Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)

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1. Title of the project:

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)

2. Name of TAR team and project 'lead'

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3. Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Care Excellence in 2004 reviewing the effectiveness and cost-effectiveness of erythropoietin-stimulating agents (ESAs) epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz]), epoetin beta (NeoRecormon [Roche Products]), epoetin theta (Eporatio [Teva UK]), epoetin zeta (Retacrit [Hospira UK]), and

darbepoetin alfa (Aranesp [Amgen]). The assessment will also assess whether the reviewed drugs are likely to be considered good value for money for the NHS.

4. Background

Anaemia is defined as a reduction of haemoglobin concentration, red cell count or packed cell volume to below normal levels. The World Health Organization has defined anaemia as a haemoglobin level of less than 12 g/dl in women and less than 13 g/dl in men. A reduction in the red blood cells can result from either the defective production of red blood cells or an increased rate of loss of cells, either by premature destruction or bleeding. Production of red blood cells (erythropoiesis) is primarily stimulated and regulated by a hormone called erythropoietin. Erythropoietin is a glycoprotein hormone that is produced naturally in the kidneys, but can also be manufactured for clinical use using recombinant DNA technology.

Anaemia can lead to a marked reduction in aspects of quality of life, such as increased fatigue, reduced exercise capacity and decreased sense of wellbeing. Fatigue is one of the commonest symptoms of anaemia. Anaemia is a common side-effect of cancer treatments and the anaemia-related fatigue has been shown to have a significant impact on cancer patients. Nearly 60% of patients with solid tumours undergoing chemotherapy became anaemic with a haemoglobin (Hb) <11 g/dl during their treatment. Anaemia is also common in haematological malignancies; up to 75% of patients with multiple myeloma are anaemic at diagnosis, and 70% of patients with lymphoma are anaemic by Cycles 3-4 of their chemotherapy.

Cancer treatment-induced anaemia is managed by adjustments to the cancer treatment regimen, iron supplementation and blood transfusion in cases of severe anaemia. NICE Technology Appraisal Guidance 142: "*Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia' recommends erythropoietin analogues* [ESAs] *only for women receiving platinum-based chemotherapy for ovarian cancer who have a blood haemoglobin level of 8 g/100 ml or lower, and also for people who have very severe anaemia and cannot receive blood transfusions*."[1]

5. Current evidence

The conclusions from the previous review were:[2]

- ESAs are effective in improving haematological response and red blood cell transfusion requirements, and appears to have a positive effect on health-related quality of life.

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

A recent Cochrane Review (2012) was identified in background searches:

- Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2012, Issue 12.[3]

This review assessed the effects of ESAs to either prevent or treat anaemia in cancer patients. It included a total of 91 trials with a total of 20,102 participants. The review found that ESAs: *"… reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affect tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.*" (Tonia T et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2012, Issue 12).[3]

6. Decision problem

6.1. Purpose of the decision to be made

The assessment will address the question: "What is the effectiveness and cost-effectiveness of ESAs (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anaemia (including review of TA142)?"

6.2. Interventions

Exogenously administered erythropoietin is the intervention under assessment. It is used in addition to, rather than a complete replacement of the existing components of management. Since the last appraisal (2004), an additional two types of recombinant human erythropoietin are available: epoetin theta and epoetin zeta; the latter is referenced to epoetin alfa. Epoetin alfa, beta, theta and zeta are recombinant human erythropoietin analogues, Epoetins are used to shorten the period of symptomatic

anaemia in patients receiving cytotoxic chemotherapy. Darbepoetin alfa is a hyperglycosylated derivative of epoetin that stimulates erythropoiesis by the same mechanism as the endogenous hormone. For the treatment of anaemia associated with cancer treatment, they are administered by injection.

