unknown	1 [6]	1 [28]	*n* = 2 (6%)	*n* = 1* (2%)	
Completed trials	0	5 [34 (cervix), 35 (MDS), 36 (mixed), 37 (solid), 38 (head/neck)]			

continued

TABLE 64 *Summary of study characteristics (cont'd)*

Study	2001–04 update, *n* = 16	Cochrane ongoing trials, *n* = 16	Total (%, *n* = 32)	Trials in NICE review (%, *n* = 46)
Malignancy treatments				
Chemo	6 [3, 8, 11, 15, 16, 17]	8 [30, 32, 33, 22, 23, 26, 27, 28]	*n* = 14 (44%)	*n* = 29 (63%) 11* + 18
Chemo + radiotherapy	3 [1, 9, 13]	0	*n* = 3 (9%)	*n* = 3 (7%) 2* + 1
Radiotherapy only	1 [5]	5 [18, 20, 21, 24, 31]	*n* = 6 (19%)	*n* = 3 (7%) 2* + 1
Radiotherapy ± chemo	1 [10]	1 [29]	*n* = 1 (3%)	–
No treatment	3 [6, 12, 14]	2 [19, 25]	*n* = 5 (16%)	*n* = 4 (9%) 1* + 3
Unknown	2 [2, 7]	0	*n* = 2 (6%)	*n* = 3* (7%)
Outcomes				
Anaemia- related outcomes	12 [1, 2, 4, 7, 9, 10, 11, 13, 14, 17]	11 [19, 20, 21, 22, 23, 25]	*n* = 23 (72%)	*n* = 45 (98%) 15* + 30
Survival	2 [1, 11]	6 [18, 20, 23, 25, 29, 31]	*n* = 8 (25%)	*n* = 28 (61%) 9* + 19
TR	7 [1, 9, 10, 11, 13, 15, 17]	3 [25, 29, 31]	*n* = 10 (31%)	*n* = 1* (2%)
HRQoL	13 [1, 2, 3, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]	9 [19, 22, 23, 27, 28, 29, 31, 32, 33]	*n* = 22 (69%)	*n* = 9* (20%)
AE	3 [9, 10, 13]	5 [18, 20, 23, 25, 29]	*n* = 8 (25%)	*n* = 25 (54%) 13* + 12
Trial maturity				
Recruiting	3 [6, 7, 8]	0	*n* = 3 (9%)	
No longer recruiting	4 [1, 2, 4, 5]	0	*n* = 4 (13%)	
Terminated	1 [9]	0	*n* = 1 (3%)	
Suspended	3 [10, 11, 12]	0	*n* = 3(9%)	
Unsure of status	5 [13, 14, 15, 16, 17]	16	21 (66%)	
Results available				
Interim results available	5 [4, 14, 15, 16, 17]	0	*n* = 5 (16%)	
Completed	1 [4]	5 [34, 35, 36, 37, 38]	*n* = 6 (3%)	

Numbers in square brackets refer to the trials listed in *Tables 62* and *63*.
* WMHTAC update trials (trials, *n* = 46).

TABLE 65 *Proportion of factors investigated*

Investigation	2001–04 update, (*n* = 16)	Cochrane ongoing trials (*n* = 16)	Total ongoing trials (*n* = 32)	Completed trials in NICE review (*n* = 46)
Agent				
Epoetin alfa	(13) 81%	(11) 69%	(24) 75%	(27) 59%
Epoetin beta	(2) 13%	(1) 6%	(3) 9%	(10) 22%
Darbepoetin alfa	(1) 6%	0%	(1) 3%	(5) 10%
Either epo a or epo b	0%	0%	0%	(1) 2%
Unknown	0%	(4) 25%	(4) 13%	(3) 7%
Tumour types				
Solid mixed sites	(1) 6%	(1) 6%	(2) 6%	(11) 24%
Solid single sites	(9) 56%	(11) 69%	(20) 63%	(14) 30%
Haem mixed	(1) 6%	(2) 13%	(3) 9%	(2) 4%
MDS	0%	(1) 6%	(1) 3%	(7) 15%
Mixed populations	(2) 13%	(2) 13%	(4) 13%	(7) 15%
Unknown	(1) 6%	(1) 6%	(2) 6%	(1) 2%
Malignancy treatments				
Chemo	(6) 38%	(8) 50%	(14) 44%	(29) 63%
Chemo + radiotherapy	(3) 19%	0%	(3) 9%	(3) 7%
Radiotherapy only	(1) 6%	(5) 31%	(6) 19%	(3) 7%
Radiotherapy ± chemo	(1) 6%	(1) 6%	(2) 6%	0%
No treatment	(3) 19%	(2) 13%	(5) 16%	(4) 9%
Unknown	(2) 13%	0%	(2) 6%	(3) 7%
Outcomes				
Anaemia related outcomes	(12) 75%	(11) 69%	(23) 72%	(26) 57%
Survival	(2) 13%	(6) 38%	(8) 25%	(28) 61%
TR	(7) 44%	(3) 19%	(10) 31%	(8) 17%
HRQoL	(13) 81%	(9) 56%	(22) 69%	(9) 20%
AE	(3) 19%	(5) 31%	(8) 25%	(25) 54%
Trial maturity				
Recruiting	(3) 19%	0%		
No longer recruiting	(4) 25%	0%		
Terminated	(1) 6%	0%		
Suspended	(3) 19%	0%		
Unsure of status	(5) 31%	(16) 100%		

TABLE 66 *Trials from 2001 to 2004 no longer recruiting*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
1	CDR0000069148 CCCWFU-62299; NCI-P01-0200; CCCWFU-BG01-193 AR Blackstock	Official title: Chemotherapy and radiation therapy with or without epoetin alfa in treating patients with stage IIIA or stage IIIB non small cell lung cancer	No longer recruiting (14/4/05) Study start date January 2002. Projected accrual, total of 202–232 patients (101–116 per treatment arm) over 1.7–2 years Aim of study: to determine the effectiveness of chemotherapy combined with radiation therapy with or without epoetin alfa in treating patients who have stage IIIA or stage IIIB non-small cell lung cancer	ClinicalTrials.gov PI: AR Blackstock Sponsor: National Cancer Institute (NCI); Comprehensive Cancer Center of Wake Forest University	Study characteristics: phase III RCT Intervention: epoetin alfa Control: standard care	Outcomes sought: Hb levels, disease progression, tumour response rate, overall survival, QoL, number of RBCT	NR
2	CDR0000288821; NCCTG-N02C2; NCT00058331. DP Steensma	Official title: Phase III randomized study of epoetin alfa in anemic patients with nonmyeloid cancer	No longer recruiting Aim of study: to study the effectiveness of epoetin alfa in treating anemia in patients who have solid tumours. Study characteristics: RCT	ClinicalTrials.gov.CCT PI: DP Steensma, Mayo Clinic Cancer Center Sponsor: National Central Cancer Treatment Group, National Cancer Institute	Patient characteristics: bit confusing, in that the aim states it is in patients with solid tumours, the patient characteristics list plasma cell disorders (including multiple myeloma), lymphoproliferative disorders (including non-Hodgkin's lymphoma and chronic lymphocytic leukaemia) and all other neoplasms. Intervention: Epoetin alfa Control: standard care	Outcomes sought: transfusion requirements, Hb levels, QoL including anaemia specific elements of QoL	NR

continued

TABLE 66 *Trials from 2001 to 2004 no longer recruiting (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
3	CDR0000066673; NCCTG-979253; NCI-P98-0133; NCT000036 TE Witzig	Official title: Phase III randomized study of epoetin alfa in anemic patients with advanced cancer undergoing chemotherapy	No longer recruiting Status: no longer recruiting (14/4/05). Study start: December 1998. First record received 1/11/99. Projected accrual: 300 patients over 11 months Aim of study: to compare effectiveness of epoetin alfa with a placebo in treating anemia in cancer patients who are receiving chemotherapy	ClinicalTrials.gov CCT PI: TE Witzig, North Central Cancer Treatment Group Sponsor: National Cancer Institute, North Central Cancer Treatment Group	Study characteristics/ patient characteristics: patients with advanced malignancy, e.g. lung cancer breast cancer, leukaemia, lymphoma, multiple myeloma Intervention: epoetin alfa Control: placebo	Outcomes sought: QoL, Hb levels and transfusion needs, effect on nephrotoxicity for patients receiving platinum based chemotherapy	Results: NR Published as: Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, *et al*. Phase III, randomized, double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *J Clin Oncol* 2004;**23**:2606–17
4	CDR0000066316; MSKCC-97125; NCI-G98-1436; ORTHO-PR-96-27; NCT00003341 DJ Straus	Official title: Phase III randomized study of epoetin alfa in patients with lymphoma, chronic lymphocytic leukemia, or multiple myeloma and chemotherapy related mild or moderate anemia	No longer recruiting Status: study start date December 1997, no longer recruiting patients (record 15/4/05) Aim of study: to determine the effectiveness of epoetin alfa on HaemR, transfusion requirements, QoL – including correlating QoL with changes in anaemia and determining the effect of changing QoL on health care resource utilisation	ClinicalTrials.gov PI: DJ Straus, Memorial Sloan-Kettering Cancer Center Sponsor: National Cancer Institute, Memorial Sloan-Kettering Cancer Center	Study characteristics: RCT Patient characteristics: Disease, patients with non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or multiple myeloma, and Hodgkin's disease with prior chemotherapy Intervention: epoetin alfa Control: standard care	Outcomes sought: HaemR, transfusion requirements, QoL	Results: see ASH 2002 #828 (which we have in file). This study is included in the ASH/ASCO abstract list and is classified as ongoing. Results data is also given in a review for Straus, which needs to be ordered

continued

TABLE 66 *Trials from 2001 to 2004 no longer recruiting (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
5	CDR0000068669 (No researcher identified)	Radiation therapy with or without epoetin alfa in treating patients with head and neck cancer ClinicalTrials.gov, CCT	No longer recruiting	National Institutes of Health			

PI, principal investigator.