This technology assessment report (TAR) will consider six pharmaceutical interventions: epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz]), epoetin beta (NeoRecormon [Roche Products]), epoetin theta (Eporatio [Teva UK]), epoetin zeta (Retacrit [Hospira UK]), and darbepoetin alfa (Aranesp [Amgen]).[4]

Epoetin alfa (Eprex, [Janssen-Cilag] and Binocrit [Sandoz]), and **epoetin zeta** (Retacrit [Hospira UK]) have UK marketing authorisations for the treatment of anaemia and for the reduction of transfusion requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma, or multiple myeloma, who are at risk of transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy). Binocrit (Sandoz) and epoetin zeta (Retacrit, Hospira UK) are biosimilar medicines references to Eprex which contains epoetin alfa. **Epoetin beta** (NeoRecormon, Roche Products), **epoetin theta** (Eporatio [Teva UK]), and **darbepoetin alfa** (Aranesp [Amgen]) have UK marketing authorisations for the treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy. A summary of the UK marketing authorisation for each intervention along with a description of administration method is given below.

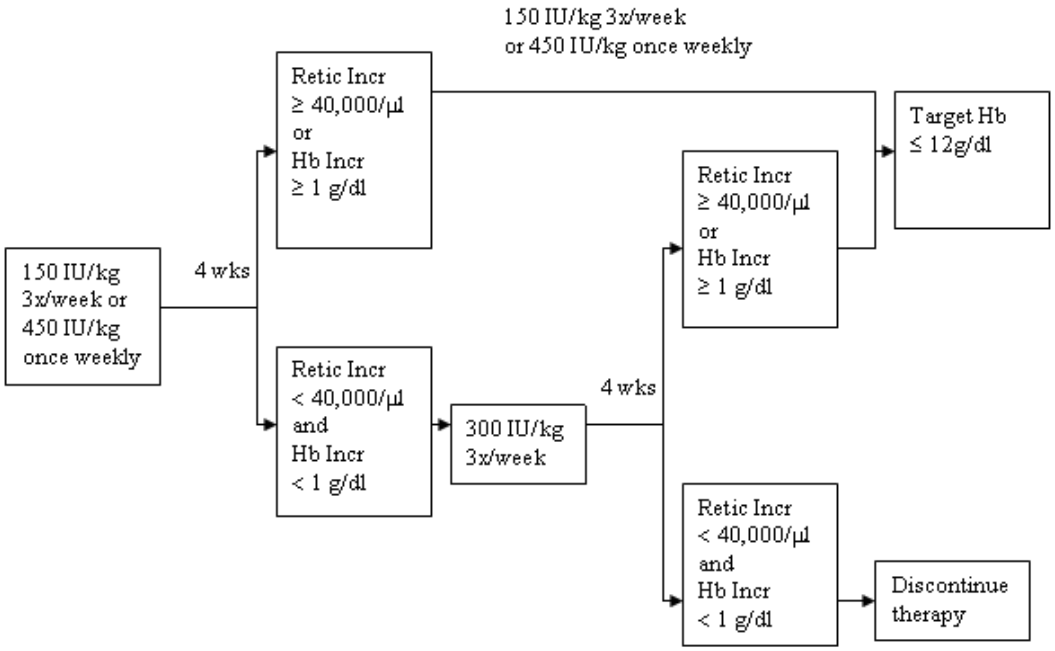
UK marketing authorisations

All interventions of interest in this review are administered by administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration < 10 g/dl (6.2 mmol/l)) in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). All therapies should be continued up to four weeks after the end of chemotherapy.

Epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz], and epoetin zeta (Retacrit, Hospira UK): the initial dose is 150 IU kg^{-1} given subcutaneously three times per week.[5-7] Alternatively, epoetin alfa can be administered at an initial dose of 450 IU kg^{-1} subcutaneously once weekly.[5-7] The maximum recommended dose is 900 IU kg^{-1} body weight per week.[5-7] Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10g/dl (6.2 mmol/l) to 12g/dl (7.5mmol/l).[5-7] A sustained haemoglobin level of greater than 12g/dl

(7.5mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceed 12g/dl (7.5mmol/l) (see Figure 1).[6-8] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level.[5-7]

Figure 1. Epoetin alfa and epoetin zeta administration guidance[5-7]