TABLE 67 *Trials from 2001 to 2004 recruiting*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
6	EPO-CAN-303; NCT00083434	Official title: Treatment of anemia in patients with cancer who are not currently receiving chemotherapy or radiotherapy	Recruiting Aim: to examine the effectiveness of epoetin alfa in treating anaemia who have cancer or who no longer have signs of cancer, but remain anaemic as a result of their treatment	ClinicalTrials.gov NCI PDQ PI: NR Sponsor: Johnson & Johnson Pharmaceutical Research & Development, LLC	Intervention: epoetin alfa Control: NR, no other details given	NR	NR

continued

TABLE 67 *Trials from 2001 to 2004 recruiting (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
7	NRR 2004 Issue 2 Publication ID M0050134698 R Leonard	Official title: To investigate the impact of NeoRecormon treatment on survival, quality of life, outcome of antineoplasty, and anaemia in patients with metastatic breast cancer	Start date 01/01/2003 End date 30/06/2006 Aim: to investigate the impact of epoetin beta on survival, QoL, outcome of antineoplasty and anaemia in patients with metastatic breast cancer	National Research Register PI: R Leonard, professor of oncology, Pembrokeshire & Derwen NHS Trust, Withybush General Hospital, Haverfordwest Sponsor: NR	Study characteristics: RCT Patient characteristics: metastatic breast cancer Intervention: epoetin beta Control: standard treatment	Outcomes sought: effects on levels of anaemia	NR
8	NRR 2004 Issue 2 Study ID numbers: N0123138194, REC 01/05/53 C Chapman	Official title: A randomised comparison of the effect of maintaining haemoglobin levels with weekly epoetin alfa or with conventional anaemia management in subjects with multiple myeloma undergoing chemotherapy (EMMY)	Start date 1/1/02 End date 6/6/05 Aim: to compare effectiveness, safety and clinical outcomes of a once weekly dosing regimen of epoetin alfa with conventional anaemia management in the treatment of patients receiving chemotherapy for multiple myeloma	National Research Register PI: C Chapman, University Hospitals Leicester, c/o Research & Development Office, Leicester General Hospital NHS Trust, Leicester, LE1 4PW Sponsor: NR	Study characteristics: RCT Patient characteristics: MM, receiving at least 12 weeks of chemotherapy Intervention: epoetin alfa Control: standard care	Outcomes sought: QoL (FACT-An)	

MM, multiple myeloma; NRR, National Research Register.

TABLE 68 *Trials from 2001 to 2004 terminated/suspended*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
9	PR00-03-006 (No researcher identified)	Official title: A double blind randomized placebo controlled study of the efficacy and safety of epoetin alfa administered weekly in patients with gastric or rectal cancers undergoing preoperative chemoradiation followed by surgery	Terminated Aim of study: to demonstrate the effectiveness of epoetin alfa on reduction in red blood cell transfusions in gastric and rectal cancer patients undergoing preoperative chemoradiation therapy followed by surgery	ClinicalTrials.gov CTT PI: NR Sponsor: Johnson & Johnson Pharmaceutical Research & Development, LLC, Ortho Biotech	Study characteristics: phase III study, not stated randomised Study patients: adults with gastric cancer or rectal cancer for whom the treatment plan is preoperative chemoradiation followed by surgery Intervention: epoetin alfa Control: NR	Outcomes sought: primary objective – reduction of red blood cell transfusions. Secondary objectives – maintenance of Hb levels during preoperative chemoradiation; to evaluate QoL (LASA, FACT-An, BFI); tumour response; safety	NR, study says its terminated
10	CDR0000067599; RTOG-9903, RTOG-DEV-1008, NCT00004917 M Machtay	Official title: phase III randomized study of radiotherapy with or without epoetin alfa in anemic patients with squamous cell carcinoma of the head and neck	Suspended? No longer recruiting. Projected accrual stated as 372 patients (186 per arm) in 3.5 years. First record received 7/3/00 Aim of study: to compare the effectiveness of radiation therapy with or without epoetin alfa in treating anaemic patients who have head and neck cancer	ClinicalTrials.gov PI: M Machtay, University of Pennsylvania Cancer Center. Sponsor: Radiation Therapy Oncology Group, National Cancer Institute	Study characteristics. Patient characteristics: patients with stage I–IV squamous cell carcinoma of the head or neck who are receiving radiotherapy with or without chemotherapy. Intervention: epoetin alfa Control: NR – assume best supportive care	Outcomes sought: assessment of local–regional control rate, survival, Hb, toxicity, QoL	NR

continued

TABLE 68 *Trials from 2001 to 2004 terminated/suspended (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
11	CDR0000068641; GOG-0191, CAN-NCIC-CX4, NCT00017004 GM Thomas	Official title: radiation therapy and cisplatin with or without epoetin alfa in treating patients with cervical cancer and anemia	Suspended. First record received 6/6/01. Aim of study: to study the effectiveness of epoetin alfa in treating anemia in patients who have cervical cancer	ClinicalTrials.gov CTT PI: GM Thomas, GlaxoSmithKline Inc; PS Craighead, Tom Baker Cancer Center – Calgary Sponsor: Gynecologic Oncology Group, National Cancer Institute, National Cancer Institute of Canada	Study characteristics: RCT Patient characteristics: patients with cervical cancer undergoing radiotherapy and chemotherapy (cisplatin) Intervention: epoetin alfa Control: standard care	Outcomes sought: Hb (assessment whether Hb levels can be raised and maintained above 12 g dl^{-1} on epoetin alfa vs maintaining Hb above 10 g dl^{-1} without epoetin and the effects of this on progression-free survival), overall survival and local control. QoL	NR
12	CDR0000069409; MDA-DM-02331; MDA-DM-0038; NCI-P02-0225; NCI00052221 MJ Fisch	Official title: Epoetin alfa in treating fatigue in patients with advanced solid tumors who are not receiving chemotherapy	Suspended. Status: no longer recruiting, Record first received 17/2/03 Aim of study: to investigate the efficacy of epoetin alfa in treating fatigue in patients, specifically focusing on QoL and functional status. Correlating self-reported energy levels with other commonly occurring symptoms such as pain etc. and correlation with anaemia. Determine internal consistency of fatigue self-reports	ClinicalTrials.gov, CCT PI: MJ Fisch, Anderson Cancer Center Sponsor: Anderson Cancer Center	Study characteristics: RCT, placebo control Patient characteristics: stage III and IV invasive non-myeloid malignancy Intervention: epoetin alfa Control: placebo	Outcomes sought: fatigue, QoL	NR

TABLE 69 *Trials from 2001 to 2004 status unknown*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
13	CDR 0000257189; AGOSG-OVAR-MO16375-MARCH; EI20217; ROCHE-MO16375; ROCH-RO2053859. H Koelbl	Official title: Phase IV randomized study of epoetin beta for anemia management in patients with stage IIB, III or IVA cervical cancer treated with cisplatin and radiotherapy	Recruiting. A total of 80–450 patients to be accrued for this study within 4–22.5 months	ClinicalTrials.gov, CTT – accessed 24/6/04, data checked 15/4/05 PI: H Koelbl, Martin Luther Universitaet, Halle, Germany	Study characteristics: patients with histologically confirmed stage IIB, III or IVA cervical cancer undergoing cisplatin and radiation therapy. Hb between 13 and 8 g dl^{-1} Intervention: epoetin beta subcutaneously, 3 times per week beginning 2 weeks before radiotherapy and continuing for 8 weeks Control: standard care	Hb levels and correlation with disease progression. Safety. Progression free and overall survival. Frequency of disease progression and metastases. QoL. Adverse events, type, frequency and degree. Overall response rate	No results reported in this publication

TABLE 70 *Trials from 2001 to 2004 ASH/ASCO abstract search*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
14	ASH #1816 V Charu	Every 2 week dosing of darbepoetin alfa in patients with anaemia of cancer (AOC): interim analysis of a randomised, controlled study	NR	ASH 2003 V Charu	Adults, history of non-myeloid malignancy, not on anti-malignancy treatments. Comparative phase wks 1–13. Tumour types lymphoid malignancy (32%), breast (22%), GU or lung (14% each). Baseline Hb DA 10.1, control 10.4	Hb, RBCT, FACT-F (measured at wks 1, 5, 9, 13)	Data available for 120 DA and 30 control through to wk 13. Hb change: DA 1.9 (SD 1.9), control 0.2 (SD 1.0). KM estimate for HaemR: DA 81%, control 26%. Results pending for RBCT, HRQoL, and hospitalisation
15	ASCO #4747 C Famoycin	A randomised phase II study of thalidomide (thal) with or without erythropoietin (EPO) in metastatic renal cell carcinoma (RCC)		ASCO 2004 C Famoycin	RCT, epoetin alfa vs control. Concomitant therapy of thal. Patients with RCC	Tumour response (at 12 wks) and QoL (FACT-An, LASA) at 4 and 24 wks	Recruited 12 epo, 13 control. Epo has produced a non-statistically significant improvement in baseline Hb, QoL will be analysed at study completion
16	ASCO #1449 J O'Shaughnessy	Effects of epoetin alfa (Procrit) on cognitive function, mood, asthenia and QoL in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy: a double blind, randomised, placebo controlled trial		ASCO 2002 J O'Shaughnessy	RCT, epoetin alfa, vs placebo. Breast cancer. Baseline Hb between 9 and 14 g dl^{-1}. Anthracycline-based chemo	Pilot trial, outcomes: cognitive function, mood, QoL, asthenia	Interim analysis, epo 36 patients placebo 29 patients. Mean Hb change: epo 0.9–1.3 g dl^{-1}, placebo –0.2–1.4 g dl^{-1}. Smaller mean decreases in epo group regarding FACT-An and LASA. Interim results suggest that epo alf improve sHb, and asthenia symptoms, attenuates QoL decline, improves mood and may improve cognitive function, a large follow-up study is planned