Epoetin beta (NeoRecormen, Roche Products): the weekly dose can be given as one injection per week or in divided doses three to seven times per week.[9] The recommended initial dose is 450 IU kg^{-1} body weight per week.[9] If, after four weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), a doubling of the weekly dose should be considered. If, after eight weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.[9] The maximum recommended dose is 900 IU kg^{-1} body weight per week.[9] Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l).[9] A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided.[9] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level.[9] Appropriate dose titration should be considered.[9]

Epoetin theta (Eporatio, Teva UK): the recommended initial dose is 20,000 IU, independent of bodyweight, given once-weekly.[10] Haemoglobin variability should be

addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l).[10] A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided.[10] If, after four weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l) a doubling of the weekly dose to 40,000 IU should be considered.[10] If, after an additional four weeks of therapy, the haemoglobin increase is still insufficient an increase of the weekly dose to 60,000 IU should be considered. The maximum dose should not exceed 60,000 IU per week.[10] If, after 12 weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.[10]

Darbepoetin alfa (Aranesp, Amgen): the recommended initial dose is 500 µg (6.75 µg kg^{-1}) given once every three weeks, or once weekly dosing can be given at 2.25 µg kg^{-1} body weight.[11] The maximum recommended dose is 4.5 µg kg^{-1} per week.[11] If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective.[11] Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25% to 50% in order to ensure that the lowest approved dose of is used to maintain haemoglobin at a level that controls the symptoms of anaemia.[11] Appropriate dose titration between 500 µg, 300 µg, and 150 µg should be considered.[11] Patients should be monitored closely, if the haemoglobin exceeds 12 g/dl (7.5 mmol/l), the dose should be reduced by approximately 25 to 50%.[11] Treatment with darbepoetin alfa should be temporarily discontinued if haemoglobin levels exceed 13 g/dl (8.1 mmol/l).[11] Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dl (7.5 mmol/l) or below.[11] If the rise in haemoglobin is greater than 2 g/dl (1.25 mmol/l) in four weeks, the dose should be reduced by 25 to 50%.[11]

6.3. Place of the interventions in the treatment pathway

NICE guidance (Technology Appraisal Guidance 142)[11] currently recommends ESAs in combination with intravenous iron as an option for:

- the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/100 ml or lower. The use of ESAs does not preclude the use of existing approaches to

the management of anaemia, including blood transfusion where necessary.[1]

- people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.[1]

Where indicated the ESA used should be the one with the lowest acquisition cost.[1]

In addition, the NICE guidance recommends ESAs for people who are currently being treated with ESAs for the management of cancer treatment-related anaemia but who do not fulfil either of the above criteria should have the option to continue their therapy until they and their specialists consider it appropriate to stop.[1]

6.4. Relevant comparators

The main comparators of interest are:[4]

- placebo
- best supportive care (including adjustment to the cancer treatment regimen, blood transfusion, and iron supplementation)
- one of the other interventions under consideration, compared in line with their marketing authorisations.

6.5. Population

The population will be:[4]

- people 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)
- people with non-myeloid malignancies who are receiving chemotherapy

There are no age restrictions; however, it is recognised that all licences for all drugs do not cover erthyropoietin use in children.

The scope issued by NICE states that if evidence allows subgroups should be considered; e.g. by cancer type and status, by chemotherapy, or by best supportive care received (see Section 7.5, page 14 for more information).

6.6. Outcomes to be addressed

Evidence in relation to the following kinds of outcomes will be considered:[4]

- haematological response to treatment
- need for blood transfusion after treatment
- tumour response (time to cancer progression)
- survival
- adverse effects of treatment
- health-related quality of life.

7. Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for the clinical effectiveness of epoetin alfa (Eprex [Janssen-Cilag], Binocrit [Sandoz]), epoetin beta (NeoRecormon [Roche Products]), epoetin theta (Eporatio [Teva UK]), epoetin zeta (Retacrit [Hospira UK]), and darbepoetin alfa (Aranesp [Amgen]).