continued

TABLE 70 *Trials from 2001 to 2004 ASH/ASCO abstract search (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
17	ASH #1801 V Recasens	A pharmacoeconomical analysis comparing epoetin alfa vs transfusion in patients with anemia associate to multiple myeloma		ASH 2003 V Recasens	RCT, MM patients. Epoetin alfa. Hb levels <12 g dl^{-1} males, <11 g dl^{-1} females. Transfusion trigger <9 g dl^{-1}	HaemR, clinical response. Also economic evaluation	69 patients evaluable, HaemR: epo 77%, control NR. Economics: epo 1391.13 €/patient, control 1326.65 €/patient. QoL: better for epo group. Response to chemo: no difference
4	ASH #828 DJ Strauss	Epoetin alfa treatment improves QoL and increases Hb levels during chemo for lymphoma, CLL, and MM in patients with mild to moderate anaemia		ASH 2002 DJ Straus/Ortho biotec	RCT, epoetin alfa vs standard care (epo given in Hb <9 g dl^{-1}). 16-wk trial. Patients with lymphoma, CLL, MM. Hb ≥ 10 ≤ 12 g dl^{-1}	Hb, QoL (FACT-An, LASA), clinic visits	Interim results data from 179/260 patients enrolled. Changes from baseline Hb (12.5 $\pm$ 1.4 g dl^{-1}): epo 0.8 $\pm$ 2.5, $p = 0.007$, cont -0.8 ± 1.0, $p < 0.001$, between group $p = 0.005$. Hb fell below 9 g dl^{-1} in 4 patients. QoL improvements for epo: FACT-An ($p = 0.036$). Clinic visits declined in epo group ($p = 0.002$)

TABLE 71 *Trials identified from the Cochrane review and no further information found*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
18	Antonadou 2001	Antonadou 2001. Erythropoietin enhances radiation treatment efficacy in patients with pelvic malignancies. Final results of a randomized phase III study	Start date: NR	Cochrane review. PI: D Antonadou, Metaxas Cancer Hospital, Radiation Oncology, Piraeus, Greece	RCT, 385 patients with pelvic malignancies undergoing radiotherapy. Epoetin vs standard treatment	Survival, safety	4 years disease-free survival. Epo group: 85.3%, control group 67.2%, $p = 0.008$
19	Broadley	Broadley. Double-blind randomised placebo-controlled trial of the effect of epoetin alfa on symptomatic anaemia and fatigue in cancer patients receiving ongoing care without planned chemotherapy	Start date: October 1998	Cochrane review. PI: K Broadley, Palliative Medicine, Royal Marsden NHS Trust, London	RCT, epoetin alfa vs placebo. Patients: metastatic breast cancer and prostate cancer. No cancer-specific treatment	Hb, QoL	
20	EORTC 22996-24002	EORTC 22996-24002. A phase III double-blind, randomised, placebo-controlled study of erythropoietin when used as an adjuvant to radiation therapy in patients with head and neck squamous cell carcinoma	Start date: February 1999	Cochrane review	RCT, epo (no brand given), vs placebo. Designed for 762 patients	Loco-regional control, overall survival, Hb, adverse events	
21	Elsaid	Elsaid. Significance of anaemia and role of erythropoietin in radiation-induced mucositis in head and neck cancer patients	Start date: NR	Cochrane review	RCT, epoetin vs standard care	Hb, incidence of mucositis	Enrolled 32 patients

continued

TABLE 71 *Trials identified from the Cochrane review and no further information found (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
22	Gallagher	Gallagher. The role of epoetin alpha in anaemia and fatigue in cancer patients	Start date: September 1998	Cochrane review. C Gallagher, Medical Oncology Department, St Bartholomew's Hospital, London	RCT, epoetin alfa vs standard care. Patients: ovarian and cervical cancer, cisplatin chemo	Hb, QoL	
23	Howell	Howell. A double-blind, randomised, placebo-controlled study to evaluate the impact of maintaining Hb using epoetin alfa in stage IV breast cancer subjects receiving chemotherapy	Start date: August 2000	Cochrane review. A Howell, Christie Hospital NHS Trust, Manchester	RCT, epoetin alfa vs placebo. Patients: breast cancer, chemo	Hb, RBCT, adverse events, overall survival, QoL	
24	MR4449/ARO98-2	MR4449/ARO98-2. Klinische Prufung von Epoetin Beta bei Patienten mit Kopf-Hals-Tumoren (MF4449)	Start date June 1996, finish date December 2002	Cochrane review. Prof. Bottcher, Johann Wolfgang Goethe-Universitat, Frankfurt am Main, Germany	RCT? Epoetin beta, plus radiotherapy	NR	NR
25	Miller	Miller. Phase III study of epoetin alfa with or without filgrastim (G-CSF) vs supportive therapy alone patients with myelodysplastic syndromes	Start date: NR	Cochrane review. KB Miller, Eastern Cooperative Oncology Group	RCT, epoetin vs best supportive care	Transfusion requirement, HaemR, disease progression, survival, toxicity	NR
26	Moebus 2001	Moebus 2001. Epoetin alpha prevents anemia and transfusions of RBCS in patients receiving dose-dense sequential chemotherapy	Start date: NR	Cochrane review	RCT, epoetin vs best supportive care. Disease – breast cancer, chemo, mean/median baseline Hb: >12 g dl^{-1}, epoetin: 91 analysed, control: 101 analysed	NR	NR

continued

TABLE 71 *Trials identified from the Cochrane review and no further information found (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
27	O'Brien	O'Brien. Open-label randomised group comparative evaluation of the effect of epoetin on anaemia and fatigue in lung cancer patients receiving palliative platinum containing chemotherapy	Start date: August 1998	Cochrane review. M O'Brien, Medicine Section, The Royal Marsden NHS Trust, Sutton	RCT, epoetin vs best supportive care	Hb, QoL, response and tolerance to chemotherapy	NR
28	O'Connell	O'Connell. Phase III randomised study of epoetin alfa in anaemic patients with advanced cancer undergoing chemotherapy	Start date: December 1998	Cochrane review. MJ O'Connell, North Central Cancer Treatment Group, USA	RCT, epoetin alfa vs placebo. Advanced cancer, chemo	Hb, RBCT, QoL	NR
29	Parliament	Parliament. Radiation therapy with or without epoetin alfa in anaemic patients with head and neck cancer	Start date: NR	Cochrane review. Cross Canada Institute, Edmonton, Alberta, Canada	RCT, epoetin alfa vs best supportive care	Hb, adverse events, QoL, tumour control, overall survival	NR
30	Rudd	Rudd. Evaluation of epoetin in lung cancer patients receiving chemotherapy	Start date: November 1998	Cochrane review. RM Rudd, Medical Oncology Department, St Bartholomew's Hospital, London	RCT, epoetin alpha, vs best supportive care	NR	NR
31	Stewart	Stewart. Open randomised comparative group evaluation of the effect of epoetin alfa on local disease free survival and quality of life in head and neck cancer patients receiving radical radiotherapy	Start date: August 1999	Cochrane review. JS Stewart, Department of Radiotherapy, Charing Cross Hospital, London	Epoetin alfa, head and neck cancer	Local tumour control, disease-free survival, overall survival, QoL	NR

continued

TABLE 71 *Trials identified from the Cochrane review and no further information found (cont'd)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
32	Thomas	Thomas. EXPREX trial. Open label comparative group evaluation of the effect of epoetin alfa on quality of life and burden of illness in anaemic cancer patients receiving platinum containing chemotherapy	Start date: June 1997	Cochrane review. R Thomas, Primrose Oncology Unit, Bedford South Wing Hospital, Bedford	RCT, epoetin alfa, vs best supportive care. Various malignancies, platinum chemo	QoL, patient burden, RBCT, Hb	NR
33	UKCCCR GN308	UKCCCR GN308. A double-blind, placebo-controlled study to assess the effects of early intervention and/or treatment of epoetin alfa on anaemia in cancer patients receiving non-platinum-containing chemotherapy	Start date: NR	Cochrane review. UKCCCR Register Co-ordinator, MRC Clinical Trials Unit, London	RCT, epoetin alfa vs placebo. Cancer patients, platinum chemo	RBCT, QoL	NR

TABLE 72 *Trials identified from both WMHTAC and described as ongoing in the Cochrane review*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
11	CDR0000068641; CDR0000068641, GOG-0191, CAN-NCIC-CX4, NCT00017004 GM Thomas	GM Thomas. Phase III randomised study of radiotherapy and cisplatin with or without epoetin alfa in patients with cervical cancer and anaemia	June 2001	ClinicalTrials.gov PI: GM Thomas, GlaxoSmithKline Inc, PS Craighead, Tom Baker Cancer Center – Calgary Sponsor: Gynecologic Oncology Group, National Cancer Institute, National Cancer Institute of Canada	Study characteristics: RCT. Patient characteristics: patients with cervical cancer undergoing radiotherapy and chemotherapy (cisplatin). Intervention: epoetin alfa. Control: standard care	Outcomes sought: Hb (assessment whether Hb levels can be raised and maintained >12 g dl^{-1} on epoetin alfa vs maintaining Hb >10 g dl^{-1} without epoetin and the effects of this on progression-free survival, overall survival and local control. QoL	Suspended
10	RTOG 99-03 M Machtay	RTOG 99-03. Phase III randomised study of radiotherapy with or without epoetin alfa in anaemic patients with squamous cell carcinoma of the head and neck	Start date: June 2000, designed for 372 patients	Cochrane review. PI: M Machtay, Radiation Therapy Oncology Group, USA	RCT, epoetin alfa, vs best supportive care	Tumour control, Hb, survival, toxicity, QoL	NR