The review will update the previous review of clinical effectiveness undertaken in 2004 to inform NICE's TA142 Guidance.[1] The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[12]

7.1. Search strategy

The search strategy will comprise the following main elements:

- searching of electronic databases using an appropriately sensitive search strategy designed and executed by an information specialist
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Database of Systematic Reviews, CENTRAL, DARE, NHS EED, HEED and HTA databases; CINAHL (EBSCO); British Nursing Index (ProQuest); Web of Science (Thomson Reuters); HMIC (Ovid); Current Controlled Trials; Clinical Trials.gov; FDA website; EMA website.

In addition the following websites will be searched for background information:

Medical societies

British Society for Haematology	http://www.b-s-h.org.uk/
The Association of Cancer Physicians	http://www.cancerphysicians.org.uk/
American Society of Hematology	http://www.hematology.org/
American Society of Clinical Oncology	http://www.asco.org/
The Canadian Oncology Societies	http://www.cos.ca/
Haematology Society of Australia and New Zealand	http://www.hsanz.org.au/
Clinical Oncology Society of Australia	http://www.cosa.org.au/
New Zealand Society for Oncology	http://www.nzsoncology.org.nz/

UK charities

Cancer Research UK	http://www.cancerresearchuk.org/home/
Macmillan	http://www.macmillan.org.uk/
Marie Curie	http://www.mariecurie.org.uk/

Non-UK charities

American Cancer Society	http://www.cancer.org/
Canadian Cancer Society	http://www.cancer.ca/
Cancer Council Australia	http://www.cancer.org.au/
Cancer Society of New Zealand	http://www.cancernz.org.nz/
World Cancer Research Fund	http://www.wcrf-uk.org/

The databases will be searched from search end-date of the last MTA on this topic (2004). Although epoetin alfa (Binocrit [Sandoz]), epoetin theta and epoetin zeta were not covered in the previous report, we believe that relevant interventional research is highly unlikely to have been published on these drugs prior to this date given that the drugs were launched in 2007 (epoetin alfa [Binocrit, Sandoz]) and 2009 (epoetin theta).

The searches will be developed using the search strategies detailed in the MTA by Wilson *et al* as the starting point (see Appendix A for more information).[2] Search filters will be used to find clinical effectiveness, cost effectiveness and quality of life studies, and all searches will be limited to English language studies.

All references will be exported into Endnote X5 (Thomson Reuters) where automatic and manual de-duplication will be performed.

7.2. Inclusion/exclusion criteria

7.2.1. Inclusion criteria

The inclusion criteria are as reported in Table 1. The review of clinical effectiveness will include any randomised controlled trial (RCT) reporting at least one of the outcomes of interest. However, if there are no RCTs reporting one of the listed outcomes of interest or if there are no RCTs with over 12 months' follow up, we will extend our inclusion criteria to controlled clinical trials to search for studies with missing outcomes or longer follow up. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review. These criteria may be relaxed for consideration of adverse events, for which non-randomised and observational studies may be included.

For the purpose of this review, a systematic review[8,12,13] will be defined as one that has:

- a focused research question
- explicit search criteria that are available to review, either in the document or on application
- explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest
- a critical appraisal of included studies, including consideration of internal and external validity of the research
- a synthesis of the included evidence, whether narrative or quantitative.

Table 1. Inclusion criteria (PICOS) as per the final scope and accompanying notes[4]

Population	People 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	There are no age restrictions; however, it is recognised that the licences for all three drugs do not cover eruthropoietin use in children. Exclude studies where erythropoietin was given in the context of myeloablative chemotherapy ahead of bone

	start of chemotherapy). People with non-myeloid malignancies who are receiving chemotherapy	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.
Intervention(s)	**Epoetin alfa** (Eprex, [Janssen-Cilag] and Binocrit [Sandoz]) **Epoetin beta** (NeoRecormon, Roche Products) **Epoetin theta** (Eporatio [Teva UK]) E**poetin zeta** (Retacrit [Hospira UK]) **Darbepoietin alfa** (Aranesp [Amgen]).	These interventions will be assessed as administered in accordance with licensed indications. <u>Concomitant anaemia therapy</u> such as granulocyte colony-stimulating factor (G-CSF) supplementation was permitted should be given equally in the control arm. This criterion was relaxed for iron supplementation which can be used in the experimental but not in the control arm as well.
Comparator(s)	Placebo Best supportive care (including adjustment to the cancer treatment regimen, blood transfusion and iron supplementation) One of the other interventions under consideration; compared in line with their marketing authorisations	<u>Concomitant anaemia therapy</u> such as granulocyte colony-stimulating factor (G-CSF) supplementation was permitted should be given equally in the intervention arm. This criterion was relaxed for iron supplementation which can be used in the experimental but not in the control arm as well.
Outcomes	Haematological response to treatment	Defined as a transfusion free increase of Hb of ≥2 g dl^{-1} or a haematocrit increase of 6%
	Need for blood transfusion after treatment	Number of patients transfused, number of units transfused per patient, and number of patients transfused per patient per four weeks
	Tumour response	Time to cancer progression

	Survival	Overall survival
	Adverse effects of treatment	Hypertension, rash/irritation, pruritus, mortality, thrombic events, seizure, haemorrhage / thrombocytopenia, fatigue, pure red cell aplasia. Particular interest thromboembolic events A note will be made of other adverse events described within the trial reports
	Health-related quality of life	Health-related quality of life – data on validated quality of life measures; e.g. FACT (FACT-General, FACT-Fatigue, FACT-Anaemia); EQ-5D, SF-36
Study design	RCTs SRs of RCTs (to be used to cross-check for any additional RCTs and to compare the findings of our review with)	For the purpose of this review, a systematic review will be defined as one that has: a focused research question; explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest; a critical appraisal of included studies, including consideration of internal and external validity of the research synthesis of the included evidence, whether narrative or quantitative. If insufficient data are available from RCTs, observational studies or non-randomised trials may be considered. For example this criterion will be relaxed for the consideration of adverse events and long term evidence of effectiveness, for which observational studies and disease registers of sufficiently long follow-up and good quality

		may be included **Exclude:** non-randomised studies; animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers; reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

7.2.2. Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound in terms of either study design or the method used to assess outcomes will be excluded from the results.

The following publication types will also be excluded from the analysis:

- non-randomised studies
- animal models
- preclinical and biological studies
- narrative reviews, editorials, opinions
- non-English language papers
- reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

7.3. Data extraction strategy

Studies retrieved from the update searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 1. First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by

discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. At each step studies which do not satisfy those criteria; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

In addition, if time and resources permit, studies included in the 2004 review may be re-abstracted using the data extraction process detailed below. This will facilitate examination of sub-groups not examined in detail in the original report.

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Included studies and industry submissions will be analysed to ensure the saturation of relevant studies (see Section 9 (page 18)).

7.4. Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the Cochrane Risk of Bias tool,[14] or criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials (RCTs).[12]

7.5. Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e. if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBugs software, with the use of fixed- and/or random-effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study

populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

A network meta-analysis was considered but not thought to be particular relevance to this topic.

We will investigate the likelihood of publication bias using funnel plots if there are sufficient included studies.

If evidence allows, the following subgroups will be considered:

- iron supplementation given with erythropoiesis-stimulating agents
- people with any type of cancer receiving platinum-based chemotherapy
- people with head and neck malignancies receiving platinum-based chemotherapy
- women with ovarian cancer
- women with ovarian cancer receiving platinum-based chemotherapy
- people unable to receive blood transfusions.

7.6. Publication bias

If time and resource permit, reporting bias* in our systematic review and meta-analyses will be assessed. We will follow best practice as recommended in the Cochrane Handbook for Reviewers, who have dedicated a whole chapter to the avoidance, identification and investigation of possible reporting bias.[14] This may include researching trials that have only ever appeared as conference abstracts in previous reviews.

8. Methods for synthesising evidence of cost-effectiveness

* Where the term 'reporting bias' covers all types of publication, language, outcome, location etc biases defined in the Cochrane Handbook.