TABLE 73 *Trials Identified from 2001 to 2004 ASH/ASCO searches and described as ongoing in the Cochrane review*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
34	Blohmer	Blohmer. Adjuvant sequential chemoradiotherapy with vs without erythropoietin in high-risk patients with carcinoma of the cervix	January 1999	Cochrane review. PI: Blohmer	RCT, epoetin alfa, vs standard treatment	Disease-free survival, Hb, RBCT	
4	Straus	Straus. Phase III randomised study of Epoetin alfa in patients with lymphoma, chronic lymphocytic leukaemia or multiple myeloma and chemotherapy-related mild or moderate anaemia	Start date: December 1997	Cochrane review. PI: DJ Straus, Memorial Sloan-Kettering Cancer Center, USA	RCT, epoetin alfa, vs standard care, haemo malignancies, chemo	HaemR, RBCT, QoL	NR

TABLE 74 *Trials included in main review and described as ongoing in the Cochrane review (abstract publications)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
35	Casedevall	Casedevall. Erythropoietin (rHuEpo) plus G-CSF in the treatment of anemia in MDS. Results of an RCT with impact of QoL and costs	Start date: January 1999	Cochrane review. PI: Casedevall	RCT, epoetin plus G-CSF vs standard care. Duration 12 wks	HaemR, QoL, cost	At time of Cochrane review the number of epo patients was 63 and control patients 55
36	H Thomas	H Thomas. Open-label comparative evaluation of the effect of epoetin on quality of life and burden of illness in anaemic patients receiving platinum-containing chemotherapy	Start date: July 1997	Cochrane review. H Thomas, Department of Clinical Oncology, Imperial College School of Medicine, London	RCT, epoetin alfa. Patients: cancer receiving platinum chemo	Hb, QoL	Ortho Biotec industry submission
37	Huddart	Huddart. Open-label evaluation to assess the effect of early intervention and/or treatment with epoetin alfa on anaemia in cancer patients receiving platinum-based chemotherapy	Start date: November 1996	Cochrane review. PI: R Huddart, Radiotherapy Section, The Royal Marsden NHS Trust, Sutton	RCT, epoetin alfa vs standard care. Patients: cancer with platinum chemo	Hb, QoL	Included trial in WMHTAC – abstract publication

TABLE 75 *Trials included in main review and described as ongoing in the Cochrane review (full-paper publications)*

No.	Trial identification	Study	Start/end dates and aim	Information source, principal investigator and sponsor	Study characteristics	Outcomes sought	Results
38	Rosen	Rosen. Multicentre randomised phase II study of 1 hour infusion of paclitaxel, fluoracil, and hydroxyurea with concomitant hyper fractionated radiotherapy with or without erythropoietin for advanced head and neck cancer	Start date: NR	Cochrane review. Chicago Oral Cancer Center, Northwestern University, Chicago, Illinois, USA	RCT, epoetin (dose 40,000 U weekly subcutaneously), duration 14 wks	Overall survival, Hb, RBCT	NR