8.1. Review of economic studies

This review aims to update the systematic review of cost-effectiveness studies which was conducted in 2004 as part of the review of evidence to inform NICE's earlier guidance on these drugs (TA142).[15]

A review, using a systematic approach, will be of economic evaluations of erythropoietin stimulating agents for the treatment of cancer treatment induced anaemia will be undertaken. Full economic evaluations will be included where they meet the inclusion criteria set out for the review of clinical effectiveness (see Section 7.2). Exceptions include: (a)non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies.); (b) full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data); and, (c) standalone cost analyses based in the UK NHS will also be sought and appraised.

The sources to be searched will be similar to those in the clinical effectiveness review (see Section 7.1), and extend to NHS EED and HEED. Searches will be limited to English language sources.

Key included economic evaluations identified in the search will be critically assessed using accepted frameworks, such as the consensus-developed list of criteria developed by Evers and colleagues[16]. For included economic evaluations based on decision models, critical appraisal of these studies will make use of guidelines for good practice in decision analytic modelling in HTA.

Methods and findings from key included economic evaluations will be summarised in a tabular format and synthesised in a narrative review. Economic evaluations carried out from the perspective of the UK NHS and Personal Social Services (PSS) perspective will be particularly highlighted.

8.2. Economic modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The evaluation will be constrained by available evidence.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE.

Resource use will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, sponsor submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Search strategies for additional information regarding model parameters or topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper ‘Methods for establishing parameter values for decision analytic models’ commissioned by the UK Dept. of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs other UK studies will be considered if appropriate.

ICERs estimated from Consultee models will be compared with the respective ICERs from the Assessment Group’s model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

8.2.1. Methods for measuring and valuing health effects

Ideally, the measurement of changes in health-related quality of life (HRQL) should be reported directly from patients. The value of changes in patients’ HRQL (that is,

utilities) should be based on public preferences using a choice-based method. The EQ-5D will be the preferred measure of HRQL for the purposes of estimating QALYs. In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).[17]

8.2.2. Time horizon, perspective and discounting

The time horizon of our analysis will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[17]

9. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the ERG no later than 02/10/2013. Data arriving after this date may not be considered.

Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where the TAR team have undertaken further analyses, using models submitted by manufacturers/sponsors or via de novo modelling and cost effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Tabulated summaries and technical commentaries on the economic models used in the manufacturer submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG *de novo* model and to discuss any differences identified in the outcomes provided.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

10. Expertise in this TAR team

Name	Institution	Expertise
Simon Briscoe	PenTAG, University of Exeter Medical School	Information Specialist
Helen Coelho	PenTAG, University of Exeter Medical School	Assessment of publication bias
Louise Crathorne	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review) and project management
Marcela Haasova	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
Martin Hoyle	PenTAG, University of Exeter Medical School	Health economics and economic modelling (lead)
Nicola Huxley	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation
Chris Hyde	PenTAG, University of Exeter Medical School	Systematic reviewing and economic evaluation. Director of TAR group and project guarantor
Tracey Jones-Hughes	PenTAG, University of Exeter Medical School	Lead systematic reviewer (quality of life review)
Linda Long	PenTAG, University of Exeter Medical School	Systematic reviewing (quality of life review)
Ruben Mujica-Mota	PenTAG, University of Exeter Medical School	Health Economist
Mark Napier	Royal Devon & Exeter Hospital, Devon	Clinical Medical Oncologist
Jaime Peters	PenTAG, University of Exeter Medical School	Advising re publication bias and mixed treatment comparison
Claudius Rudin	Royal Devon & Exeter Hospital, Devon	Consultant Haematologist
Kate Scatchard	Royal Devon & Exeter Hospital, Devon	Consultant Oncologist
Tristan Snowsill	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation

Other external experts: We are also collaborating with Simon Stanworth of the NHS Blood and Transplant Centre (NHSBT), and Julia Bohlius and Thomy Tonia from the Cochrane Haematological Malignancies Group.

Other PenTAG resources: Depending on the agreed scope of work we will draw on other PenTAG resources as required.

11. TAR centre

11.1. About PenTAG:

The Peninsula Technology Assessment Group is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE Centre for Public Health Excellence, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model

- Machine perfusion systems and cold static storage of kidneys from deceased donors.