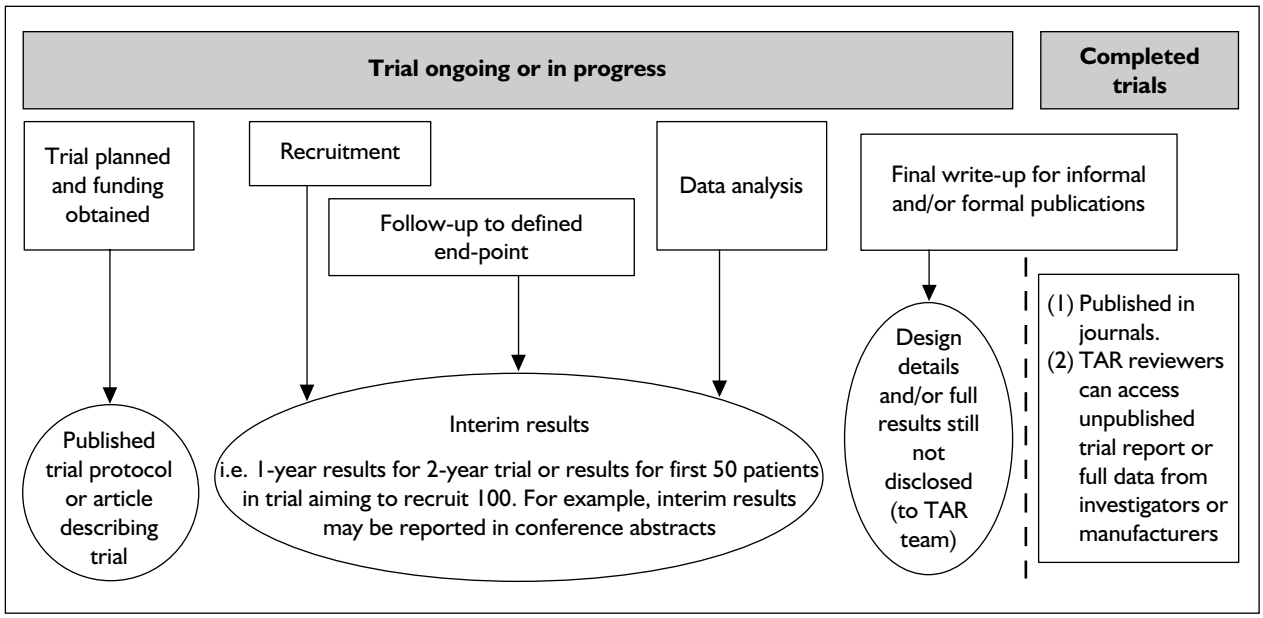

FIGURE 22 *Stages of trial: with particular reference to the definition of ongoing trial*[170]

Inclusion and exclusion criteria

Study design

Only RCTs were included. Non-randomised trials, in particular quasi-randomised such as where allocation is based on date of birth or day of month, were excluded. Also excluded were RCTs with fewer than 10 patients in any study arm.

Population

Patients had to be diagnosed with malignant disease, using clinical and histological/cytological criteria (any type of malignant disease was included, irrespective of stage or previous therapy); trials in patients with anaemia resulting from chemotherapy and/or radiotherapy or underlying malignant disease were included. Other causes of anaemia such as haemolysis, iron deficiency and occult bleeding should have been excluded in the participants of the included trials. There were no age restrictions; however, it is recognised that the licences for all three drugs do not cover erythropoietin use in children. Studies where erythropoietin was given in the context of myeloablative chemotherapy ahead of bone marrow or peripheral blood stem cell transplantation, or for short-term preoperative treatment to correct anaemia or to support collection of autologous blood prior to cancer surgery, were excluded.

Intervention

Epoetin alfa (Exprex®, Ortho Biotec), epoetin beta (NeoRecormon®, Roche) or darbepoetin alfa (Nesp®, Amgen). Concomitant anaemia therapy such as iron or G-CSF supplementation was permitted, as were red blood cell transfusions (RBCT).

Comparator

Within the Cochrane review[171] any comparator was acceptable provided that the only difference between the treatment and control arms was the use of erythropoietin. However, at the NICE consultee meeting on 2 September 2004, after discussion, it was felt that there may be trials in which concomitant supportive anaemia treatments such as G-CSF or iron supplementation had been given to patients receiving erythropoietin, but not to patients in the control arm, which if excluded would cause valuable information to be lost. It was therefore agreed to include these trials, but also to acknowledge that these trials do have different comparators to trials where concomitant supportive anaemia treatments are given to patients equally in each arm of the trials.

It was anticipated that comparators would be either placebo or best supportive care. In both, it was anticipated that RBCT would be given when a patients Hb fell to an unacceptably low level. Ideally a protocol for when RBCT should be instigated should have been described (i.e. 'transfusion trigger'). The same rules on rescue regarding RBCT should also have been applied in the erythropoietin arm.

Outcomes

Outcomes sought from the studies fell into four categories: anaemia-related outcomes, malignancy-related outcomes, adverse events data and patient-

specific outcomes such as QoL outcomes and patients preferences.

- Anaemia-related outcomes: haematological response to treatment (defined as a transfusion-free increase of Hb of ≥ 2 g dl^{-1} or a haematocrit (Hkt) increase of 6%); mean Hb change; RBCT requirements, including number of patients transfused, number of units transfused per patient and number of units transfused per patient per 4 weeks.
- Cancer-related outcomes sought were tumour response, and overall survival.
- Adverse events: hypertension, rash/irritation, pruritis, mortality, thrombic events, seizure, haemorrhage/thrombocytopenia, fatigue, and pure red cell aplasia. (Pure red cell aplasia was included as a specific adverse event after discussion at the NICE committee meeting on the 2 September 2004.) A note was made of other adverse events described within the trial reports.
- QoL: data on validated QoL measures was sought, anticipated QoL measures would include FACT (including FACT-G, FACT-F and FACT-An), however, notes were made of any HRQoL measure if they were reported.

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We look forward to hearing from you.

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