- The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults

- The harmful health effects of recreational Ecstasy: A systematic review of observational evidence

- Assessment of surrogate outcomes in model-based cost effectiveness analyses within UK health technology reports: a methodological review

- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over.

- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years.

- The effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: a systematic review and economic model.

- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease: a systematic review and economic model

- The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation.

- Surveillance of cirrhosis for the development of hepatocellular carcinoma: systematic review and economic analysis.

- Surveillance of Barrett's oesophagus: exploring the uncertainty.

- The cost effectiveness of testing for hepatitis C in former injecting drug users.

- Do the findings of case series vary systematically by methodological characteristics.

- The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.

- The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

- The effectiveness and cost-effectiveness of microwave and thermal balloon endometrical ablation for heavy menstrual bleeding: a systematic review and economic modelling.

- Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
- Systematic review of endoscopic Sinus Surgery for Nasal Polyps.
- Screening for hepatitis C in GUM clinic attenders and injecting drug users.
- The effectiveness and cost effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

12. Competing interests of authors

None

13. Timetable/milestones

Action	**Expected due date**
Draft protocol due	3 June 2013
Comments on draft protocol sent to AG	10 June 2013
Final protocol due	13 June 2013
Sign-off of final protocol	24 June 2013
Consultee information meeting	12 August 2013
Manufacturers submissions due	2 October 2013
Progress report due	9 October 2013
Draft assessment report due	10 December 2013
Comments on draft assessment report	17 December 2013
Assessment report due	15 January 2014
1st Appraisal Committee meeting	19 March 2014

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Appendix A: MEDLINE search strategies

Clinical effectiveness

1. (erythropoietin* or EPO).tw.
2. Erythropoietin/
3. Receptors, erythropoietin/
4. erythropoiesis.tw.
5. Erythropoiesis/
6. (epoetin adj1 (alfa or beta or theta or zeta)).tw.
7. darbepoetin.tw.
8. CERA.tw.
9. (eprex or erypo or HEXAL or procrit or abseamed or epogen or binocrit or neorecormon or eporatio or retacrit or silapo or aranesp).tw.
10. or/1-9
11. an?emi?.tw.
12. exp anemia/
13. 11 or 12
14. (cancer* or carcinom* or leukemia or neoplasm* or malignan* or tumo?r* or myelo* or lymphoma* or oncolog* or chemotherap*).tw.
15. exp neoplasms/
16. 14 or 15
17. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
18. randomized controlled trial.pt.
19. 17 or 18
20. 10 and 13 and 16 and 19
21. limit 20 to (english language and yr="2004 -Current")

Cost effectiveness (economics and model)

Lines 1-16 as clinical effectiveness search strategy

17. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.
18. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.
19. ("resource* alloca*" or "resource* use").tw.
20. exp Economics/
21. exp models, economic/
22. exp "Costs and Cost Analysis"/
23. Cost of illness/
24. ec.fs.
25. (decision adj2 (model* or tree* or analy*)).tw.
26. markov.tw.
27. decision trees/
28. or/17-27
29. 10 and 13 and 16 and 28
30. limit 29 to (english language and yr="2004 -Current")

Quality of life

Lines 1-16 as clinical effectiveness search strategy

17. ("quality of life" or QoL or HRQL or HRQoL).tw.
18. quality of life/
19. ("quality adjusted life year*" or QALY*).tw.
20. quality-adjusted life years/
21. "activities of daily living".tw.
22. activities of daily living/
23. ("quality of wellbeing" or QWB or "QWB SA").tw.
24. ("health* year* equivalent*" or HYE*).tw.
25. "health status".tw.
26. health status/
27. health status indicators/
28. Psychometrics/
29. psychometric*.tw.
30. ("short form 36" or "SF-36" or SF36).tw.
31. ("short form 20" or "SF-20" or SF20).tw.
32. ("short form 12" or "SF-12" or SF12).tw.
33. ("short form 8" or "SF-8" or SF8).tw.
34. (Euroqol or "EQ-5D").tw.
35. exp Questionnaires/
36. or/17-35
37. 10 and 13 and 16 and 36
38. limit 37 to (english language and yr="2004 -Current")